CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022432Orig1s000

Trade Name: H.P. Acthar Gel

Generic Name: Repository Corticotropin Injection

Sponsor: Questcor Pharmaceuticals, Inc.

Approval Date: October 15, 2010

Indications: an adrenocorticotropic hormone (ACTH) analogue indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age;

Indicated for the treatment of exacerbations of multiple
sclerosis in adults;

May be used for the following disorders and diseases: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous state

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022432

NDA APPROVAL

Questcor Pharmaceuticals, Inc.
Attention: Sian Bigora, Pharm.D.
Vice President, Regulatory Affairs
3260 Whipple Road
Union City, CA 94587

Dear Dr. Bigora:

Please refer to your New Drug Application (NDA) dated June 16, 2006, received June 23, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for H.P. Acthar® Gel (repository corticotropin) Injection.

We acknowledge receipt of your amendments dated December 10, 2009, and January 19, April 1, 22, and 28, June 8, and August 10, 2010.

The December 10, 2009, submission constituted a complete response to our May 10, 2007, action letter.

This new drug application provides for the use of H.P. Acthar® Gel (repository corticotropin) to treat infantile spasms.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, except with the revisions listed below, as soon as they are available, but no more than 30 days after they are printed.

1. Because H.P. Acthar Gel is a multiple-dose injectable product, the strength per total volume should be the primary and prominent expression on the principle display panel, followed in close proximity by the strength per mL enclosed by parenthesis per USP standards. Please revise the strength expression on all labels and labeling to read as follows:

   400 USP units/5 mL
   (80 USP units/mL)

2. Relocate the strength expression immediately following the established name presentation in all labels and labeling.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022432**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt

from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letter dated September 27, 2010.

H.P. Acthar Gel (repository corticotrophin) was approved on April 29, 1952, for multiple indications. The label was later expanded to include multiple sclerosis (MS) in 1972. We are now adding the indication of infantile spasms in pediatric patients. The known risks of infections and blood pressure elevation in MS patients have also been identified as risks in the pediatric population based on clinical trial data. Additionally, the risk of adrenal insufficiency seen in other patient populations is an important potential serious adverse event in the pediatric population. The extension of the indication to pediatrics changes the risk benefit profile of H.P. Acthar Gel (repository corticotrophin) and is considered to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.
Your proposed REMS, submitted on September 28, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide and timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

An evaluation of patients' understanding of the serious risks of H.P. Acthar® Gel (repository corticotropin).

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you will also need to submit a REMS, REMS supporting document, and any required appended documents for that authorized generic, to this NDA. In other words, you must submit a complete proposed REMS that relates only to the authorized generic product. Review and approval of the REMS is required before you may market your product.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 008372 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 008372
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 008372
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original **NDA 008372** for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
10/15/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use H.P. Acthar Gel safely and effectively. See full prescribing information for H.P. Acthar Gel.

H.P. Acthar Gel (repository corticotropin) INJECTION, GEL for INTRAMUSCULAR | SUBCUTANEOUS use

Initial U.S. Approval: 1952

----------RECENT MAJOR CHANGES----------

- Indications and Usage, (1) 10/10
- Dosage and Administration, (2) 10/10
- Contraindications, Infantile Spasms (4) 10/10
- Warnings and Precautions (5) 10/10

----------INDICATIONS AND USAGE----------

- H.P. Acthar Gel is an adrenocorticotropic hormone (ACTH) analogue indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age. (1.1)
- H.P. Acthar Gel is indicated for the treatment of exacerbations of multiple sclerosis in adults. (1.2)
- H.P. Acthar Gel may be used for the following disorders and diseases: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous state; (1.3 to 1.9)

----------DOSAGE AND ADMINISTRATION----------

- In the treatment of infantile spasms, the recommended dose is 150 U/m^2 divided into twice daily intramuscular injections of 75 U/m^2. After 2 weeks of treatment, dosing should be gradually tapered and discontinued over a 2-week period. (2.1)
- In the treatment of acute exacerbations of multiple sclerosis, daily intramuscular or subcutaneous doses of 80-120 units for 2-3 weeks may be administered. It may be necessary to taper the dose. (2.2)
- In the treatment of other disorders and diseases, dosing will need to be individualized depending on the disease under treatment and the medical condition of the patient. It may be necessary to taper the dose. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- 5 mL multi-dose vial containing 80 USP units per mL (3)

----------CONTRAINDICATIONS----------

- H.P. Acthar Gel should never be given intravenously.
- H.P. Acthar Gel is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, or sensitivity to proteins of porcine origin.
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of H.P Acthar Gel.
- H.P. Acthar Gel is contraindicated in children under 2 years of age with suspected congenital infections. (4)
- Treatment of conditions listed within the INDICATIONS section is contraindicated when they are accompanied by primary adrenocortical insufficiency or adrenocortical hyperfunction. (4)

----------WARNINGS AND PRECAUTIONS----------

- Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination or reactivation of latent infections. Signs and symptoms of infection may be masked. (5.1)
- Adrenal Insufficiency after Prolonged Therapy: Monitor for effects of hypothalamic-pituitary-axis suppression after stopping treatment. (5 2)
- Cushing's Syndrome: May occur after prolonged therapy. Monitor for signs and symptoms. (5.2)
- Elevated Blood Pressure, Salt and Water Retention and Hypokalemia: Monitor blood pressure and sodium and potassium levels. (5.3)
- Vaccination: Do not administer live or attenuated vaccines to patients on immunosuppressive doses. (5.4)
- Masking of Symptoms of Other Underlying Disease/Disorders. Monitor patients for signs of other underlying disease/disorders that may be masked. (5.5)
- Gastrointestinal Perforation and Bleeding: There is a risk for gastric ulcers and bleeding. There is an increased risk of perforation in patients with certain GI disorders. Signs and symptoms may be masked. Monitor for signs of perforation and bleeding. (5.6)
- Behavioral and Mood Disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression and psychosis. Existing conditions may be aggravated (5.7)
- Comorbid Diseases: Symptoms of diabetes and myasthenia gravis may be worsened with treatment. (5.8)
- Ophthalmic Effects: Monitor for cataracts, infections and glaucoma. (5.9)
- Immunogenicity Potential: Neutralizing antibodies with chronic administration may lead to a loss of endogenous ACTH activity. (5.10)
- Use in Patients with Hypothyroidism or Liver Cirrhosis: May result in an enhanced effect. (5.11)
- Negative Effects on Growth and Physical Development: Monitor pediatric patients on long term therapy. (5.12)
- Decrease in Bone Density: Monitor for osteoporosis in patients on long term therapy. (5.13)
- Use in Pregnancy: Embryocidal effect. Apprise women of potential harm to the fetus. (5.14)

----------ADVERSE REACTIONS----------

- Common adverse reactions for Acthar Gel are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain. (6)
- Specific adverse reactions resulting from drug use in children under 2 years of age are increased risk of infections, hypertension, irritability, Cushingoid symptoms, cardiac hypertrophy and weight gain. (6.1.1)
-

To report SUSPECTED ADVERSE REACTIONS, contact Questcor Pharmaceuticals, Inc. at (800) 411-3065 or (510) 400-0700 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- H.P. Acthar Gel may accentuate the electrolyte loss associated with diuretic therapy. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: H.P. Acthar Gel has been shown to have an embryocidal effect and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)Pediatric Use: Prolonged use of H.P. Acthar Gel in children may inhibit skeletal growth. If use is necessary, it should be given intermittently with careful observation. (5.12 and 8.3)

See 17 **for Patient Counseling Information and FDA-approved Medication Guide**

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Infantile spasms:

H.P. Acthar Gel (repository corticotropin injection) is indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.

1.2 Multiple Sclerosis:

H.P. Acthar Gel (repository corticotropin injection) is indicated for the treatment of acute exacerbations of multiple sclerosis in adults. Controlled clinical trials have shown H.P. Acthar Gel to be effective in speeding the resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that it affects the ultimate outcome or natural history of the disease.

1.3 Rheumatic Disorders:

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Psoriatic arthritis, Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), Ankylosing spondylitis.

1.4 Collagen Diseases:

During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis).

1.5 Dermatologic Diseases:

Severe erythema multiforme, Stevens-Johnson syndrome.

1.6 Allergic States:

Serum sickness.

1.7 Ophthalmic Diseases:

Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis; optic neuritis; chorioretinitis; anterior segment inflammation.

1.8 Respiratory Diseases:

Symptomatic sarcoidosis

1.9 Edematous State:

To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.

2 DOSAGE AND ADMINISTRATION

2.1 Specific Recommended Dosage Regimen for Infantile Spasms in Infants and Children Under 2 Years of Age

In the treatment of infantile spasms, H.P. Acthar Gel must be administered intramuscularly. The recommended regimen is a daily dose of 150 U/m^2 (divided into twice daily intramuscular injections of 75 U/m^2) administered over a 2-week period. Dosing with H.P. Acthar Gel should then be gradually tapered over a 2-week period to avoid adrenal insufficiency. The following is one suggested tapering schedule: 30 U/m^2 in the morning for 3 days; 15 U/m^2 in the morning for 3 days; 10 U/m^2 in the morning for 3 days; and 10 U/m^2 every other morning for 6-days.

H.P. Acthar Gel is typically dosed based on body surface area (BSA). For calculation of body surface area, use the following formula

$$BSA(m^2) = \sqrt{\frac{weight\ (\mathrm{kg}) \times height\ (\mathrm{cm})}{3600}}$$

2.2 Recommended Dosage Regimen for the Treatment of Acute Exacerbations in Adults with Multiple Sclerosis.

The recommended dose is daily intramuscular or subcutaneous doses of 80-120 units for 2-3 weeks for acute exacerbations.
Dosage should be individualized according to the medical condition of each patient. Frequency and dose of the drug should be determined by considering the severity of the disease and the initial response of the patient.

Although drug dependence does not occur, sudden withdrawal of H.P. Acthar Gel after prolonged use may lead to adrenal insufficiency or recurrent symptoms which make it difficult to stop the treatment. It may be necessary to taper the dose and increase the injection interval to gradually discontinue the medication.

2.3 Recommended Dosage Regimen for Other Indications for Adults and Children Over 2 Years of Age

Dosage should be individualized according to the disease under treatment and the general medical condition of each patient. Frequency and dose of the drug should be determined by considering severity of the disease and the initial response of the patient.

The usual dose of H.P. Acthar Gel is 40-80 units given intramuscularly or subcutaneously every 24-72 hours.

Although drug dependence does not occur, sudden withdrawal of H.P. Acthar Gel after prolonged use may lead to adrenal insufficiency or recurrent symptoms which make it difficult to stop the treatment. It may be necessary to taper the dose and increase the injection interval to gradually discontinue the medication.

2.4 Preparation

H.P. Acthar Gel should be warmed to room temperature before using.

Caution should be taken not to over-pressurize the vial prior to withdrawing the product.

3 DOSAGE FORMS AND STRENGTHS

5 mL multi-dose vial containing 80 USP Units per mL.

4 CONTRAINDICATIONS

H.P. Acthar Gel is contraindicated for intravenous administration.

H.P. Acthar Gel is contraindicated where congenital infections are suspected in infants.

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of H.P Acthar Gel.

H.P. Acthar Gel is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origin.

5 WARNINGS AND PRECAUTIONS

The adverse effects of H.P. Acthar Gel are related primarily to its steroidogenic effects. Not all of the adverse events described below have been seen after treatment with H.P. Acthar Gel, but might be expected to occur. [*see Adverse Reactions (6.3)*].

5.1 Infections

H.P. Acthar Gel may increase the risks related to infections with any pathogen, including viral, bacterial fungal, protozoan or helminthic infections. Patients with latent tuberculosis or tuberculin reactivity should be observed closely, and if therapy is prolonged, chemoprophylaxis should be instituted.

5.2 Cushing's Syndrome and Adrenal Insufficiency Upon Withdrawal

Treatment with H.P. Acthar Gel can cause hypothalamic-pituitary-axis (HPA) suppression and Cushing's syndrome. These conditions should be monitored especially with chronic use.

Suppression of the HPA may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Patients should be monitored for signs of insufficiency such as weakness, hyperpigmentation, weight loss, hypotension and abdominal pain.

The symptoms of adrenal insufficiency in infants treated for infantile spasms can be difficult to identify. The symptoms are non-specific and may include anorexia, fatigue, lethargy, weakness, excessive weight loss, hypotension and abdominal pain. It is critical that parents and caregivers be made aware of the possibility of adrenal insufficiency when discontinuing Acthar Gel and should be instructed to observe for, and be able to recognize, these symptoms [*see Information for Patients (17)*]

The recovery of the adrenal gland may take from days to months so patients should be protected from the stress (e.g. trauma or surgery) by the use of corticosteroids during the period of stress.

The adrenal insufficiency may be minimized in adults and infants by tapering of the dose when discontinuing treatment.

Signs or symptoms of Cushing's syndrome may occur during therapy but generally resolve after therapy is stopped. Patients should be monitored for these signs and symptoms such as deposition of adipose tissue in characteristics sites (e.g., moon face, truncal obesity), cutaneous striae, easy bruisability, decreased bone mineralization, weight gain, muscle weakness, hyperglycemia, and hypertension.

5.3 Elevated Blood Pressure, Salt and Water Retention and Hypokalemia

H.P. Acthar Gel can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium and calcium. Dietary salt restriction and potassium supplementation may

be necessary. Caution should be used in the treatment of patients with hypertension, congestive heart failure, or renal insufficiency.

5.4 Vaccination

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of H.P. Acthar Gel. Killed or inactivated vaccines may be administered; however, the response to such vaccines can not be predicted. Other immunization procedures should be undertaken with caution in patients who are receiving H.P. Acthar Gel, especially when high doses are administered, because of the possible hazards of neurological complications and lack of antibody response.

5.5 Masking Symptoms of Other Diseases

H.P. Acthar Gel often acts by masking symptoms of other diseases/disorders without altering the course of the other disease/disorder. Patients should be monitored carefully during and for a period following discontinuation of therapy for signs of infection, abnormal cardiac function, hypertension, hyperglycemia, change in body weight and fecal blood loss.

5.6 Gastrointestinal Perforation and Bleeding

Acthar Gel can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Signs of gastrointestinal perforation, such as peritoneal irritation, may be masked by the therapy. Use caution where there is the possibility of impending perforation, abscess or other pyogenic infections, diverticulitis, fresh intestinal anastomoses, and active or latent peptic ulcer.

5.7 Behavioral and Mood Disturbances

Use of H.P. Acthar Gel may be associated with central nervous system effects ranging from euphoria, insomnia, irritability (especially in infants), mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated.

5.8 Comorbid Diseases

Patients with a comorbid disease may have that disease worsened. Caution should be used when prescribing H.P. Acthar Gel in patients with diabetes and myasthenia gravis.

5.9 Ophthalmic Effects

Prolonged use of H.P. Acthar Gel may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi and viruses.

5.10 Immunogenicity Potential

H.P. Acthar Gel is immunogenic. Limited available data suggest that a patient may develop antibodies to H.P. Acthar Gel after chronic administration and loss of endogenous ACTH and H.P. Acthar Gel activity. Prolonged administration of H.P. Acthar Gel may increase the risk of hypersensitivity reactions. Sensitivity to porcine protein should be considered before starting therapy and during the course of treatment should symptoms arise.

5.11 Use in Patients with Hypothyroidism or Liver Cirrhosis

There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver.

5.12 Negative Effects on Growth and Physical Development

Long-term use of H.P. Acthar Gel may have negative effects on growth and physical development in children. Changes in appetite are seen with H.P. Acthar Gel therapy, with the effects becoming more frequent as the dose or treatment period increases. These effects are reversible once H.P. Acthar Gel therapy is stopped. Growth and physical development of pediatric patients on prolonged therapy should be carefully monitored.

5.13 Decrease in Bone Density

Decrease in bone formation and an increase in bone resorption both through an effect on calcium regulation (i.e. decreasing absorption and increasing excretion) and inhibition of osteoblast function may occur. These, together with a decrease in the protein matrix of the bone (secondary to an increase in protein catabolism) and reduced sex hormone production, may lead to inhibition of bone growth in children and adolescents and to the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating therapy, and bone density should be monitored in patients on long term therapy.

5.14 Use in Pregnancy

H.P. Acthar Gel has been shown to have an embryocidal effect. Apprise women of potential harm to the fetus. [*see Use in Specific Populations (8.1)*]

6 ADVERSE REACTIONS

Please refer to *Adverse Reactions in Infants and Children Under 2 Years of Age (Section 6.1.1)* for consideration when treating patients with Infantile Spasms. The adverse reactions presented in Section 6.2 are primarily provided for consideration in use in adults and in children over 2 years of age, but these adverse reactions should also be considered when treating infants and children under 2 years of age.

H.P. Acthar Gel causes the release of endogenous cortisol from the adrenal gland. Therefore all the adverse effects known to occur with elevated cortisol may occur with H.P. Acthar Gel administration as well. Common adverse reactions include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

6.1.1 Adverse Reactions in Infants and Children Under 2 Years of Age

While the types of adverse reactions seen in infants and children under age 2 treated for infantile spasms are similar to those seen in older patients, their frequency and severity may be different due to the very young age of the infant, the underlying disorder, the duration of therapy and the dosage regimen. Below is a summary of adverse reactions specifically tabulated from source data derived from retrospective chart reviews and clinical trials in children under 2 years of age treated for infantile spasms. The number of patients in controlled trials at the recommended dose was too few to provide meaningful incidence rates or to permit a meaningful comparison to the control groups.

TABLE: Incidence (%) of Treatment Emergent Adverse Events Occurring in ≥ 2% of H.P. Acthar Gel (repository corticotropin injection) Infants and Children under 2 years of Age

System Organ Class	Recommended 75 U/m^2 bid n=122, (%)	150 U/m^2 qd n=37 (%)
Cardiac disorders		
Cardiac Hypertrophy	**3**	**0**
Endocrine disorders		
Cushingoid	3	22
Gastrointestinal disorders		
Constipation	0	5
Diarrhea	3	14
Vomiting	3	5
General disorders and administration site conditions		
Irritability	7	19
Pyrexia	5	8
Infections and infestations		
Infection [1]	20	46

System Organ Class	Recommended 75 U/m^2 bid n=122, (%)	150 U/m^2 qd n=37 (%)
Investigations		
Weight gain	1	3
Metabolism and nutrition disorders		
Increased appetite	0	5
Decreased appetite	3	3
Nervous system disorders		
Convulsion[2]	12	3
Respiratory, thoracic and mediastinal disorders		
Nasal Congestion	1	5
Skin and subcutaneous tissue disorders		
Acne	0	14
Rash	0	8
Vascular disorders		
Hypertension	11	19

[1] Specific infections that occurred at ≥2% were candidiasis, otitis media, pneumonia and upper respiratory tract infections.[2] In the treatment of Infantile Spasms, other types of seizures/convulsions may occur because some patients with infantile spasms progress to other forms of seizures (for example, Lennox-Gastaut Syndrome). Additionally the spasms sometimes mask other seizures and once the spasms resolve after treatment, the other seizures may become visible.

These adverse reactions may also be seen in adults and children over 2 years of age when treated for other purposes and with different doses and regimens.

6.2 Postmarketing Experience

The following adverse reactions associated with the use of H.P. Acthar Gel have been identified from postmarketing experience with H.P. Acthar Gel. Only adverse events that are not listed above as adverse events reported from retrospective chart reviews and non-sponsor conducted clinical trials and those not discussed elsewhere in labeling, are listed in this section. Because the adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to use with H.P. Acthar Gel. Events are categorized by system organ class. Unless otherwise noted these adverse events have been reported in infants, children and adults.

6.2.1 Allergic Reactions

Allergic responses have presented as dizziness, nausea and shock (adults only).

6.2.2 Cardiovascular

Necrotizing angitis (adults only) and congestive heart failure.

6.2.3 Dermatologic

Skin thinning (adults only), facial erythema and increased sweating (adults only).

6.2.4 Endocrine

Decreased carbohydrate tolerance (infants only) and hirsutism.

6.2.5 Gastrointestinal

Pancreatitis (adults only), abdominal distention and ulcerative esophagitis.

6.2.6 Metabolic

Hypokalemic alkalosis (infants only).

6.2.7 Musculoskeletal

Muscle weakness and vertebral compression fractures (infants only).

6.2.8 Neurological

Headache (adults only), vertigo (adults only), subdural hematoma, intracranial hemorrhage (adults only), and reversible brain shrinkage (usually secondary to hypertension) (infants only).

6.3 Possible Additional Steroidogenic Effects

Based on steroidogenic effects of H.P. Acthar Gel certain adverse events may be expected due to the pharmacological effects of corticosteroids. The adverse events that may occur but have not been reported for H.P. Acthar Gel are:

6.3.1 Dermatologic

Impaired wound healing, abscess, petechiae and ecchymoses, and suppression of skin test reactions.

6.3.2 Endocrine

Menstrual irregularities.

6.3.3 Metabolic

Negative nitrogen balance due to protein catabolism.

6.3.4 Musculoskeletal

Loss of muscle mass and aseptic necrosis of femoral and humeral heads.

6.3.5 Neurological

Increased intracranial pressure with papilledema, (pseudo-tumor cerebri) usually after treatment, and subdural effusion.

6.3.6 Ophthalmic

Exophthalmos.

7 DRUG INTERACTIONS

Formal drug-drug interaction studies have not been performed.

H.P. Acthar Gel may accentuate the electrolyte loss associated with diuretic therapy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Class C: H.P. Acthar Gel has been shown to have an embryocidal effect. There are no adequate and well-controlled studies in pregnant women. H.P. Acthar Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from H.P. Acthar Gel, when treating a nursing mother, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the risk and benefit to the mother.

8.4 Pediatric Use

H.P. Acthar Gel is indicated as monotherapy for the treatment of infantile spasms in infants and children less than 2 years of age. Both serious and other adverse reactions in this population are discussed in Warnings and Adverse Reactions in Infants and Children Under 2 Years of Age [*see Sections 5 and 6.1.1*].

The efficacy of H.P. Acthar Gel for the treatment of infantile spasms in infants and children less than 2 years of age was evaluated in a randomized, single blinded (video EEG interpreter

blinded) clinical trial and an additional active control supportive trial [*see Clinical Studies (14)*]. A responding patient was defined as having both complete cessation of spasms and elimination of hypsarrhythmia.

Safety in the pediatric population for infantile spasms was evaluated by retrospective chart reviews and data from non-sponsor conducted clinical trials [*see Adverse Reactions (6.1.1)*]. While the types of adverse reactions seen in infants and children under 2 years of age treated for infantile spasms are similar to those seen in older patients, their frequency and severity may be different due to the very young age of the infant, the underlying disorder, the duration of therapy and the dosage regimen. Effects on growth are of particular concern [*see Warnings and Precautions (5.12)*]. Serious adverse reactions observed in adults may also occur in children [*see Warnings and Precautions (5)*].

10 OVERDOSAGE

While chronic exposure to H.P. Acthar Gel at high doses can be associated with a variety of potential serious adverse effects, it is not expected that a single high dose, or even several large doses, has the potential for serious adverse effects compared to a standard dose. There have been no reports of death or acute overdose symptoms from H.P. Acthar Gel in clinical studies or in the published literature.

The intramuscular route of administration makes it unlikely that an inadvertent acute overdose will occur. The typical daily dose of H.P. Acthar Gel to treat an infant that has a BSA of 0.4 m^2 would be 60 U/day. Using the 1-cc syringe supplied with H.P. Acthar Gel, the maximum amount that can be injected is 80 U/injection, which is a well-tolerated single dose.

11 DESCRIPTION

H.P. Acthar Gel is a highly purified sterile preparation of the adrenocorticotropic hormone in 16% gelatin to provide a prolonged release after intramuscular or subcutaneous injection. Also contains 0.5% phenol, not more than 0.1% cysteine (added), sodium hydroxide and/or acetic acid to adjust pH and water for injection.

ACTH is a 39 amino acid peptide with the following chemical formula:

H-	Ser-	Tyr-	Ser-	Met-	Glu-	His-	Phe-	Arg-	Trp-	Gly-
	1	2	3	4	5	6	7	8	9	10
	Lys-	Pro-	Val-	Gly-	Lys-	Lys-	Arg-	Arg-	Pro-	Val-
	11	12	13	14	15	16	17	18	19	20
	Lys-	Val-	Try-	Pro-	Asp-	Gly-	Ala-	Glu-	Asp-	Gln-
	21	22	23	24	25	26	27	28	29	30
	Leu-	Ala-	Glu-	Ala-	Phe-	Pro-	Leu-	Glu-	Phe-	OH
	31	32	33	34	35	36	37	38	39	

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of H.P. Acthar Gel in the treatment of infantile spasms is unknown.

H.P. Acthar Gel and endogenous ACTH stimulate the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a number of weakly androgenic substances. Prolonged administration of large doses of H.P. Acthar Gel induces hyperplasia and hypertrophy of the adrenal cortex and continuous high output of cortisol, corticosterone and weak androgens. The release of endogenous ACTH is under the influence of the nervous system via the regulatory hormone released from the hypothalamus and by a negative corticosteroid feedback mechanism. Elevated plasma cortisol suppresses ACTH release.

H.P. Acthar Gel is also reported to bind to melanocortin receptors.

The trophic effects of endogenous ACTH and H.P. Acthar Gel on the adrenal cortex are not well understood beyond the fact that they appear to be mediated by cyclic AMP.

ACTH rapidly disappears from the circulation following its intravenous administration; in people, the plasma half-life is about 15 minutes. The pharmacokinetics of H.P. Acthar Gel have not been adequately characterized.

The maximal effects of a trophic hormone on a target organ are achieved when optimal amounts of hormone are acting continuously. Thus, a fixed dose of H.P. Acthar Gel will demonstrate a linear increase in adrenocortical secretion with increasing duration for the infusion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate and well-controlled studies have not been done in animals. Human use has not been associated with an increase in malignant disease. [*see Warnings and Precautions (5.14) and Use in Specific Populations (8.1)*].

14 CLINICAL STUDIES

The effectiveness of H.P. Acthar Gel as a treatment for infantile spasms was demonstrated in a single blinded (video EEG interpreter blinded) clinical trial in which patients were randomized to receive either a 2 week course of treatment with H.P. Acthar Gel (75 U/m^2 intramuscular twice daily) or prednisone (1 mg/kg by mouth twice daily). The primary outcome was a comparison of the number of patients in each group who were treatment responders, defined as a patient having complete suppression of both clinical spasms and hypsarrhythmia on a full sleep cycle video EEG performed 2 weeks following treatment initiation, rated by an investigator blinded to treatment. Thirteen of 15 patients (86.7%) responded to Acthar Gel as compared to 4 of 14

patients (28.6%) given prednisone ($p<0.002$). The 2-week treatment was followed by a 2-week period of taper. Nonresponders to the prednisone treatment were eligible to receive H.P. Acthar Gel treatment. Seven of 8 patients (87.5%) responded to H.P Acthar Gel after not responding to prednisone. Similarly, the 2 nonresponder patients from the H.P. Acthar Gel treatment were eligible to receive treatment with prednisone. One of the 2 patients (50%) responded to the prednisone treatment after not responding to Acthar.

A supportive single-blind, randomized clinical trial comparing high-dose, long-duration treatment (150 U/m^2 once daily for 3 weeks, n=30) of H.P. Acthar Gel with low-dose, short-duration treatment (20 U once daily for 2 weeks, n=29) for the treatment of infantile spasms was also evaluated in infants and children less than 2 years of age. Nonresponders (defined as in the previously described study) in the low-dose group received a dose escalation at 2 weeks to 30 U once daily. Nominal statistical superiority of the high dose treatment, as compared to the low dose treatment, was observed for cessation of spasms but not for the resolution of hypsarrhythmia.

16 HOW SUPPLIED / STORAGE AND HANDLING

H.P. Acthar Gel (repository corticotropin injection) is supplied as 5 mL multi-dose vial (63004-7731-1) containing 80 USP Units per mL. H.P. Acthar Gel (repository corticotropin injection) should be warmed to room temperature before using. Do not over pressurize the vial prior to withdrawing the product.

Store H.P. Acthar Gel (repository corticotropin injection) under refrigeration between 2°-8°C (36°-46°F). Product is stable for the period indicated on the label when stored under the conditions described.

17 PATIENT COUNSELING INFORMATION

Caretakers of patients with infantile spasms should be informed of the availability of a Medication Guide, and they should be instructed to read the Medication Guide prior to administering H.P Acthar Gel. Patients should be instructed to take H.P. Acthar Gel only as prescribed. They should not stop treatment suddenly unless instructed by their physician to do so.

Patients, their caregivers and families should be advised as to the importance of the need for careful monitoring while on and during titration from H.P. Acthar Gel treatment and the importance of not missing and scheduled doctor's appointments.

Patients, their caregivers and families should be advised that if the patient develops an infection or fever they should contact their physician. They should be educated that a fever may not necessarily be present during infection. The patient should also try to limit contact with other people with infections to minimize the risk of infection while taking H.P. Acthar Gel. [*see Warnings and Precautions (5.1) and Adverse Reactions (6.1.1)*]

Patients, their caregivers and families should be advised that if the patient experiences an increase in blood pressure they should contact their physician. [*see Warnings and Precautions (5.3) and Adverse Reactions (6.1.1)]*

Patients, their caregivers and families should be advised that if the patient or the caregiver notices blood or a change in color of the patient's stool they should contact their physician. [*see Warnings and Precautions (5.6)*].

Caregivers and families of infants and children treated with H.P. Acthar Gel should be informed that the patient may show signs of irritability and sleep disturbances. These effects are reversible once H.P. Acthar Gel therapy is stopped. [*see Warnings and Precautions (5.7) and Adverse Reactions (6.1.1)*].

Patients, their caregivers and families should be advised that changes in appetite, most often leading to weight gain, are seen with H.P. Acthar Gel therapy, becoming more frequent as the dose or treatment period increases. These effects are reversible once H.P. Acthar Gel therapy is stopped. [*see Warnings and Precautions (5.12) and Adverse Reactions (6.1.1*].

Patients, their caregivers and families should be advised that the patient may be monitored for signs of adrenal insufficiency such as weakness, fatigue, lethargy, anorexia, weight loss, hypotension, abdominal pain or hyperpigmentation (adults only) after treatment has stopped. Since the recovery of the adrenal gland varies from days to months, patients may need to be protected from the stress of trauma or surgery by the use of corticosteroids during the period of stress. [*see Warnings and Precautions (5.2)*].

Patients should be advised not to be vaccinated with live or live attenuated vaccines during treatment with H.P. Acthar Gel. Additionally, other immunization procedures in patients or in family members who will be in contact with the patient should be undertaken with caution while the patient is taking H.P. Acthar Gel. [*see Warnings and Precautions (5.4)*].

Patients, their caregivers and families should be advised that prolonged use of H.P. Acthar Gel in children may result in Cushing's syndrome and associated adverse reactions, may inhibit skeletal growth, and may cause osteoporosis and decreased bone density. If prolonged use is necessary, H.P. Acthar Gel should be given intermittently along with careful observation. [*see Warnings and Precautions (5.2), (5.12), and (5.13) and Adverse Reactions (6.1.1)*].

Patients, their caregivers and families should be informed that H.P. Acthar may mask symptoms of other diseases/disorders without altering the course of the other disease/disorder. The patient will need to be monitored carefully during and for a period following discontinuation of therapy for signs of infection, abnormal cardiac function, hypertension, hyperglycemia, change in body weight, and fecal blood loss. [*see Warnings and Precautions (5.5)*].

In the treatment of Infantile Spasms, other types of seizures may occur because some patients with infantile spasms progress to other forms of seizures (for example, Lennox-Gastaut Syndrome). Additionally the spasms sometimes mask other seizures and once the spasms resolve after treatment with H.P. Acthar gel, the other seizures may become visible. Parents and caregivers should inform their physician of any new onset of seizures so that appropriate management can then be instituted. [*see Adverse Reactions (6.1.1)*].

H.P. Acthar® Gel
(repository corticotropin injection)

Manufactured for Questcor Pharmaceuticals, Inc.

QUESTCOR®
Questcor Pharmaceuticals, Inc.
3260 Whipple Road
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PL065/Rev. 02 No. 1350
Issued: 10/2010

MEDICATION GUIDE

H.P. Acthar® Gel (H P AK-thar jel)
(repository corticotropin)
Injection

This Medication Guide provides information only about the use of H.P. Acthar Gel for the treatment of Infantile Spasms. If your doctor prescribes H.P. Acthar Gel for you or your child for any other reason, talk to your doctor for information about how this medicine is used to treat your medical condition.

Read this Medication Guide before your child receives H.P Acthar Gel and each time you refill your child's prescription. There may be new information. This Medication Guide does not take the place of talking with your doctor about your child's medical condition or treatment.

What is the most important information I should know about H.P. ACTHAR GEL?

H.P. Acthar Gel can cause serious side effects including:

1. **Increased risk of infections.** H.P Acthar Gel is a medicine that can affect your child's immune system. When your child is taking H.P. Acthar Gel, it can lower the ability of your child's immune system to fight infections. H.P. Acthar Gel may:
   - make your child more likely to get new infections
   - worsen an infection that your child already has
   - cause an inactive infection to become active, such as tuberculosis (TB)

   Before starting H.P. Acthar Gel, tell your doctor if your child has:
   - an infection or signs of an infection, such as:
     - fever
     - cough
     - vomiting
     - diarrhea
     - other signs of illness or flu
   - a family member with an infection or signs of an infection

   While taking H.P. Acthar Gel, your child should:
   - stay away from people who are sick or who have infections
   - tell your doctor right away if your child has any sign of infection such as:
     - fever (but your child may not have a fever with an infection)
     - cough
     - vomiting
     - diarrhea or

- other signs of illness or flu and
- any open cuts or sores on his or her body

2. Effects on the adrenal gland after stopping H.P. Acthar Gel.

When your child stops taking H.P. Acthar Gel, his or her body may not produce enough of a hormone called cortisol on its own (adrenal insufficiency). Your child may need to take steroid medicine to protect the body until the adrenal gland recovers and is working well again, especially to protect the body if they have surgery or trauma. **Do not stop giving your child injections of H.P. Acthar Gel without talking to your doctor first.** Your doctor will tell you when and how to slowly stop giving the injections to avoid serious side effects.

While slowly stopping your child's injections of H.P. Acthar Gel or after you stop giving the injections, call your doctor right away if your child has any of the following:

- appears weak
- loses weight or has a decrease in appetite
- appears tired or lacking energy
- appears pale
- has stomach pain
- appears sick or is with a fever

3. Effects on the adrenal gland while taking H.P. Acthar Gel

When your child is taking H.P. Acthar Gel, his or her adrenal gland may produce too much cortisol. This can cause symptoms of Cushing's syndrome. Cushing's syndrome is more common in children who take H.P. Acthar Gel for a long time.

Symptoms of Cushing's syndrome include:

- increased upper body fat around the neck, but not the arms and legs
- weight gain
- rounded or "moon" face
- thin skin, easy bruising, and stretch marks on thighs, belly and trunk
- slowed growth rates in children
- weak bones (osteoporosis)

While receiving treatment with H.P. Acthar Gel other side effects can happen that are like side effects that happen due to treatment with steroid medicines. The risk of getting side effects may increase the longer your child is treated with H.P. Acthar Gel. Side effects may include:

- **increased blood pressure.** Your doctor may check your child's blood pressure during treatment. If your child's blood pressure increases, your doctor may talk with you about possible treatment choices.

- **too much water in the body (water retention), increased amount of body salts, and low potassium in the blood.** H.P. Acthar Gel may cause your child to have an increased amount of body salts and water that stays in the body, and may lower the amount of potassium in your child's blood. Follow your doctor's instructions about if you need to decrease your child's salt intake or if you need to feed your child foods high in potassium.

4. **Your child should not receive certain vaccines during treatment with H.P. Acthar Gel.** Your child may receive killed or inactivated vaccines while receiving Acthar Gel. Before your child receives any vaccines, talk to your doctor about which vaccines are safe for your child. Certain vaccines could cause your child to have serious side effects, or the vaccine may not be effective.

5. **Hiding (masking) symptoms of other conditions or diseases.** It may be more difficult for your doctor to diagnose other conditions or diseases in your child during treatment with H.P. Acthar Gel. During treatment and after treatment ends, tell your doctor if your child has:
    - any signs or symptoms of infection. See number 1 of this section in the Medication Guide.
    - changes in body weight
    - bloody or black tarry stool
    - vomiting
    - stomach pain
    - excessive tiredness
    - increased thirst
    - fast heart rate
    - difficulty breathing

6. **Stomach and intestinal problems. H.P. Acthar Gel may cause bleeding of the stomach or intestine.** Your child has an increased risk for bleeding from the stomach or having a stomach ulcer. . Tell your doctor if your child has any pain in the stomach area (abdominal pain), vomits blood, or has bloody or black stools.
7. **Changes in mood and behavior.** During treatment with H.P. Acthar Gel your child may be irritable, have rapid changes in his or her mood, be depressed, have other changes in his or her behavior, or have trouble sleeping.

Tell your doctor if your child has any of the side effects or symptoms listed above.

What is H.P. ACTHAR GEL?
H.P. Acthar Gel is a prescription medicine that is used to treat infantile spasms in infants and children under 2 years of age.

What should I tell my doctor before my child takes H.P. ACTHAR GEL?

Before your child takes H.P. Acthar Gel, read the section above "What is the most important information I should know about H.P. Acthar Gel?" and tell your doctor if your child has:

- an infection
- Diabetes
- heart problems
- kidney problems
- stomach or intestinal problems
- thyroid problems
- liver problems
- neuromuscular problems
- convulsions or seizures
- had exposure to someone with Tuberculosis (TB)
- a previous allergic reaction such as hives, itching or trouble breathing, to H.P. Acthar Gel or pork products
- had recent surgery
- had a recent vaccination or is scheduled to receive a vaccination
- a family member who is receiving vaccinations

Tell your doctor about all the medicines your child takes, including prescription and non-prescription medicines, vitamins and herbal supplements. Do not start giving a new medicine to your child without first speaking to your doctor.

How should I give H.P. Acthar Gel to my child? H.P. Acthar Gel is given as an injection into the muscle. Do not inject it under the skin, into a vein, or give it to your child by mouth.

- Inject H.P. Acthar Gel exactly as your doctor tells you. Your doctor will tell you where to give the injection, how much to give, how often and when to give it to your child.
- Do not use H.P. Acthar Gel until your doctor has taught you how to give the injection to your child.
- To give H.P. Acthar Gel:
    - Take the bottle from the refrigerator. Do not open the bottle or pry the cap (rubber stopper) off.
    - Warm the contents by rolling the bottle between your hands for a few minutes.
    - Wash your hands.

- Prepare the skin where you are going to give the injection by wiping it with a new sterile alcohol wipe. Before giving the injection, look at the site prepared for the injection and make sure that it no longer looks wet. A wet site can cause burning.
- Wipe the top of the vial rubber stopper with a new sterile alcohol wipe.
- Use a new sterile needle and syringe to draw up the amount of H.P. Acthar Gel the doctor has told you to use.
- Give the injection the way the doctor has instructed you.
- Return the bottle to the refrigerator as soon as possible.

- **Keep all of your child's follow-up appointments with your doctor**

- It is important for you to tell your doctor if your child's spasms continue or change in any way during treatment or after treatment has stopped so that they can monitor your child's progress.

  Infantile Spasms sometimes hides (masks) other seizures your child or infant may have. Once treated with H.P. Acthar Gel, the Infantile Spasms symptoms may disappear. This may allow the other seizures to become visible for the first time. Tell your child's doctor right away if you see a change in your child's seizures/spasms.

What are the possible side effects of H.P. Acthar Gel?

H.P Acthar Gel can cause serious side effects.

- **See "What is the most important information I should know about Acthar Gel."**

- **H.P. Acthar Gel may make certain other medical conditions worse, such as diabetes (may increase blood sugar).**

- **Eye problems**. Your child can get cataracts, increased pressure in the eye (glaucoma), and possible damage to the optic nerve if treated with H.P. Acthar Gel for a long time.

- **Allergic reactions to H.P. Acthar Gel.** Your child may have an allergic reaction to H.P. Acthar Gel. Allergic reactions may not happen until your child has received several injections of H.P. Acthar Gel. Tell your doctor right away if your child has any of the following signs of an allergic reaction:
  - skin rash
  - swelling of the face, tongue, lips, or throat
  - trouble breathing

- **Changes in growth and physical development.** H.P. Acthar Gel may affect your child's growth and physical development and may weaken his or her bones. This is more likely to happen with long term use of Acthar Gel.

- **Enlarged heart.** H.P. Acthar Gel may cause an increase in the size of your child's heart. This is more likely to happen with long term use of Acthar Gel but usually goes away after H.P. Acthar Gel is stopped.

Common side effects of Acthar Gel may include:

- infections
- increased blood pressure
- irritability and changes in behavior
- changes in appetite and weight
- diarrhea
- vomiting

These are not all the possible side effects of H.P. Acthar Gel. Tell your doctor if your child has any side effect that bothers them or does not go away. For more information ask your child's doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store H.P. ACTHAR GEL?

- Store vials of H.P. Acthar Gel in the refrigerator between 36^0F to 46^0F (2^0C to 8^0C).
- Throw away any vials after the expiration date printed on the label.

Keep H.P. Acthar Gel and all other medicines out of the reach of children

General information About H.P. Acthar Gel

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use H.P. Acthar Gel for a condition for which it has not been prescribed. Do not give H.P. Acthar Gel to other people, even if they have the same symptoms. It may harm them.

This Medication Guide summarizes the most important information about H.P. Acthar Gel. If you would like more information, talk with your child's doctor. You can ask your child's doctor or pharmacist for information about H.P. Acthar Gel that is written for healthcare professionals. For more information, go to www.acthar.com or call 1-800-465-9217.

What are the ingredients in H.P. Acthar Gel?

Active ingredient: Corticotropin

Inactive ingredients: gelatin, phenol, cysteine, sodium hydroxide and/or acetic acid to adjust pH, and water for injection

Manufactured for:
Questcor Pharmaceuticals, Inc.
3260 Whipple Road
Union City, CA 94587 USA

PL122/ Rev. 00
Issued: 10/2010

This Medication Guide has been approved by the U.S. Food and Drug Administration.

PL063/Rev. 04 (17500-03) Questcor Label Size: 13/16” x 2-9/16”

5 mL multiple dose vial

NDC 63004 7731 1

H.P.* Acthar® Gel

(repository corticotropin injection)

80 USP UNITS PER mL

FOR INTRAMUSCULAR OR SUBCUTANEOUS USE

Dispense the enclosed Medication Guide to each patient

Store in refrigerator, 2°-8°C (36°-46°F).

℞ only *HIGHLY PURIFIED

Questcor Pharmaceuticals, Inc.
Union City, CA 94587 USA

17500-03

LOT # 1564-XX

EXP MM/YYYY

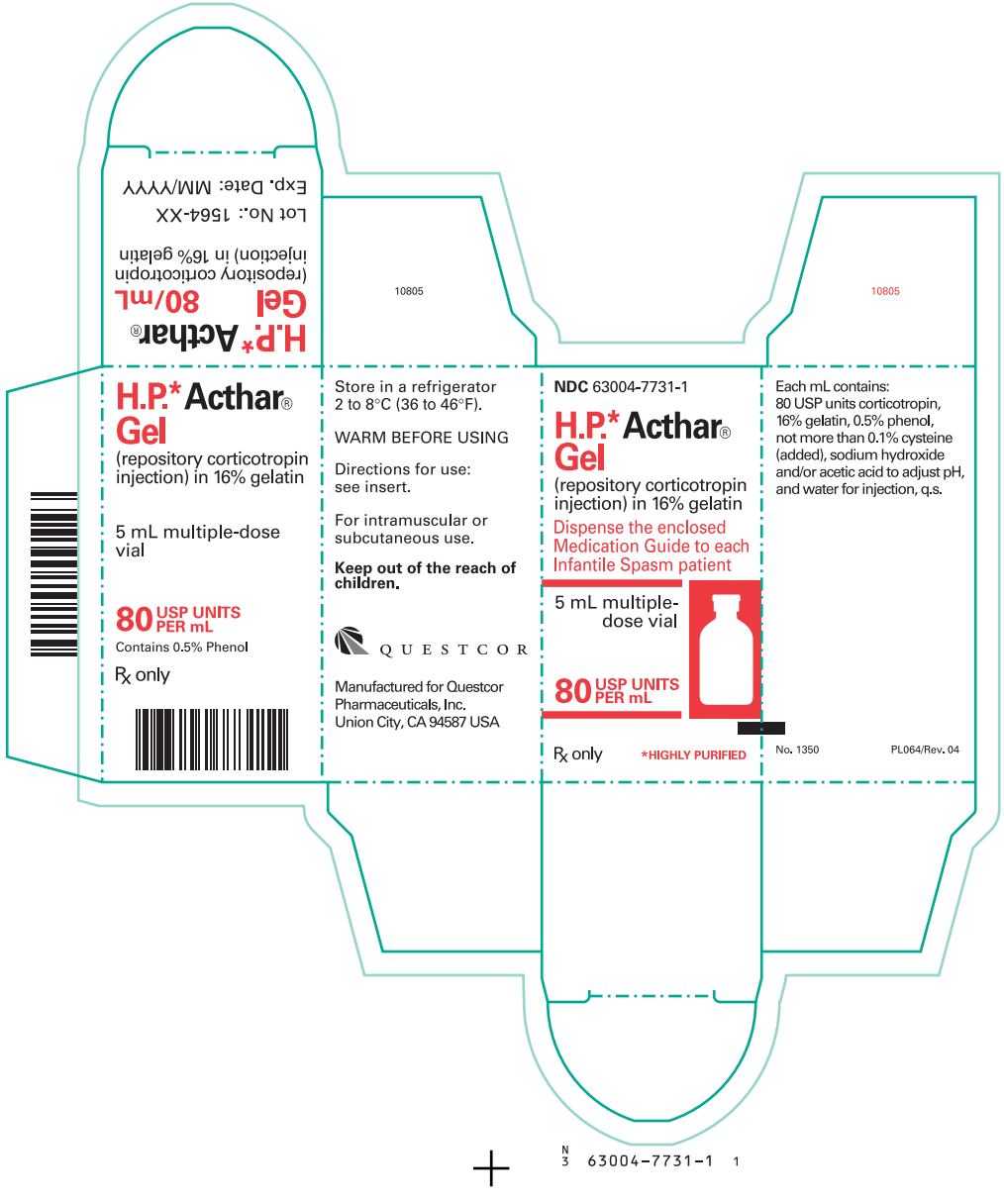
Warm before using.

Directions for use: see insert.

Each mL contains: 80 USP units corticotropin, 16% gelatin, 0.5% phenol, not more than 0.1% cysteine(added), sodiumhydroxide and/or acetic acid to adjust pH, and water for injection, q.s.

No. 1350 PL063/Rev. 04

(b) (4)


H.P.* Acthar® Gel 80/mL
(repository corticotropin injection) in 16% gelatin
Lot No.: 1564-XX
Exp. Date: MM/YYYY
10805
H.P.* Acthar® Gel
(repository corticotropin injection) in 16% gelatin
5 mL multiple-dose vial
80 USP UNITS PER mL
Contains 0.5% Phenol
℞ only
Store in a refrigerator 2 to 8°C (36 to 46°F).
WARM BEFORE USING
Directions for use: see insert.
For intramuscular or subcutaneous use.
Keep out of the reach of children.
QUESTCOR
Manufactured for Questcor Pharmaceuticals, Inc. Union City, CA 94587 USA
NDC 63004-7731-1
H.P.* Acthar® Gel
(repository corticotropin injection) in 16% gelatin
Dispense the enclosed Medication Guide to each Infantile Spasm patient
5 mL multiple-dose vial
80 USP UNITS PER mL
℞ only
*HIGHLY PURIFIED
10805
Each mL contains:
80 USP units corticotropin, 16% gelatin, 0.5% phenol, not more than 0.1% cysteine (added), sodium hydroxide and/or acetic acid to adjust pH, and water for injection, q.s.
No. 1350
PL064/Rev. 04
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

REMS

APPENDIX A
Initial REMS Approval: 10/2010

NDA 022432 and NDA 008372

H.P. ACTHAR® GEL (Repository Corticotropin Injection)

Questcor Pharmaceuticals, Inc.
3260 Whipple Road
Union City, CA 94587

Contact Information:
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Phone: 410-953-0337
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Risk Evaluation and Mitigation Strategy

I. Goals

The goal of the REMS is to inform parents or caregivers of patients taking H.P. Acthar Gel for the treatment of infantile spasms of the serious risks, including adrenal insufficiency, infections, and blood pressure elevation.

II. REMS Elements

A. Medication Guide

Questcor Pharmaceuticals, Inc. will ensure that a Medication Guide is dispensed with each H.P. Acthar Gel prescription and in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments of the REMS

Questcor will submit REMS Assessments to the FDA 18 months, 3 years, and 7 years from the date of approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Questcor will submit each assessment so that it will be received by the FDA on or before the due date.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
10/15/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

SUMMARY REVIEW

MEMORANDUM

DATE: April 5, 2010

FROM: Russell Katz, M.D.
Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-432

SUBJECT: Action Memo for NDA 22-432, for the use of H.P. Acthar Gel (repository corticotrophin injection) in the treatment of Infantile Spasms (IS)

NDA 8-372/S-039, for the use of H.P. Acthar Gel (repository corticotrophin injection) in the treatment of Infantile Spasms (IS), was submitted by Questcor Pharmaceuticals, Inc., on 6/16/06 to the Division of Metabolism and Endocrinology Products. Though not approved for the treatment of IS (Acthar Gel was approved in 1952 and has been approved subsequently for numerous indications), Acthar Gel has been the treatment of choice for IS for many years. The supplement consisted of a meta-analysis of published clinical trials, and the Agency issued a Not Approvable (NA) letter on 5/10/07, citing numerous deficiencies, including the lack of a bridge between this specific product and the products used in the various published studies.

Subsequent to the NA letter, the company and the Division of Neurology Products (DNP) entered into discussions about how this indication could be pursued. The sponsor had not conducted any trials of its own, and, in brief, we determined that the sponsor should attempt to obtain primary data for several trials published in the archival literature that, potentially, could provide substantial evidence of effectiveness for Acthar Gel for IS. The sponsor obtained data from three of these studies, as well as safety data from various sources. With these data, the sponsor has submitted a response to the CR letter on 12/10/09. This submission was considered a Type 6 NDA, and was given the new number, NDA 22-432.

The application has been reviewed by Dr. Philip Sheridan, medical officer, Drs. Quynh-Van Tran and Sharon Watson, Division of Drug Marketing, Advertising, and Communications, Mary Dempsey and Sharon Mills, Division of Risk Management, Dr. Jialu Zhang, statistician, Dr. Ju-Ping Lai, Office of Clinical Pharmacology, Dr. Martha Heimann, chemist, and Dr. Norman Hershkowitz, neurology team leader. In addition, this application was the subject of a meeting of the Peripheral and Central Nervous Systems Advisory Committee (PCNS AC) on 5/6/10.

The review team recommends that the application be approved. In this memo, I

will briefly describe the relevant safety and effectiveness data, and offer the rationale for the division's action.

Effectiveness

As noted above, the sponsor has submitted data from three controlled studies that they believe provide substantial evidence of effectiveness for Acthar Gel as a treatment for IS.

Study 01

This was a single blind, parallel group study in which patients with IS were randomized to receive either ACTH 150 Units/meter^2/day given as a 75 Unit/meter^2 dose twice a day or prednisone 2 mg/kg/day (in a 1 mg/kg BID regimen) for 2 weeks. Each treatment was tapered to 0 over the subsequent 2 weeks. This study was performed by Dr. Baram in 1996.

The primary outcome was based on a video EEG performed at 2 weeks; the video EEG was to be for 24 hours, but in all cases was to be at least 4 hours (to include a full sleep-wake cycle). An Overall Success was defined as a patient who experienced no spasms and elimination of hypsarrythmia, the characteristic EEG pattern in these patients. The investigator did not pre-specify primary or secondary outcomes; the outcome described here was chosen by the sponsor and represents the widely accepted definition of clinical success by the expert community. Seizure frequency was also monitored and recorded by the patient's caregiver during the 2 weeks of the study.

The treating physician was not blinded to treatment assignment, but the video-EEGs were read by a blinded rater.

Results

A total of 15 patients were randomized to receive ACTH, and 14 were randomized to receive prednisone. About 86% of each group had symptomatic IS and about 14% had cryptogenic IS. The mean age was about 5-7 months old.

A total of 13/15 (87%) of ACTH patients were classified as an Overall Success compared to 4/14 (29%) of prednisone patients (p=0.0025, according to Dr. Zhang). An examination of the proportion of patients who met criteria for an EEG response revealed 13/15 (87%) ACTH patients compared to 4/14 (29%) prednisone patients (p=0.0025), and 14/15 (93%) of ACTH patients and 4/14 (29%) of prednisone patients met clinical success criteria (p=0.0005).

According to the sponsor, of the 13 patients who originally responded to ACTH, 2 relapsed. Of the 11 remaining infants who had responded, 3 had no recurrence (though they were only followed for a month), and 8 were reported to have had no recurrences, after having been followed for at least 6 months (mean 17 months). Presumably, recurrences were based on caretaker reports.

Study 05

This study compared a high dose of ACTH to a low dose.

In this study (performed by Dr. Hrachovy in 1994), patients received ACTH at 150 Units/meter^2 (HD) given once a day or ACTH 20 Units/day (LD**)**, both given IM. The HD was given for 3 weeks, followed by a 9 week taper, and the LD was given for 2 weeks followed by a 2 week taper.

As in Study 01, the primary outcome was complete cessation of spasms and complete resolution of the EEG pattern on video EEG. In the HD group, the video EEG was performed at Week 12, after the taper period. In the LD group, the video EEG was performed at the end of the initial 2 week treatment period. If patients did not respond in the HD group, they were treated with prednisone, 2 mg/kg/day for 4-6 weeks, and then followed in a "routine clinical manner". If patients in the LD group did not respond at 2 weeks, their ACTH dose was increased to 30 Units/day for an additional 4 weeks, and then tapered over a 2 week period.

Results

A total of 59 patients were randomized to treatment (the current sponsor was able to obtain original data for 58).

A total of 30 patients were randomized to HD and 29 to LD. Four (4) HD patients did not complete the study, compared to 5 LD patients. The sponsor analyzed the following populations:

Modified intent-to-treat (mITT): Patients who received at least one dose of drug and had adequate data to assess the overall response.

Intent-to-treat: All patients randomized.

Spasms Population: All patients with "sufficient" data to evaluate the complete spasm response. Presumably, "sufficient" data meant any data collected on this outcome; there need not have been EEG data to be included in this population.

Completed Patients: All patients who completed the study in the opinion of the investigator

The following outcomes were assessed:

Overall Response: Any patient who had complete cessation of spasms and resolution of the EEG at any time during the study

Spasm Control Response: Any patient who had completed cessation of spasms at any time during the study. This included all patients with cessation of spasms during treatment or follow-up as assessed by clinical observation or parental report.

Hypsarrhythmic EEG Pattern Response: Any patient who had resolution of the EEG pattern at any time during the study.

The median age was 6.7 months old.

The following table displays the results of the various outcomes in the several populations.

Pop.	Treatment	Overall Response	Spasm Control	EEG Response
mITT	HD	15/24 (63%)	19/24 (79%)	16/24 (67%)
	LD	13/27 (48%)	14/27 (52%	14/27 (52%)
P-value		0.28	0.03	0.27
ITT	HD	15/30 (50%)	23/30 (77%)	16/30 (53%)
	LD	15/29 (52%)	16/29 (55%)	13/29 (45%)
P-value		0.94	0.07	0.52
Spasm	HD	15/28 (54%)	23/28 (82%)	16/28 (57%)
	LD	13/27 (48%)	14/27 (52%)	14/27 (52%)
P-value		0.64	0.013	0.66
Completed	HD	15/26 (58%)	21/26 (81%)	16/26 (62%)
	LD	13/24 (54%)	14/24 (58%)	14/24 (58%)
P-value		0.82	0.08	0.83

A total of 3/15 (20%) of HD and 2/13 (15%) of LD patients relapsed (these are patients who met the Overall response criteria at some point, but later were noted to have failed these criteria, based on video EEG verification performed based on caretaker reports of recurrent spasms).

Study 04

This was a double-blind, randomized trial comparing ACTH and prednisone. The study was performed by Dr. Hrachovy in 1983.

In this study, patients were randomized to receive ACTH 20 Units/day IM and prednisone placebo or ACTH placebo and prednisone 2 mg/kg/day PO for 2 weeks.

If the patient responded to the drug (same responder definition as in the previous studies) at 2 weeks, the drug was tapered over 1-2 weeks. These patients were monitored at 2 and 6 weeks after the end of the taper period. If the patient did not respond in the first 2 weeks, they continued the original treatment for 4 weeks. If they did not respond during this 4 week period they were switched to the other drug after a one week washout. If they did respond after the 4 week period, they had drug tapered over 1-2 weeks.

Results

A total of 24 patients were randomized, 12 to each group.

The median age was 8.2 months. Similar outcomes (Overall Response, Spasm Response, and EEG Response) were analyzed.

The following table displays the results for the initial phase of the study, presumably meaning the first 2 weeks.

Treatment	Overall	Spasm	EEG
ACTH	5/12 (42%)	5/12 (42%)	9/12 (75%)
Prednisone	4/12 (33%)	4/12 (33%)	4/12 (33%)
P-value (for the Overall Variable)	0.99	0.99	0.99

Safety

The sponsor obtained analyzable safety data from 3 sources:

1) A retrospective chart review performed by Partikian and Mitchell (N=84).

2) Another retrospective chart review from 4 clinical sites (N=178).

3) Safety data from Study 05 (N=57).

Together, these sources provide safety data from a total of 319 patients.

Drs. Partikian and Mitchell reviewed charts from all patients treated for IS (in patient and out-patient) at the Children's Hospital of Los Angeles (CHLA) between January 1996 and August 2006. These patients were treated with a standard protocol: ACTH 150 Units/meter^2/day (given as a BID regimen) for 1-2 weeks, followed by a taper of 4-5 weeks.

Patients were evaluated at all visits from 1-3 weeks after treatment initiation, at 4-8 weeks after treatment initiation, and at 3 months or more after treatment initiation. Assessments included adverse events reported by caregivers, weight and blood pressure, medication changes and the development of new seizure types.

As noted above, a total of 84 patients received initial treatment of ACTH in this cohort.

As noted by Dr. Sheridan, common adverse events included irritability, increased appetite, infections, and difficulty sleeping. These were mostly reported during the first follow-up visit, and decreased as drug was tapered.

Serious adverse events included seizures (not known if this represented new seizure types or exacerbation of IS), infections, and hospitalizations.

Mean changes in weight of 11%, 18%, and 26% were seen at the first, second, and third follow-ups, respectively. As Dr. Sheridan notes, it is difficult to know if this weight gain was related to ACTH or growth of the patient over time.

At baseline, 18% of patients had at least one significant increase in systolic blood pressure (SBP), compared to 33% at the first follow-up. The percent of patients who had at least one significant increase in SBP was 21% and 4% at the second and third visits, respectively.

At baseline, 14% of patients had at least one significant increase in diastolic blood pressure (DBP), compared to 24%, 11%, and 5% at the first, second, and third follow-up, respectively.

The second study involved retrospective chart review at 4 clinical centers, covering a period from January 2000 to May 2008. These patients received ACTH in a range of 135-160 Units/meter^2/day in a BID regimen (Questcor Recommended Dose); > 80 Units/meter^2/day but outside the recommended range, or within the recommended range, but once a day (Other high dose); or <80 Units/meter^2/day (Low dose). Adverse events were assessed at baseline, subsequent visits, and a final visit (any visit at least 2 weeks after the last dose of ACTH).

As noted above, data on 178 patients was collected.

A total of 59% of patients had at least one adverse event. In the Recommended and Other high dose groups, 62% and 64%, respectively, had at least one AE compared to a rate of 30% in the Low dose group. The most common AEs in the Recommended dose group were hypertension (18%), irritability (12%) and left ventricular hypertrophy (8%). In the Other high dose group, Cushingoid appearance (13%) and increased appetite (11%) were also seen.

A total of 20 patients had at least one Serious AE (SAE). A total of 10 patients had an SAE of hypertension (most recovered with specific treatment of drug discontinuation), 5 patients had infections (mostly pneumonia), and there was one case each of hepatomegaly, fever, respiratory failure, diarrhea, reflux, convulsion, hypertrophic cardiomyopathy, and renal failure.

There was one death, due to aspiration pneumonia.

Other common adverse events included upper gastrointestinal irritability, infections, drowsiness, sleep difficulties, fever, and increased secretions.

There were reversible blood pressure increases that returned to baseline with discontinuation of treatment.

Study 05

This was the study that compared the 150 Units/meter^2/day given as a single IM dose for 3 weeks followed by a 9 week taper compared to a 2 week dose of 20 Units/day or additional treatment for 4 weeks with 30 Units/day in non-responders.

There were a total of 57 patients in this study; 93% in the high dose and 86% of the patients in the low dose had at least one adverse event. The most common adverse events and clinical findings are given below:

Event	High dose	Low dose
Candidiasis	36%	38%
Cushingoid	29%	21%
Otitis media	25%	21%
Irritability	14%	17%
Fever	18%	14%
Acne	21%	10%
Diarrhea	21%	7%
Increased BP	18%	7%
Vomiting	11%	10%
Drowsiness	18%	10%
Sleep difficulties	46%	35%
Increased appetite	50%	24%
Decreased appetite	43%	31%

One child, a 3 month old boy with multiple medical problems, developed pulmonary edema, respiratory failure, and died of cardiac arrest after several weeks of treatment (20 Units-40 Units/day).

Serious AEs in the high dose group (N=4 patients) were dehydration, pneumonia, increased blood pressure, decreased appetite, and skin discoloration.

Four (4) patients (1 high dose, 3 low dose) discontinued treatment due to adverse events. These events included high blood pressure, skin discoloration, fever, and otitis media.

Across all 319 patients, 134 were dosed with the Recommended Dose, 133 with the Other High Dose, and 52 with the Low Dose. Across these dose groups, the adverse event pattern reflects, of course, the types and incidences of events seen in the individual studies (see Dr. Sheridan's review, page 42, which reprints the sponsor's table of the common AEs across doses); there is no obvious dose response for any given adverse event. The most common AEs are infections, irritability, Cushingoid appearance, and hypertension.

Post-Marketing reports

The sponsor has presented reports of adverse events from the spontaneous reporting system from 1952 to June 2009. The sponsor identified AEs in patients treated for IS or in infants between 1-24 months. Of course, we do not have information on how many patients have been treated for this indication or in this age group.

There were a total of 76 reports meeting these criteria, with 33 considered serious. Dr. Sheridan describes these events; they are mostly similar to those

events already described.

Advisory Committee Meeting

As noted above, this application was discussed at a meeting of the PCNS AC on 5/6/10.

The Committee concluded by a vote of 22 Yes and 1 No that the sponsor had submitted substantial evidence of effectiveness for Acthar gel as a treatment for Infantile Spasms, although they agreed that there was no evidence that the treatment prevented other seizure types or other clinical sequelae.

They also voted (16 Yes, 7 No) that the effect was shown to have been "sustained", although there was considerable sentiment for the view that the specific duration of effect was not well characterized.

When asked if they felt that the adverse effects were predictable, easily recognized, manageable, and reversible upon discontinuation, a slight majority voted no (10 Yes, 12 No); however, they voted overwhelmingly (20 Yes, 1 No, 2 Abstain) that the sponsor had submitted sufficient evidence of safety to support approval.

Discussion

The sponsor has submitted data from three controlled trials that they believe provide substantial evidence of effectiveness for Acthar Gel as a treatment for patients with IS. In addition, they have provided safety data from 319 patients treated with Acthar Gel, under various treatment conditions, with 134 treated at the recommended dose (75 Units/meter^2/day BID), and another 135 treated at doses close to that, but given once a day.

The data that the sponsor has provided differ considerably from that typically submitted in an NDA. As noted earlier, none of the studies were commissioned or conducted by the sponsor, and detailed protocols, and, in particular, detailed statistical plans for the analyses of these studies, did not exist. The sponsor has presented the results of these studies in a uniform way; that is, the primary outcome in each trial (Overall Response) was taken to be the same, and mirrored the expectations of the expert community regarding an effective treatment for IS; namely, complete cessation of spasms and normalization of the typical EEG pattern. The sponsor presents one of the studies, Study 01, as the "pivotal" study, one of the studies, Study 05, as a "supportive" study, and Study 04 as an "additional" study.

Although Study 01 did not, apparently, have a detailed statistical plan, the results showed a clear statistically significant superiority to prednisone not only on the overall response, but on the individual components (EEG and spasms). This

result occurred with a total sample size of only 29 patients. This result has been confirmed by the Agency's statistician, based on her review of the primary data that the sponsor obtained from the investigator.

The results of Study 05 are more difficult to interpret. There were no differences between the Overall Response Rates in the high and low dose groups (and the treatment paradigms were different in the two groups), and the only (nominally) statistically significant differences were seen in the Spasm Control variable, with nominal p-values varying between 0.01 and 0.08, depending upon the population analyzed.

The third study, Study 04, was of a complicated design, making interpretation difficult. In any event, no differences were seen between the two treatment groups (ACTH and prednisone).

Study 01 lends itself to a fairly straightforward interpretation, but this seems not to be the case for the other two studies. Dr. Sheridan does point out that the response rates, though basically not different between the treatment groups in these 2 latter studies, do seem to be greater than published estimates of the placebo response rates (he cites a placebo response rate of about 5% for a study by Appleton, et al., a study previously relied upon, to some extent, by the Agency when we considered the approval of Sabril for IS). However, it is fair to say that the interpretation of an active control trial that does not demonstrate a difference between treatments (the case for these latter two studies) is problematic, at best.

The Food, Drug, and Cosmetic Act requires that the Agency find that a sponsor has submitted substantial evidence of effectiveness (in addition to adequate safety) in order to approve a New Drug Application. Substantial evidence of effectiveness is defined as data from adequate and well-controlled clinical investigations (typically interpreted to mean more than one such trial) or data from a single such trial and confirmatory evidence (neither the circumstances under which this latter standard should apply nor what constitutes "confirmatory evidence" is defined in the Act). As a general matter, this latter standard is applied in the setting of a serious or life-threatening condition in which a second trial is essentially impossible to perform (for any of a number of reasons), and a wide variety of evidence can be considered "confirmatory" (e.g., a very low p-value, multiple sub-groups and or study sites strongly positive, multiple outcomes strongly positive, etc.). However, whether to apply this latter standard to any given data set, and what constitutes confirmatory evidence, are issues that need to be considered on a case by case basis.

As described above, the PCNS AC clearly concluded that the sponsor had provided substantial evidence of effectiveness. The review team agrees, as do I.

I believe that the sponsor has met the statutory standard of substantial evidence of effectiveness based on having submitted a single adequate and well-controlled trial and confirmatory evidence. Study 01, though small, produced clear and convincing evidence of effectiveness on an outcome widely considered by the community of experts to be a clinically important measure of the utility of a treatment of IS (indeed, one could consider such a strong finding of effectiveness from such a small study as further evidence of the robustness of the result). The fact that, in this study, ACTH was clearly superior to an "active" control (albeit, admittedly, one not known from previous trials to be effective), and that one component (EEG) of the primary outcome was an objective measure of spasm control, further support the conclusion. The additional studies, though not being interpretable by themselves as being "positive", do, in my view, suggest an effect of the drug (especially Study 04, which, as noted by Dr. Sheridan, produced treatment responses far greater than those seen in patients treated with placebo in at least one other study).

With regard to the question of effectiveness, there is another important question that needs to be addressed.

ACTH has been the standard of care for patients with IS for many years. The typical treatment course consists of a short (e.g., two weeks) period of treatment, followed by a tapering period. If patients experience a recurrence of spasms, another short course is often given. It has long been considered that such short courses are all that is necessary to control the spasms after the treatment is discontinued. The controlled trial data establishing effectiveness did not systematically address the persistence (i.e., duration) of effectiveness of a single course of therapy; follow-up of patients in Study 01 suggested a lack of recurrence of spasms out to several months in at least some patients (they assert that 2/13 patients who originally responded had recurrence of spasms), but the duration of follow-up was very variable, and recurrences were not systematically looked for. Further, the studies did not examine the effects of a second treatment course. The sponsor has submitted literature to attempt to address the question of whether or not a second treatment course is useful in treating recurrences, but these data do not provide useful guidance about treatment of recurrences. The review team agrees that labeling should be silent on the utility of treating recurrences.

The sponsor has also submitted safety data of the sort that is not typically contained in an NDA. Specifically, a typical NDA contains complete reports of a cohort of patients prospectively followed forward in time. This permits a complete (or near complete) accounting of the experience of all patients started on a particular treatment (e.g., how many patients discontinued, what all of the adverse events were, etc.). That is not the case here.

As described, much of the data presented has been obtained from a retrospective review of charts of patients treated with ACTH at various institutions

over the course of several years. The data were not collected for the purpose of establishing the safety of the treatment, as would be the case in typical company-sponsored drug trials. However, the adverse events described are, for the most part, those known to be associated with treatment with ACTH, and there were no unexpected or significant adverse events that would, in my view, preclude approval. As noted above, the AC overwhelmingly agreed. Several committee members did, however, note the potential seriousness of adrenal insufficiency, and the necessity for caregivers to be made aware of the clinical presentation of this potential event should it occur during discontinuation of the drug (the committee also felt that caregivers should be made aware that discontinuing treatment abruptly carries significant risk and danger).

As noted above, H.P. Acthar Gel has been approved for many years, and current approved labeling includes numerous (>50) approved indications. With this action, labeling will be brought into conformance with current labeling requirements, and the sponsor has agreed to remove numerous of the previously included indications.

The sponsor has also proposed a Risk Evaluation and Mitigation Strategy (REMS), consisting of a Medication Guide. The Medication Guide will discuss only the IS indication, because infants are particularly at risk for several serious adverse events, and IS will be the only approved indication for infants.

For the reasons given above, then, I will issue with attached Approval letter, with attached labeling to which the sponsor has agreed.

Russell Katz, M.D.

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/s/

RUSSELL G KATZ
10/15/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 022432

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Janice Brown
Susan Daugherty
Mary Dempsey
Martha Heimann
Norman Hershkowitz
Carol Holquist
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	9/27/10
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22432 (000)
Applicant	Questcor Pharmaceuticals
Date of Submission	9/30/10
PDUFA Goal Date	9/11/10
Proprietary Name / Established (USAN) names	H.P. Acthar Gel (repository corticotropin injection)
Dosage forms / Strength	Injection Solution: 5 mL multi-dose vial containing 80 USP Units per mL (b) (4)
Proposed Indication(s)	1. Infantile Spasms
Recommended:	(Approval vs. Approvable vs. Not Approvable vs. Complete Response)

1. Introduction

Acthar gel was originally approved in 1952, prior to the period of time when the FDA was required to demonstrate substantial benefit. Later DESI review permitted a number of indications including use for adrenalcorticol function testing and the treatment of a number of disorders for which steroids were also indicted (e.g. rheumatic disorders, collagen disease, dermatologic disorders, etc. The administrative responsibility for this NDA is that of DMEP. However, a later efficacy supplements (1979), adding the treatment of acute exacerbation of multiple sclerosis, was reviewed by review by this division (DNDP).

The present application's history begins with an efficacy supplement submitted for review to DMEP in 2006 for the treatment of Infantile Spasms (IS). This application was reviewed by that division but was not approved (b) (4) . Following the complete response a decision was made to transfer the supplement to DNP. It is noteworthy that there has been no industry Sponsored planned perspective controlled trials. The evidence for efficacy is based upon published trials performed by independent investigators. A type C meeting was held with the Sponsor and DNP on 11/5/07, regarding their response to the CR letter, and the following recommendations were made: 1) source efficacy data should be provided from the 5 published, randomized control studies where Acthar was evaluated for the treatment of patients with IS along with an independent analyses of this data (Askalan et al. 2003[1], Baram

[1] Askalan R, Mackay M, Brian J, Otsubo H, McDermott C, Bryson S, et al. Prospective preliminary analysis of the development of autism and epilepsy in children with infantile spasms. *J Child Neurol.* 2003 Mar;18(3):165-170.

1996 et al.[2]; Dreifuss et al. 1986[3]; Hrachovy et al. 1994[4]; Hrachovy et al. 1983[5]); 2) source safety data should be obtained and analyzed from hospitals that had treated patients in the last 10 years; 3) enough safety data on IS patients treated with Acthar should be provided to define the safety profile and to assert that the benefit outweighs the risk. Subsequent to this the Sponsor attempted to obtain data from all 5 studies, but because studies were performed some time ago, data were not available for 2 studies. Data were obtained for the Hrachovy et al. (1983) Hrachovy et al. (1994) Baram et al. (1996) and studies, the latter study likely being the most important one.

2. Background

Infantile Spasms (IS) is a syndrome that develops in children younger then 2 years old and is associated with frequent recurrent seizures (or spasms) and marked EEG abnormalities. The disease is frequently associated with delayed development, permanent cognitive impairment and the occurrence of other seizure types upon maturation. Death may also occurs. The long term prognosis of infantile spasms is bleak. Fewer than 5% of patients are neurodevelopmentally normal. While there are no definitive data that treatment of the spasms will improve long term neurologic prognosis, there are limited data suggesting that this is the case. The prevalence of IS is approximately 0.25 and 0.42 per 1000 live births per year. There is presently only one drug labeled for the treatment of IS, Sabril, which was recently approved. A number of other drugs, most notable Acthar Gel and Valproic Acid are used off label. Indeed Acthar Gel has been used for decades and is generally considered, by the pediatric Neurology community, as the treatment of choice.

3. CMC/Device

Dr. Heimann, the chemistry reviewer, recommended approval without post-approval commitments or requirements.

4. Nonclinical Pharmacology/Toxicology

No new information.

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[2] Baram TZ, Mitchell WG, Tournay A, Snead OC, Hanson RA, Horton EJ. High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study. Pediatrics. 1996;97:375-379.

[3] Dreifuss F, Farwell J, Holmes G, Joseph C, Lockman L, Madsen JA, et al. Infantile spasms. Comparative trial of nitrazepam and corticotropin. *Arch Neurol.* 1986 Nov;43(11):1107-1110.

[4] Hrachovy RA, Frost JD Jr, Glaze DG. High-dose, long-duration versus low-dose, short duration corticotropin therapy for infantile spasms. J Pediatr. 1994 May;124(5 Pt 1):803- 806.

[5] Hrachovy RA, Frost JD, Jr, Kellaway P, Zion TE. Double-blind study of ACTH vs prednisone therapy in infantile spasms. J Pediatr. 1983;103(4):641-655.

5. Clinical Pharmacology/Biopharmaceutics

6.

The Sposnor has provided additional new information on the PK of Acthar Gel in pateints with IS. This informtion has been included in the label as per the clinical pharmacology labeling review.

7. Clinical Microbiology

The product is already marketed and there is no new additional comments.

8. Clinical/Statistical- Efficacy

Philip Sheridan, MD (Medical reviewer) and Jialu Zang, PhD (Statistical reviewer) performed the efficacy review.

Studies provided by the Sponsor to support "substantial evidence" for efficacy consisted of published investigative reports of Baram et al. (1996; also refered to as study 01), Hrachovy et al. and (1983; also referred to as study 04) Hrachovy et al. (1994; also refered to as study 05), previously noted. Data from the publications as well as original data was obtained by the Sponsor to prepare study reports provided to the FDA. The Sponsor considers 01 a pivotal trial and 05 as supportive. An additional study, 04, is also described in this application.

Study 01

This was a prospective, randomized, single-blind (blinded to the video-EEG reader), controlled study that compared intramuscular Acthar 150 U/m2/day (divided as 75 U/m2/bid) administered for a two week period to oral prednisone at 2 mg/kg/day (divided as 1 mg/kg/bid) admistered for a 2 week period. Both cohorts 2 week treatment period was followed by a 2 week taper on the same medications. After the 2-week period a video-EEG was performed. The recording was to include at least one sleep wake cycle. The goal was to obtain a 24 hour recording, but some were as short as 4 hours. The primary endpoint required cessation of both the EEG and clinical expression of this disorder: i.e. both hypsarrhythmia and spasms, respectively. A seizure diary was also kept by the family/guardian. Dr Sheridan makes two important comments regarding the study design. First he notes that while this is a single blind study, it may be considered tantamount to a double blind study as it is unlikely that the use of intramuscular versus oral treatment would alter EEG and clinical behavior of the infant. Second, he notes that the primary endpoint is considered the "gold standard' for studies in IS. I agree with both points.

A total of 29 patients were randomized. There was a similar percent of symptomatic and cryptogenic patients in both treatment groups (e.g. 14.3 % and 13.3 % cryptogenic in the

prednisone and Acthar Gel groups, respectively). This is particularly important considering the difference in prognosis of these two groups. The Acthar Gel group had a higher number of female patients (73.4% vs. 42.9%). Prednisone treated patients tended to me slightly older then those of Acthar gel patients (a median of 7.0 vs. 5.0 months).

The following table presents the data from the study. The primary outcome of the absence of hypsarrhythmia and clinical spasm during the video EEG is denoted by "Overall Control." Data on clinical and EEG outcomes are also presented in the two additional columns. Data in other studies (see below) are presented in a similar fashion.

Treatment	Overall Control	Spasm Control	Hypsarrhythmia Control
Acthar Gel	13/15 (87%)	14/15 (93%)	13/15 (87%)
Prednisone	4/14 (28.6%)	4/14 (28.6%)	4/14 (29%)
p-value	0.015	0.0003	0.0015

Analysis of the primary endpoint indicated that Acthar Gel was superior to prednisone. Thus, the response rate for Acthar Gel was 86.7% (13/15) as compared to that of prednisone at 28.6% (4/14,). This was statistically significant, with a p-value of 0.0015 (Chi-square). Adjustment for age still resulted in a significant difference. Examination of spasm alone or hypsarrhythmia alone revealed statistical superiority of Acthar Gel to prednisone. As noted above there was some degree of disparity between male and female populations in both treatment groups . The statistical reviewer noted because of the small number of patients in the overall study that it was hard to determine how sex factored into the final results.

The FDA statistical analysis reproduced that of the Sponsor. In addition the statistical reviewer noted that it would be more appropriate to use a Fisher's exact test. This analysis was performed and was found to reveal a similar similar significant outcome.

Boutt The Medical and Statistical Reviewer conclude that this trial demonstrates superiority of Acthar Gel to prednisone regimen. I agree.

Study 05

This prospective, randomized, single-blind study compared high-dose, long-duration to low-dose short-duration treatment with Acthar Gel. The Acthar high-dose regimen consisted of Acthar given at a dose of 150 U/m2/day as a single (150 U/m2/QD) intramuscular dose for 3 weeks followed by a 9-week taper; the Acthar low-dose regimen consisted of Acthar 20 U/day (20 U/QD) as a single intramuscular dose for 2 weeks followed by a 2-week taper in responders or a dose escalation to 30 U/QD IM in non-responders.

The primary endpoint was complete cessation of both spasms and hypsarrhythmia (overall) at the time of measurement. Secondary endpoints include cessation of hypsarrhythmia alone or cessation of spasm at any time during the study. The time of measurement was unbalanced in

that in the high dose group this was performed following the complete titration from drug (12 weeks after its initiation) and in the low dose group this was performed 2 weeks after the initial treatment was initiated. A total of 30 patients were randomized to high dose and 29 to low dose groups.
Two populations of analysis were identified for analysis: 1) the ITT population (all randomized patients, n=59); in this case a worst case scenario was assumed for patients with missing data (n=9), 2) an mITT population (all patients randomized for which there was at least one single post treatment measurement of efficacy, n=51).

Except for the low dose group having disproportionally percent low percent of females (29.6% vs. 50%) the demographics were balanced across treatment groups. Of note, similar percent of cryptogenic and symptomatic patients were studied in each treatment group.

The following table presents primary and secondary endpoints in the two principal analyzed populations. None of the primary endpoint analyses showed statistical significant difference between high and low dose groups, although there was a nominal trend for a greater response the mITT population. Secondary endpoints also appeared to show a similar trend of greater control in the high dose groups. Other sub-divided populations were examined which showed a similar trend. As per the statistics reviewer , the study was inconclusive.

Population	Treatment	Overall Response	Spasm Control	Hypsarrhythmia Control
mITT	High Dose	15/24 (63%)	19/24 (79%)	16/24 (67%)
	Low Dose	13/27 (48%)	14/27 (52%)	14/27 (52%)
p-value		0.28	0.03	0.27
ITT	High Dose	15/30 (50%)	23/30 (77%)	16/30 (53%)
	Low Dose	15/29 (52%)	16/29 (55%)	13/29 (45%)
p-value		0.94	0.07	0.52

The Sponsor concludes that this at least supports the use of Acthar Gel. Dr Sheridan suggests that the reason that obvious superiority was not demonstrated in the high over the low dose group may be related to an adeqaute cortisol response. Thus, he notes that the high dose was given once a day and that the twice daily dosing, as in study 01, may increase the endogenous cortisol more efficiently.

Study 04

This was a randomized, controlled, double-blind, double-dummy study that compared Acthar at a dose of 20 to 30 U/day administered as a single daily intramuscular dose (20 to 30 U/QD) (Acthar low-dose) to a single oral prednisone (2 mg/kg/day). Patients received Acthar 20 U/QD IM and a prednisone placebo PO or prednisone 2 mg/kg/day PO and an Acthar placebo IM, for 2 weeks. Patients were accessed for a response (cessation of spasms and hypsarrhythmia) after 2 weeks of therapy and:

- **If the patient responded to the initial 2 weeks of treatment** they were tapered for a 1 to 2 week period and monitored for continued response at 2 and 6 weeks after the discontinuation of treatment. If patients spasms returned at the 2 week period they were changed to the alternative medication or the original medication was continued for an additional 4 weeks after which they underwent a 2 week taper.
- **If there was no response after the initial 2 weeks of treatment** (or the additional 4 weeks of treatment with the original drug, see first bullet) patients were started on the alternative treatment following a one week washout period.

The primary endpoint was considered complete cessation of hypsarrhythmia and spasms (overall control) as determined by a video-EEG performed following the initial 2-weeks of therapy. Secondary endpoints included in the analysis included EEG changes in non-responders and changes in mental and developmental status.

A total of 24 patients were randomized to the study with 12 in each group.

The following table presents the results for the primary (overall) and some secondary endpoints . Although there was a trend toward an effect in all measures, none reached statistical significance. The statistical reviewer was able to reproduce the Sponsor's conclusions. The Sponsor notes that the level of a statistically significant effect may result from the study being underpowered and the low dose of ACTH. Dr Sheridan also notes that the response rate for both treatments are suggestive of an effect of both as the control rates are greater then what is usually historically observed.

Treatment	Overall	Spasm Control	Hypsarrhythmia Control
Acthar Gel	5/12 (42%)	5/12 (42%)	9/12 (75%)
Prednisone	4/12 (33%)	4/12 (33%)	4/12 (33%)
p-value	0.99	0.99	0.99

Discussion on substantial Proof of Efficacy

These data consist of only one positive study. Although small, this study exhibited a rather large statistically significant effect, when compared to a presumed positive control. This study was considered by both the medical and statistical reviewer as an adeqaute positive study. Both additional studies, which also utilized presumed active controls, while not positive, did trend in the direction of an effect in the majority of measures. As to why an effect was not apparent is a matter of speculation. The Sponsor notes there may be inadequate power (study 04) or inadequate dosage regimens (study 05). The fact that all studies used active controls was a likely contributor to the difficulty in designing studies that provide adeqaute power. Considering the severity of this disease, this reviewer believes that an active control study design or an adjunctive design would be the only ethical design for such a study. The Sponsor

also notes that although some studies did not demonstrate statistical significance, in two studies the response rates are above that which is historically anticipated. Also noted by Dr Sheridan is the fact that many of similar dosages across studies exhibited similar treatment effects. Such arguments are not unreasonable but lack the rigor usually required by the FDA for approval of an indication. This may also be considered against the background of the fact that Acthar Gel has been used for decades by pediatric Neurologists to control infantile spasms and is generally considered as the treatment of choice. The FDA requires substantial evidence of proof before we approve an indication. This is usually interpreted as two positive studies on efficacy, but under certain conditions one strong study and additional supportive data may be used. Because the issue of approval was not readily obvious the agency, a Advisory Committee was convened, whose makeup consisted of a number of expert pediatric epileptologists.

Of note, the data presented by the Sponsor contains no careful examination of dose-response, comparison of different dose regimen or the utility of retreatment in the case of treatment failure or remission. On face, cross study comparison would suggest that the best dose was obtained with the dose regimen examined in study 01, however there was no single in study comparison of regimens in a single study. The dose utilized in study 01 will therefore be proposed.

Of importance , while this reviewer believes that the Sponsor appears to have demonstrated that Acthar Gel suppresses infantile spasms there is no demonstration that this treatment improves the long term outcome (e.g. loss of developmental milestones) of this disorder.

As will be described below, the Advisory Committee decided that there was adeqaute data to conclude that the requirement of substantial evidence was fulfilled.

Additional Analysis Relapse Rate and Retreatment

The Sponsor was asked, during the review process, to provide additional data that would address relapse rate and the utility of additional Acthar Gel treatments.

The Sponsor submitted information on relapse rates observed from published studies. These are presented in the form of a table, which is reproduced below. Note that the Baram 96, Hrachovy 94, and Hrachovy 83 studies in the table correspond to Studies 01, 05, and 04, respectively, which are discussed in this review.

Study	Type of Study: Treatments	Acthar/Comparator Dose	# of Patients	Response Rate	Relapse Rate	Average±SD (Range) Time of Follow-Up [months]
Baram 96	RCT: Acthar vs.	150 U/m^2 /d (75U/m^2 BID)	15	87%	15%	15.1±13.66 (2-48)
	Prednisone	2mg/kg (1 mg BID)	14	27%	NR	16.9±14.39 (2-46)
Snead 83	Retrospective: Acthar	150 U/m^2 /d (75U/m^2 BID)	30	97%	20%	24.6
	vs. Prednisone	3 mg/kg/d	22	50%	15%	47.1
Snead 89	Prospective: Acthar	150 U/m^2 /d (75U/m^2 BID)	15	93%	14%	43.3
Hrachovy 94*	RCT: Acthar Low Dose	20 U QD (≈50U/m^2 QD)	26	58%	21%	1.9±0.47 (0.5-2.6)
	vs. Acthar High Dose	150 U/m^2 QD	24	50%	15%	3.1±1.55 (1.4-9.5)
Hrachovy 83#	RCT: Acthar vs.	20 U QD (≈50U/m^2 QD)	12	42%	33%	12-33
	Prednisone	2 mg/kg QD	12	33%	28%	12-33
		Acthar Patients	122	89/122 (73%)	18/89 (20%)	

NR = Not reported
* Time to follow-up data was not included in the publication: this data was calculated based on Questcor's analyses (CSR 222107-05)
# The complex design of this study and the data provided did not allow Questcor to calculate a relapse rate or even confirm these published relapse rates

One conclusion made by the Sponsor , based upon this analysis, is that the Baram dose exhibited the lowest relapse rate (15%). Dr. Sheridan notes this conclusion is not definitive as follow-up periods during the study differ. I agree and would add, that other treatments may be occurring during this period, and that these other treatments may also affect relapse rate. I do not believe that this information should be included in the label as it is highly speculative.

There also does not appear to be any definitive data on retreatment. The Sponsor concludes that retreatment with Acthar Gel after a recurrence should be a decision made by the physician and parent. Dr Sheridan and I agree. I do not believe that there is adeqaute information on this issue to include in the label.

9. Safety

As Acthar Gel is presently marketed, safety information is already contained in the label. Much of the information described in label is similar to that for glucocorticosteroids. (e.g. immune suppression, ophthalmological effects, metabolic effects etc.). Indeed, DMEP assisted of drugs in the labeling review and changes initiated by them was to harmonize the label with information contained of the class of glucocorticosteroids. The Sponsor has provided additional data for safety in IS patients.

Clinical Studies safety Data

Young children with IS may be considered a particularly vulnerable population. The Sponsor was asked to obtain additional safety information. To provide this information the Sponsor obtained safety information from 3 principal sources: 1) Retrospective chart review for patients from one treatment center (Children's Hospital of Los Angeles), which was also the

subject of a publication (Partikian and Mitchell 2007[6]) with some patients having presumably participated in the Baram study (study 01), this is referred to as study CSR 222017-02 (n=84), 2) A retrospective review of charts for infants treated with Acthar Gel at four treatment centers (n=178), this is referred to as study CSR QSC007-ACT-002, 3) Safety data from the two studies published by Hrachovy and Colleagues, which are described in the efficacy section above.

The database includes a total of 319 patients who receive Acthar Gel. The database included patients exposed to different dosages including those similar to the pivotal trial 01 (dose range within the range ≥ 135 to ≤ 160 U/m2/day, n= 134,), higher then pivotal trial doses (≥ 80 U/m2/day, n=133) and doses lower <80 U/m2/day, n=52) then the pivotal trials. Demographic profile of the patients adequately covered the intended population to be treated. Although a majority of patients had symptomatic IS (59%) there were a number with cryptogenic IS (39%).

Three deaths were reported. Two were a result of pneumonia thought to possible be the result of the ACTH treatment. The third death appears to be complicated by the patients general neurologic status (microcephaly). This patient was admitted to the hospital with severe respiratory symptoms and was said to have died from "respiratory failure and cardiac arrest." The possibility of infections, probably contributed by this drugs immunosuppressive effect, will be clearly noted in the Warnings and Precautions section of the label.

Serious adverse events occuring in greater in 3 patients or greater (≥ 0.9% of patients) included convulsions (20.1%), infections (5.0%), hypertension (3.8%), and pyrexia (1.9%). Other notable events occurring in 1 to 2 patients included aspiration pneumonia, osteoporotic fracture, irritability, cardiac hypertrophy and diarrhea/hemorrhage. These are consistent with what is known about steroid toxicity and will be appropriately labeled.

Data on drug discontinuation were very limited. Thus, it was unclear at times as to whether the discontinuations were planned or due to noncompliance or an adverse effect. When present, however, the reasons for discontinuation were consistent with the reported serious adverse events.

Treatment emergent adverse event occurring in >2%of patients included Cushing's, diarrhea, vomiting, irritability, pyrexia, infections, weight gain, convulsions, acne, rash and hypertension. The convulsions are likely part of the disease process. Because these data do not consist of placebo controlled trials it is difficult to absolutely determine causality, but many of these adverse events are known as common adverse events associated with ACTH and steroids and will be noted in the label.

In general, there was a trend for a greater incidence of adverse events with higher doses.

[6] Partikian A, Mitchell WG. Major adverse events associated with treatment of infantile spasms. J Child Neurol. 2007 Dec;22(12):1360-1366.

Post-Marketing Safety Information

The Sponsor provided an analysis of postmarketing safety reports in young children treated for IS. The Sponsor identified eight deaths. At least 4 of these were related to respiratory infections. The other 4 appeared to be related to the patients underlying disease, although in one case of ACTH related metabolic acidosis was thought to exacerbate that condition. The Sponsor identified 76 serious adverse event reports. The most common and notable events were similar to those identified in the above studies and/or are already described in the label. These include the following that were reported in 3 or more patients: Cushing's syndrome, fever lethargy, sepsis, dehydration, hyperkalemia, metabolic acidosis, seizure, irritability, pneumocystis carni pneumonia, rash and hypertension. Again, these events are generally described in label to some degree. For example although pneumocystis carni pneumonia is not specifically noted, susceptibility to infection is and although acidosis is not mentioned acidosis may be associated with adrenal hypo-function related to steroid withdrawal (Addison's), which is noted in the label.

10. Advisory Committee Meeting

The Peripheral and Central Nervous System Drugs Advisory Committee
Advisory panel was convened on May 6, 2010. This panel consisted of the division's core members and a number of experts in pediatric epilepsy.

The Committee voted overwhelmingly (22 yes and 1 no) that the sponsor presented substantial evidence of effectiveness for Acthar Gel as a treatment for patients with Infantile Spasms (IS). The committee agreed in a consensus that effectiveness was expressed as cessation of spasms and amelioration of the EEG, but not in the prevention of other seizure types or improvement in long-term developmental outcome. A majority of committee members voted that the effect of Acthar Gel was sustained (16 yes and 7 No). Amongst those who voted against a sustained effect, there was an expression that what was meant by a sustained effect was ambiguous.

The Committee was asked to vote as to whether the serious adverse events were predictable, easily recognized, manageable, and reversible upon drug discontinuation. A slight majority voted against this (yes 10,no 12). Those who voted yes based their decision on 50 years of experience of the use of Acthar Gel in the treatment of IS. Those who voted no based their decision on the limitations of data provided by the Sponsor in the application (e.g. small database and retrospective analysis). Despite the latter vote the Committee overwhelmingly voted that the sponsor had submitted sufficient evidence of the safety of Acthar Gel at an effective dosing regimen (20 yes, 1 no, 2 abstain). The committee, however, believed that patients should be closely monitored and that post-marketing surveillance is needed.

Some on the committee suggested that the sponsor may wish to better study maintenance of effect and alternative dosing regimens in the future. Also the committee noted that labeling should very clearly describe adverse events including infections , adrenal insufficiency and elevated blood pressure. The committee also recommended that good physician and patient education was crucial in the safe use of this drug. The Sponsor noted that Acthar Gel was distributed through specialty pharmacies. Some speakers thought that this may make a registry easy, which can then collect data on the use of the drug.

There was some recommendations, however, that the FDA should not make it to complicated for physicians to use Acthar Gel.

Although the committee discussed the potential of additional studies the recruitment and the execution of such studies may be difficult considering the small number of patients suffering this disorder and the fact that the presently recommended dose of Acthar Gel is the only dosage that has demonstrated efficacy and is the dosage recommended by the American Academy of Neurology and the Child Neurology Society. The division does believe that additional patient education should be performed and believes that this can be accomplished with a MedGuide based REMS. A single issue indication (IS) MedGuide has been requested. The argument for a single indication, rather then multiple indications, MedGuide was expressed in a Memo (9/10/10) by this reviewer. The argument, transcribed from that memo, is as follows:

> "One of the most worrisome side effects of ACTH is the lowering of immunologic resistance. As a child's immature immune system is already considered compromised, as a result of its immaturity[7], the additional immuno–suppressive effect of ACTH is thought to add an additional risk to this population. It is also noteworthy that while it is generally difficult to identify whether a child at this very young age is infected, the cognitive/behavioral deficits associated with Infantile Spasms make it even more difficult[2]. Moreover, Acthar Gel may suppress normal signs of infection such as fever. Thus, parents would have to be educated to these facts and highly vigilant for any potential signs of infection that may be limited to changes in behavior (e.g. decreased responsiveness or feeding). Moreover, parents of children must also be educated and advised to monitor other symptoms of Acthar Gel toxicity (e.g. post treatment adrenal insufficiency). The parents must also be educated as to the importance of adequate follow up for their children so that other potential serious adverse events (hypertension) can be monitored."

11. Pediatrics

The present study examined and labeled the pediatric population (< 2 years of age) for which IS is known to occur. IS essentially does not occur in older children. This is an orphan indication, and as such does not require a PERC commitment.

12. Other Relevant Regulatory Issues

Dr Sheridan reviewed the Financial Disclosure Forms in his review and determined there was no conflict.

[7] Rudolph's Pediatrics – 21st Ed. (2003), Chapter 13 by Julie A. Jaskiewicz "Fever Without Localizing Signs In Infants And Children."

DMEP determined , upon the initial review of this application at filling, that a DSI audit was unnecessary.

The application was initially submitted as a 505(b)(2) application, but was reclassified as a 505(b)(1) based upon the fact that, while studies were published, the Sponsor acquired the right to use these studies and provide the division with their own final study report as a response to the complete response.

13. Labeling

The labeling review was a joint effort by this division and that of DMEP. It included a conversion to the PLR format and removal of a number of DESI indications, which was negotiated with the Sponsor.

14. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: Approval.

Risk Benefit Assessment: There was a general consensus from myself, the review team and the Advisory Committee that approval of Acthar Gel provided an adeqaute risk-benefit. While the treatment with Acthar Gel is not without serious consequences, these may be dealt with by adeqaute patient education (e.g. in the form of a MedGuide) a

Recommendation for Postmarketing Risk Management Activities: The division recommends a MedGuide so as to better educate parents and guardians of children on the risks of ACTH use.

Recommendation for other Postmarketing Study Commitment: None. For a discussion on this the reader is referred to the section on the Advisory committee.

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/s/

NORMAN HERSHKOWITZ
09/27/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022432
Priority or Standard	P
Submit Date(s)	December 10, 2009
Received Date(s)	December 10, 2009
PDUFA Goal Date	September 11, 2010
Division / Office	Division of Neurology Products, ODE-1
Reviewer Name(s)	Philip H. Sheridan, M.D.
Review Completion Date	September 27, 2010
Established Name	Repository Corticotropin
(Proposed) Trade Name	Acthar Gel
Applicant	Questcor Pharmaceuticals
Formulation(s)	For Intramuscular Injection
Dosing Regimen	BID
Indication(s)	Infantile Spasms
Intended Population(s)	Pediatric

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval is recommended for the treatment of infantile spasms, (b) (4) . A REMS and changes to proposed labeling are needed as discussed in sections 9.2 and 9.3 of this review.

The efficacy and safety study data, although strongly suggestive of efficacy and relative safety, do not meet the usual Agency standard for NDA approval as discussed in this review. However, given the inherent difficulties of further studying the efficacy and safety of Acthar Gel therapy for infantile spasms and the continued off-label use of Acthar Gel for this indication, the appropriateness of approving Acthar Gel for the treatment of infantile spasms on the basis of the data presented was reviewed by the Peripheral and Central Nervous System Drugs Advisory Committee on May 6, 2010 as discussed in section 9.3 of this review.

1.2 Risk Benefit Assessment

The single pivotal study (CSR 222017-01 by Baram) is strongly suggestive but not definitive (by usual Agency standards) for establishing efficacy in eliminating the spasms. Two controlled studies by Hrachovy (CSR 222017-05 and CSR 222017-04) are also consistent with efficacy but are supportive data rather than pivotal efficacy trials. As discussed in detail in this review, all three studies have significant flaws in design and analysis. The usual standard for NDA approval is not met. The safety data is extensive but largely retrospective.

The argument for approval based on the submitted data could be made as follows. Although vigabatrin was recently approved for the treatment of infantile spasms in the United States (after recommendation by an advisory committee which accepted less than the usual standard of evidence for efficacy and safety), vigabatrin raises significant safety concerns (visual field deficits and intramyelinic edema) that are not yet adequately defined and/or detectable by monitoring and which require an extensive REMS. Most American patients with infantile spasms are currently treated off-label with Acthar Gel even though there is considerable variability in the dosage and duration of treatment. As discussed in this review and in a recent AAN review cited in this submission (MacKay, 2004), available efficacy and safety data suggest that the proposed dosage (high dosage, short duration) is probably effective and relatively safe in controlling spasms (although its effect on long-term neurodevelopmental status is not

established). Approval would establish reasonable dosage and duration guidelines for prescribers.

The adverse effects documented in these studies are consistent, readily recognizable, manageable, and usually reversible after the relatively short treatment period is completed.

The argument against such an approval in the absence of the usual criteria for efficacy is that the usual standards for efficacy should be met. A proposal to market Acthar Gel to treat infantile spasms would be more compelling if, in addition to stopping spasms, there was evidence demonstrating or strongly suggesting that stopping the spasms improves the long-term neurodevelopmental prognosis for the affected infants. Although it may be that long-term developmental prognosis improves if spasms can be stopped early-on infantile spasms, the evidence is not convincing for either Acthar Gel or vigabatrin.

Infantile spasms is a catastrophic epileptic syndrome that would justify use of a probably effective therapy even given some uncertainty over efficacy, safety, and optimal dosage. As discussed in section 9.3 of this review, the advisory committee supported the approval of Acthar Gel for the treatment of infantile spasms with recommendations for precautions and future long-term studies (as dsicussed in section 9.3 of this review).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

REMS to provide a MedGuide for the infantile spasm indication.

Revision of labeling as discussed in section 9.2 of this review

1.4 Recommendations for Postmarket Requirements and Commitments

None. See discussion in section 9.3 of this review.

2 Introduction and Regulatory Background

2.1 Product Information

See currently approved label.

2.2 Tables of Currently Available Treatments for Proposed Indications

Vigabatrin (Sabril) was recently approved for treatment of infantile spasms.

2.3 Availability of Proposed Active Ingredient in the United States

Currently approved and marketed for other indications.

2.4 Important Safety Issues with Consideration to Related Drugs

The primary safety issues of Acthar Gel are related to its stimulation of endogenous steroid production. The adverse effect profile is thus similar to that of steroid medications including irritability, Cushingoid appearance, hypertension, and decreased resistance to infection;

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Acthar Gel was approved in 1952 and was successively owned by several companies including Armour Pharmaceutical Company, Rhone-Poulenc Rorer, and Aventis. Aventis was formed by the merger of Rhone-Poulenc Rorer with Hoechst AG.

In 2001, Questcor purchased the marketing rights to Acthar from Aventis. Since that time, with active collaboration with the Food and Drug Administration (FDA), Questcor has been working to submit a Supplemental New Drug Application (sNDA) that would support the approval of Acthar for the treatment of patients with infantile spasm (IS).

Questcor received a Complete Response letter to its sNDA submission with specific deficiencies in May 2007. In a subsequent Type C Meeting with FDA in November 2007 (09 November 2007 Type C Meeting Minutes, correspondence), Questcor was encouraged to do the following, where possible:
1. Obtain the source data from the 5 published, randomized control studies where Acthar was evaluated for the treatment of patients with IS and perform independent analyses of the data (Askalan 2003, Baram 1996; Dreifuss 1986; Hrachovy 1994; Hrachovy 1983); 2. Obtain source data from hospitals that had treated patients in the last 10 years and then to perform its own independent safety analyses of these data.
3. Provide FDA with safety on enough IS patients treated with Acthar to define the safety profile in these patients and to support that the benefit outweighs the risk.

Following this meeting, Questcor attempted to obtain data from the 5 RCTs, and was successful in obtaining data from 3 of those 5 studies (Baram 1996, Hrachovy 1994, Hrachovy 1983). Data for the other 2 RCTs were no longer available due to the age of

those studies. In addition, Questcor obtained data from a safety study conducted in 2007 (Partikian 2007) and also conducted its own retrospective chart review protocol to obtain source safety data from IS patients treated at 4 hospitals.

2.6 Other Relevant Background Information

Not applicable

3 Submission Quality and Integrity

3.1 Submission Quality and Integrity

As discussed in detail in this review, the three studies presented in support of efficacy and the four studies presented in suport of safety do not meet usual Agency standards for approval. The Sponsor has shown due diligence in obtaining the most complete data available and in presenting them with scientific integrity.

Efficacy Data Quality:

Most NDA submissions provide efficacy data collected prospectively using prespecified protocol and comprehensive patient data collection forms from a double blinded randomized study of the NDA study drug versus a control (placebo or active control). Because the studies supporting this NDA were done as small academic studies and not intended to support an NDA submission, this quality of efficacy data is not available. Furthermore, there was no formal follow-on protocol after the pivotal efficacy study or after the supportive efficacy study that could provide a reliable relapse rate for all responders over a 6 month or greater time period. Longer-term data concerning neurodevelopment or the later appearance of other forms of epilepsy among the responders are not available.

A complete prospective protocol, comprehensive patient data collection forms, and prespecified statistical analysis plan were not available.

Safety Data Quality:

Most NDA submissions provide safety data collected prospectively using prespecified protocol and comprehensive patient data collection forms from a double blinded randomized study of the NDA study drug versus a control (placebo or active control). Because the studies supporting this NDA were done as academic studies and not intended to support an NDA submission, this quality of safety data is not available. The

safety data presented was compiled retrospectively in an unblinded fashion from the charts of patients who had participated in academic randomized clinical studies or who were treated for infantile spasms independent of a randomized trial at an academic center. The data available in the charts was not collected according to predetermined prospective protocol and patient data collection forms. Thus, the data is prone to be incomplete. The patient charts from the pivotal efficacy study were not available to the Sponsor so this study did not directly contribute any safety data.

This safety information is supplemented by adverse event reports submitted to the Sponsor and by a survey of adverse events attributed to Acthar Gel in the published literature. These are useful in screening for adverse effects observed in the larger treatment population (beyond the safety studies used in this submission) that were not identified in the relatively small number of study patients receiving Acthar Gel (319 patients in 3 safety studies). However, the likelihood of an observed adverse effect being reported from this larger population is unknown making the numerator of an estimated incidence of an observed adverse effect uncertain. Furthermore, the size of this larger treatment population is not known so there is also no denominator for estimating incidence of adverse effects observed.

3.2 Compliance with Good Clinical Practices

Adequate

3.3 Financial Disclosures

Questcor submitted the following statement with Form FDA-3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) dated 8/31/09 regarding the three efficacy studies and one of the safety studies (Partikian 2007 or CSR 222017-02):

Attachment to Form FDA-3454

Investigators and Subinvestigators with No Financial Arrangement with Sponsor

(b) (4)

[redacted]

As the applicant who is submitting studies sponsored by a firm or party other than the applicant, Questcor certifies that based on information obtained from participating clinical investigators, the listed clinical investigators above did not participate in any financial arrangement with Questcor. Due to the literature source of the above studies, Questcor has listed the primary author as the principal investigator and the co-authors of the publications as the subinvestigators.

With respect to Safety Study QSC007-ACT-002, Questcor submitted the following list with Form FDA-3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) dated 8/31/09

Attachment to Form FDA-3454

Investigators and Subinvestigators with No Financial Arrangement with Sponsor

(b) (6)

(b) (6) and (b) (6) are identified as subinvestigators for Study (b) (4) and also as having a paid consulting arrangement with Questcor. My review of their stated roles in the study does not suggest the likelihood of the introduction of bias to this study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Not applicable

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Efficacy Studies	Title
CSR 222017-01	Pivotal Efficacy Study: High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study (Baram, 1996)
CSR 222017-05	Supportive Efficacy Study: High-dose, Long-duration versus Low-dose, Short-duration Corticotropin Therapy for Infantile Spasms (Hrachovy, 1994)
CSR 222017-04	Additional Data for Efficacy: High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms, A Prospective, Randomized, Blinded Study (Hrachovy, 1983)

Safety Studies	Description	Number of Acthar Gel-treated patients contributed to Integrated Safety Tables
CSR 222017-02	Partikian and Mitchell retrospective chart review	84
CSR QSC007-ACT-002	Questcor retrospective chart review at 4 sites	178
CSR 222017-05	Hrachovy 1994 Study of Acthar Gel High vs Low Dose (charts reviewed retrospectively for safety data)	57
CSR 222017-04	Hrachovy 1983 study of ACTH vs Prednisone (patients on Acthar gel not identifiable in retrospective chart review)	None
Total Patients in Integrated Safety Tables	See section 7.2.1 of this review	**319**

5.2 Review Strategy

I have reviewed the individual clinical study reports and the integrated summaries of efficacy and safety for the efficacy and safety studies. I have also reviewed the published articles from the three efficacy studies and from the Partikian safety study, and I have compared them to the corresponding clinical study reports.

Questcor obtained source efficacy data from the study conducted by Dr. Baram (Baram 1996). Questcor's analyses of these data are presented as CSR 222017-01. CSR 222017-01 is presented as the pivotal efficacy study.

Questcor also obtained source efficacy data from the 2 additional RCTs conducted and published by Dr. Hrachovy and colleagues (Hrachovy 1994, Hrachovy 1983). Questcor's independent analyses of these data are presented as CSR 222017-05 and CSR 222017-04, respectively.

CSR 222017-05 is presented as the supportive efficacy study. Additional efficacy data supporting the use of Acthar for the treatment of IS patients is presented in CSR 222017-04.

All three studies assessed the efficacy of Acthar Gel by the combined primary endpoint of cessation of spasms (determined by video EEG sessions) and the elimination of the hypsarrhythmia.

The safety data submitted in this Complete Response from the independent analyses of the data obtained in studies conducted by Drs. Partikian and Mitchell (CSR 222017-02) which presumably included safety data from CSR 222017-01 not otherwise available, the Questcor Retrospective Study (CSR QSC007-ACT-002), and the studies conducted by Hrachovy and colleagues (CSR 222017-05 and CSR 222017-04), together with the data in the Questcor postmarketing surveillance safety database and the published literature

5.3 Discussion of Individual Studies/Clinical Trials

The Sponsor presents three individual studies in support of efficacy in this NDA submission:

Pivotal Study for Efficacy CSR 222017-01 (Baram, 1996)

The pivotal study was entitled, "High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study". It compared Acthar 150

U/m2/day administered as 75 U/m2/bid IM for 2 weeks with a taper to zero for an additional 2 weeks and prednisone 2 mg/kg/day administered as 1 mg/kg/bid orally (PO) for 2 weeks with a taper to zero over 2 weeks in patients with IS.

The patients were assessed for both the elimination of clinical spasms as well as a remission of hypsarrhythmic EEG pattern characteristically seen in these patients.

Reviewer's Note:
This combined endpoint (elimination of spasms and of hypsarrhythmia) is generally recognized as the most clinically meaningful endpoint for efficacy studies of infantile spasms. Unlike the efficacy success of treatments of other seizure types where reduced seizure frequency is significant, success for efficacy studies of infantile spasms is an "all-or-none" phenomenon.

The use of video-EEG for assessment of spasms elimination and the elimination of hypsarrhythmia is also essential to a good infantile spasms study. Even experienced clinicians may miss subtle spasms (undercount) or mistake a nonepileptic infantile movement for a spasm (overcount) without a simultaneous EEG tracing for detection or confirmation. Video EEG also allows for a blinded EEG interpreter who does not know to which arm of the study an infant is assigned to determine if the infant's response satisfies the primary endpoint.

This study is considered single blind because the infants were not subjected to a "double-dummy" study where twice-daily sham injections would be given to infants randomized to oral prednisone. However, given that an infant would not be expected to associate one treatment over the other with likely improvement in its condition (or even associte the experience of being treated with any expected benefit) and that the endpoint is objective rather than subjective, it is unlikely that a placebo response affected the outcome. Thus, the study almost can be considered "double-blind".

Dr. Baram and her colleagues had previously published the study results from their analyses of the data (Baram 1996). Questcor obtained the primary efficacy data from the investigators and, with the investigators' permission, Questcor performed an independent analysis for submission in this sNDA; these analyses are presented in CSR 222017-01.

Reviewer Note:

The data available from Dr. Baram was largely limited to her published article (1996) and her spreadsheet of patients. Regrettably, the safety data was not available to Questcor. It is presumed that the 15 patients initially randomized to Acthar Gel and the 9 patients who crossed over to Acthar Gel after initially being randomized to prednisone are included in the patients who were retrospectively

studied by Partikian (See section 7.1.1 of this review). However, none of the patients are definitely identifiable as being from the Baram study.

Design: Patients eligible for enrollment into this study were diagnosed with clinical IS, defined according to Jeavons (1964). An infant previously treated with any steroid or Acthar treatment was not eligible for the study. Informed consent was obtained from each patient's parent or guardian. All patients had a 24-hour video-EEG to ascertain the presence of hypsarrhythmia before initiation of treatment. Seizure frequency was monitored throughout the 2-week treatment period by parents who maintained seizure diaries. After 2 weeks of treatment, a repeat video-EEG was performed, and both clinical and EEG responses were assessed by a blinded EEG interpreter. Video-EEG monitoring was performed for a minimum of 4 hours and, optimally, for 24 hours, always including a full sleep wake cycle.

Reviewer Note:
It is important that at least one full sleep-wake cycle be observed since the incidence of infantile spasms varies during the cycle. It would be cleaner if all infants had a 24 hour post-treatment video EEG. From available data, It cannot be determined an equal number of the less than 24 hour video EEG sessions occurred in each arm of the study. However, given the "all-or-none" nature of a positive response to infantile spasm therapy, this flaw is probably less significant than it might be in a study of another seizure type.

Adverse events such as hypertension and hyperglycemia were monitored; urine specimens were checked for glucose throughout the duration of treatment, and blood pressure was measured biweekly. The safety results were not included in the published article (Baram, 1996) and were not available for Questcor to include in the clinical study report.

Acthar 150 U/m2/day was administered as 75 U/m2/bid IM for 2 weeks and then tapered to zero for an additional 2 weeks. Prednisone 2 mg/kg/day was administered as 1 mg/kg/bid PO for 2 weeks, and then tapered to zero over 2 weeks. Patients with persistent spasms or hypsarrhythmia after initial treatment were offered the alternative treatment.

Video-EEG was used to establish response to treatment. For a patient to be considered an Overall Responder to treatment, both of the following had to occur: remission of clinical spasms and a resolution of the characteristic pattern of hypsarrhythmia on EEG. Electrographic response consisted of resolution of the hypsarrhythmic pattern on both

sleep and wake EEG. The emergence of background slowing or other epileptiform patterns was considered a positive response

Efficacy Findings

Results: Thirty-six (36) patients met clinical and EEG criteria for entry into the study. Two (2) were ineligible for treatment, 1 had severe hypertension and 1 experienced resolution of spasms after shunt placement. Thirty-four (34) patients were, therefore, eligible to enroll in the study.

Twenty-nine (29) of the 34 eligible infants with clinical IS were enrolled in the study; the 5 who were not enrolled were due to parental refusal (2), unavailability of legal guardian (2), and other issues (1).

Fifteen (15) patients were randomized to Acthar and 14 patients were randomized to prednisone. Twenty-five (25) patients (25/29, 86.2%) had symptomatic etiology of IS and 4 patients (4/29, 13.8%) had cryptogenic etiology of IS. No stratification was done prior to randomization, but 2 cryptogenic patients were randomized to each arm.

Reviewer Note:
The older medical literature suggests that cryptogenic patients may respond more often than symptomatic patients. The published article (Baram, 1996) notes that, given modern neuroimaging and other diagnostic testing, the cryptogenic category is smaller than in older reports. In this small study, there was no significant difference in response between cryptogenic and symptomatic patients.

The Questcor analysis of the efficacy data of CSR 222017-01 demonstrated the following:

- The combined clinical endpoint of spasm cessation combined with cessation of the hypsarrhythmic EEG indicated greater efficacy of Acthar (13/15, 86.7%) compared to prednisone (4/14, 28.6%), P=0.0015.
- The differences between Acthar and prednisone for the separate EEG and clinical response of spasm cessation were statistically significant (P=0.0015 and P=0.0003, respectively) favoring the Acthar treatment group. Electroencephalogram response was 86.7% for Acthar and 28.6% for prednisone. Corresponding clinical response rates for spasm cessation were 93.3% and 28.6%, respectively.
- Age distributions appeared to be slightly different between the treatment groups, but these differences were not statistically significant. `

- Adjusting for age group the secondary analyses confirmed that differences between Acthar and prednisone for the combined clinical endpoint and for the separate EEG and clinical spasms responses remained statistically significant (P<0.01, for any age grouping).
- One (1) of 2 patients (1/2, 50%) crossed-over to prednisone responded by both EEG and clinical criteria. Seven (7) of 8 patients (7/8, 87.5%) with data available documenting cross-over to Acthar responded by both EEG and clinical spasm criteria.

Reviewer Note: The published article indicates that 2 patients relapsed of the 14 responding to ACTHAR originally (15% rate). The period of follow-up is not specified. When asked about relapse data, the Sponsor on March 26, 2010 said they had no further information. Further discussion of relapse data is summarized in section 6.1.9 of this review.

Questcor Conclusions: This study demonstrated that Acthar 150 U/m2/day administered as 75 U/m2/bid IM was superior to prednisone 1 mg/kg/bid PO for elimination of clinical spasms and hypsarrhythmia in patients with IS using a 2-week high-dose regimen with a 2-week taper. This Acthar regimen was superior to prednisone when analyzing the overall response endpoint (combined measure of cessation of spasms and eliminating the hypsarrhythmia on EEG) (the more definitive measure of treatment success) as well as in the individual measurements of spasm cessation and elimination of the hypsarrhythmic EEG pattern.

Reviewer Note: All but one of the patients who responded with cessation of spasms also showed disappearance of hypsarrhythmia. The fact that this one patient was on Acthar Gel rather than prednisone is not likely to be significant since there were many more patients with cessation of spasms on Acthar gel (14/15) than on prednisone (4/14).

Supportive Efficacy Study: CSR 222017-05 (Hrachovy 1994)

The supportive efficacy study CSR 222017-05 was entitled, “High-dose, Long-duration versus Low-dose, Short-duration Corticotropin Therapy for Infantile Spasms,” a prospective, controlled, randomized, single-blind study that compared an Acthar high-dose regimen to Acthar low-dose regimen in patients with IS.

The Acthar high-dose regimen consisted of Acthar given at a dose of 150 U/m2/day as a single (150 U/m2/QD) IM dose for 3 weeks followed by a 9-week taper; the Acthar low-dose regimen consisted of Acthar 20 U/day (20 U/QD) as a single IM dose for 2

weeks followed by a 2-week taper in responders or a dose escalation to 30 U/QD IM in nonresponders.
The principal investigator, Dr. Hrachovy, and his colleagues had previously published the study results from their analyses of the data (Hrachovy 1994). Questcor obtained the primary efficacy data from the investigators, and with the investigators' permission, Questcor performed an independent analysis for submission in this sNDA; these analyses are presented in CSR 222017-05.

Reviewer Note:
Unfortunately, although the "high dose" of 150 U/m2/day is the same total daily dose used in the pivotal study (CSR 222017-01, Baram), this "supportive efficacy study" gave the injection once daily rather than dividing the injection BID. The BID dosage is believed to increase the cortisol response which may be related to the mechanism of action for causing cessation of spasms. Also, the high dose is given for 3 weeks and tapered for 9 weeks but the CSR 222017-01 pivotal study gave the high dose for 2 weeks and tapered for 2 weeks. Furthermore, the different timing of the EEG between the two arms of the study makes this study difficult to interpret.

Study Design: Patients enrolled in the study were diagnosed with IS defined by both the presence of clinical spasms and a hypsarrhythmic EEG pattern. All study participants were under the age of 4 years, had onset of spasms prior to the age of 12 months, and continued to have spasms at the time of entry into the study. Patients who had previously received ACTH or corticosteroid therapy for their spasms were not eligible for the study.

Informed consent was obtained from each patient's parent or guardian. Prior to the initiation of treatment, patients were monitored using a video-EEG for up to 24 hours in order to confirm the presence of IS and to establish a baseline seizure frequency. Patients were monitored with video-EEGs 2 to 3 times during the treatment period; the treatment period was 12 weeks for the high-dose and 6 weeks for low-dose. As per the study protocol, the 2 dosing groups had different schedules as to when the post-Acthar EEGs were to be performed. The patients randomly assigned to the Acthar low-dose group were scheduled to have their first post-Acthar EEG performed 2 weeks after the start of treatment, whereas patients in the Acthar high-dose group did not have their first post-Acthar EEG performed until after the Acthar was tapered to zero, a full 12 weeks after the initiation of therapy and 9 weeks after the maintenance dose of 150 U/m2/QD had been administered. Patients were evaluated throughout the study for spasm cessation and safety.

Treatment Protocol: Eligible patients were first stratified as having either cryptogenic or symptomatic IS and then randomized to receive treatment with either high-dose Acthar (150 U/m2/QD IM for 3 weeks, followed by 80 U/m2/QD IM for 2 weeks, then 80 U/m2/every other day [QOD] IM for 3 weeks, then 50 U/m2/qod IM for 1 week, and then

Acthar was tapered to zero over 3 weeks) or Acthar low-dose (20 U/QD IM for 2 weeks). Nonresponders to the high-dose Acthar regimen were treated with prednisone 2 mg/kg/day PO for 4 to 6 weeks, and then followed in a routine clinical manner. Nonresponders to low-dose Acthar had their Acthar increased to 30 U/QD for an additional 4 weeks followed by a taper to zero over a 2-week period.

Data Methods: Procedures used to collect, to analyze, and to ensure the integrity of study data are provided in the final study report (see CSR 222017-05).

Efficacy Measures: The primary efficacy endpoint was the Overall Response. An Overall Response was defined as both cessation of spasms and resolution of the hypsarrhythmic EEG pattern at any time during the study. The secondary efficacy endpoints were the assessment of efficacy based on spasm cessation alone (Spasm Control Response) and by resolution of the hypsarrhythmic EEG pattern (Hypsarrhythmia EEG Pattern Response) alone between the 2 treatment groups.

Reviewer Note:
The stratification of cryptogenic vs. symptomatic IS is a good feature of this study which the pivotal study (CSR 222017-01, Baram) did not have. Some reports in the literature suggest that infants with cryptogenic IS have a better initial response overall prognosis.

The length of the video EEG sessions varied. The sponsor does not have records of how long each session was or whether one arm of the study might have averaged longer sessions than the other arm.

There were 4 efficacy analysis populations for this study. These were defined as follows:

- Modified Intent-to-Treat Population: The modified Intent-to-treat (mITT)Population, the primary efficacy population, included all patients who were randomized, received ≥ 1 dose of Acthar study medication, and had sufficient data to evaluate the Overall Response (see CSR 222017-05, Section 9.8.8.1).

- Intent-to-Treat Population: The Intent-to-treat (ITT) Population included all patients randomized to treatment. A sensitivity analysis of treatment efficacy was performed using the ITT Population (see CSR 222017-05, Section 9.8.3.2).

- Spasms Population: The Spasms Population included all patients with sufficient data to evaluate the Spasm Control Response.

- Completed Patients Population: The Completed Patients Population included all patients in the study who completed the treatment with Acthar as designed by the

protocol (i.e., were not prematurely withdrawn from the study), and were judged to have completed the protocol by the investigator.

The analysis of treatment response was performed in each of the 4 efficacy populations for each of the 3 responder groups:

- Overall Responders,
- Spasm Control Responders, and
- Hypsarrhythmic EEG Pattern Responders.

Each patient was classified as a Responder or Nonresponder for the determination of Overall Response (i.e., spasm cessation combined with resolution of the hypsarrhythmic EEG pattern), as well as for the determination of Spasm Control Response alone and Hypsarrhythmic EEG Pattern Response alone based on data collected to the Treatment Response case report form page as explained below:

- Overall Response: Overall Responders in this study included all patients with both cessation of spasms and resolution of the hypsarrhythmic EEG pattern at any time during the study.
- Spasm Control Response: Spasm Control Responders included all patients with cessation of spasms at any time during the study. Patients were evaluated for spasms through the treatment and follow-up periods. For the purpose of this analysis, Spasm Control Responders included all patients with cessation of spasms at any time during the treatment or follow-up periods identified by clinical assessment and/or parental reports that were recorded in the patient charts. Any patient noted to have cessation of spasm with who subsequently was observed to have spasms would be considered to have relapsed.

- Hypsarrhythmic EEG Pattern Response: Hypsarrhythmic EEG Pattern Responders included all patients with resolution of hypsarrhythmia as assessed by any post-treatment EEG at any time during the study. Serial long-term EEG and/or video monitoring studies (up to 24 hours) were used to determine the EEG response. If a patient had resolution of hypsarrhythmia on a post-treatment EEG but a later post –treatment EEG showed hypsarrhythmia, that patient would be considered relapsed.

The analysis of relapse was only performed in the Overall Responders in the mITT Population. A relapsed patient was defined as any patient in the mITT Population who, first, met the Overall Responder definition and then had 1 or both of the following conditions occur: 1) the patient demonstrated continued spasms or reduction of spasms following a noted cessation of spasms, or 2) the patient demonstrated any type of hypsarrhythmia on any EEG subsequent to an EEG that showed resolution of hypsarrhythmia.

For the ITT Population only, a sensitivity analysis was performed by applying the following "worst case scenario" definitions to patients with missing data in order to classify them as either Responders or Nonresponders for all 3 endpoints: the Spasm Control Response, the Hypsarrhythmia EEG Pattern Response, and then, by definition, the Overall Response, as follows:

- If a patient assigned to the Acthar low-dose group was not assessed for spasms cessation, then the patient was counted as a Spasm Control Responder.
- If a patient assigned to the Acthar low-dose group was not assessed for resolution of hypsarrhythmic EEG, then the patient was counted as a Hypsarrhythmic EEG Pattern Responder.
- If a patient assigned to the Acthar high-dose group was not assessed for spasms cessation, then the patient was counted as a Nonresponder for the Spasm Control Response.
- If a patient assigned to the Acthar high-dose group was not assessed for resolution of hypsarrhythmic EEG, then the patient was counted as a Nonresponder for Hypsarrhythmic EEG Pattern Response.

Results: The study enrolled 59 patients (30 high-dose, 29 low-dose). Nine patients (4 in the high-dose group, 5 in the low-dose group) did not complete the treatment protocol. Dr. Hrachovy was able to provide charts from 58 patients of the study patients: 50 who completed the study protocol and 8 of the 9 patients who prematurely withdrew from the study. The chart for the remaining patient was not able to be located.

Table 1.1 is a summary of the available dose record (exposure) data, efficacy data, and analysis populations by treatment group.

Table 1.1 Dose Record Data, Efficacy Data, and Analysis Populations by Treatment Group

	Acthar High Dose[a] n=30	Acthar Low Dose[b] n=29	Acthar All Patients N=59
Populations for Efficacy Analysis, n (%)			
ITT Population	30 (100.0)	29 (100.0)	59 (100.0)
mITT Population	24 (80.0)	27 (93.1)	51 (86.4)
Spasms Population	28 (93.3)	27 (93.1)	55 (93.2)
Completed Patients Population	26 (86.7)	24 (82.8)	50 (84.7)

a. Acthar High Dose: 150 U/m²/qd for 3 weeks, then 80 U/m²/qd for 2 weeks, then 80 U/m²/qod for 3 weeks, then 50 U/m² qod for 1 week, and then tapered to 0 U/qd over 3 weeks.

b. Acthar Low Dose: 20 U/qd for 2 weeks, then the dose was escalated or tapered based on response.

The median age of onset of spasms of all patients in the mITT Population was 6.62 months (range: 1.9 to 28.2 months). The median age of all patients was 6.7 months (range: 2 to 28 months) at start of treatment. The median lag time for all patients from date of diagnosis of IS to start of treatment was 0.1 month (range: 0 to 2 months). The median age of onset of spasms, the median age at start of treatment, and the median lag time to start of treatment was similar in the Acthar high-dose and the Acthar low-dose groups. More patients were male (31/51, 60.8%) than female (20/51, 39.2%); the Acthar low-dose group had a higher proportion of male patients (70.4%) than did the Acthar high-dose group (50.0%). The majority of patients had symptomatic etiology of IS (35/51, 68.6%). Consistent with a stratified design, the distribution of symptomatic and cryptogenic etiology of IS was similar in the Acthar high-dose (70.8% and 29.2%) and Acthar low-dose (66.7% and 33.3%) groups.

Table 1.2 is a summary overview of the primary, secondary, and confirmatory analyses.

Table 1.2 Summary Overview of Overall Response, Spasm Control Response, and Hypsarrhythmic EEG Pattern Response by Treatment Group (Each Efficacy Population)

Populations	Acthar Treatment[a,b]	N	Overall Response	Spasm Control Response	Hypsarrhythmic EEG Pattern Response
mITT Population	High Dose	24	*P*=0.2768	*P*=0.0329	*P*=0.2686
	Low Dose	27			
ITT Population[c]	High Dose	30	*P*=0.9443[d]	*P*=0.0691	*P*=0.5209[d]
	Low Dose	29			
Spasms Population	High Dose	28	*P*=0.6363	*P*=0.0126	*P*=0.6580
	Low Dose	27			
Completed Patients Population	High Dose	26	*P*=0.8225	*P*=0.0782[c]	*P*=0.8349
	Low Dose	24			

a. Acthar High Dose: 150 U/m²/qd for 3 weeks, then 80 U/m²/qd for 2 weeks, then 80 U/m²/qod for 3 weeks, then 50 U/m²/qod for 1 week, and then tapered to 0 U/qd over 3 weeks.

b. Acthar Low Dose: 20 U/qd for 2 weeks, then the dose was escalated or tapered based on response.

c. Sensitivity analysis, data imputed to favor Acthar Low Dose.

d. Mantel-Haenszel test was used to compare response rates between treatments, stratified on etiology. All contrasts showed numerically higher response rate for Acthar high-dose compared to Acthar low-dose except as noted.

Reviewer Note:

The records from this study do not indicate how many of the "low dose" arm patients were increased from 20 U QD to 30 U QD during the treatment period. The "High Dose" arm was given 150 U/m2/day QD which for most patients would be about 40 U QD.

The Questcor analyses of the efficacy data of CSR 222017-05 was as follows:

- In the mITT Population (the primary efficacy population), the Overall Response was similar in the Acthar high-dose (15/24, 62.5%) and the Acthar low-dose (13/27, 48.1%) groups, P=0.2768. However, the Spasm Control Response to treatment did demonstrate statistical significance: this response was greater in the Acthar high-dose group (19/24, 79.2%) than in the Acthar low-dose group (14/27, 51.9%), P=0.0329. The Hypsarrhythmic EEG Pattern Response was similar between the 2 treatment groups: Acthar high-dose (16/24, 66.7%) and the Acthar low-dose (14/27, 51.9%), P=0.2686.

- In the Spasms Population, the Spasm Control Response endpoint demonstrated statistical significance in that there were higher rates of response in the Acthar high-dose group (23/28, 82.1%) compared to the Acthar low-dose group (14/27, 51.9%), P=0.0126.

- A trend in the Spasm Control Response favoring the Acthar high-dose group was observed in both the ITT and Completed Patients Populations. The ITT sensitivity analysis, which used data imputation biased in favor of the Acthar low-dose group, showed a trend towards higher Spasm Control Response rates in the Acthar high-dose group (23/30, 76.7%) compared to the Acthar low-dose group (16/29, 55.2%), P=0.0691. In the Completed Patients Population, the treatment comparison was a Spasm Control Response rates in the Acthar high-dose group (21/26, 80.8 %%) compared to the Acthar low-dose group (4/24, 58.3%), P=0.0782.

- In the mITT and Spasms Populations, the Spasm Control Response rates were higher for patients with cryptogenic IS etiology compared to symptomatic IS etiology in either dose group: Acthar high-dose (7/7, 100% compared to 12/17, 70.6%, respectively) versus Acthar low-dose group (6/9, 66.7% compared to 8/18, 44.4%, respectively).

- An exploratory analysis of relapse suggested that approximately 20% (3/15) of patients in the Acthar high-dose group and 15% (2/13) of patients in the Acthar low-dose group relapsed after treatment.

Questcor Conclusions for CSR 222017-05 efficacy: In the primary, mITT Population, the analysis of the Spasm Control Response by IS etiology showed a statistically significant difference between the Acthar high-dose and Acthar low-dose treatment groups in favor of Acthar high-dose (P=0.0329). This statistical difference in favor of the

Acthar high-dose by IS etiology was also demonstrated in the Spasms Population (P=0.0126).

A trend in favor of the Acthar high-dose group was also demonstrated in the ITT sensitivity analysis (P=0.0691) and in the Completed Patients Population (P=0.0782). In all cases, the Spasm Control Response rates appeared higher in patients with cryptogenic etiology compared to those with a symptomatic etiology in each dose group; however, the study was not designed nor was the study powered to make statistical conclusions about these observed differences based on IS etiology.

The analysis of Overall Response (spasms cessation and resolution of the hypsarrhythmic pattern on EEG) showed no statistically significant differences between the 2 treatment groups in any of the 4 defined populations. In addition, the analysis of the secondary endpoint of the remission of the Hypsarrhythmic EEG Pattern Response did not show any statistically significance differences between the 2 treatment groups in any of the defined study populations. As previously stated, this study was underpowered in its ability to demonstrate differences between the 2 treatment groups.

In addition, both the Overall Response endpoint and the Hypsarrhythmic EEG Pattern Response were dependent on the EEG results. As per the study protocol, the 2 dosing groups had different schedules as to when the post-Acthar EEGs were to be performed. The patients randomly assigned to the Acthar low-dose group were scheduled to have their first post-Acthar EEG performed 2 weeks after the start of treatment, whereas patients in the Acthar high-dose group did not have their first post-Acthar EEG performed until after the Acthar was tapered to zero, a full 12 weeks after the initiation of therapy and 9 weeks after the maintenance dose of 150 U/m2/QD had been administered. In addition, there were patients in this study without any evidence of EEG testing after the initiation of Acthar treatment. Of note is that, in this study, Acthar was administered as a once-daily dose of 150 U/m2. Although this daily dose was equivalent to the total daily dose in CSR 222017-01, the Acthar in the CSR 222017-01 was administered as 2 divided daily doses (i.e., 75 U/m2 per dose). This difference in the dosing regimens results in a single ACTH plasma peak concentration in CSR 222017-05 compared to 2 ACTH plasma peak concentrations from the twice-daily dosing in CSR 222017-01.
The Sponsor concludes that the data from CSR 222017-05 at least support the efficacy of Acthar high-dose monotherapy with respect to one of the secondary endpoints (the Spasm Control Response)
even when the daily dose was administered once a day rather than as a divided dose administered twice a day as in CSR 222017-01.

Reviewer Note:
As discussed previously in this review, the endpoint of clinical interest is the combined endpoint (Overall Response) of both spasm cessation and

disappearance of hypsarrhythmia (the endpoint used in the pivotal study). There is no statistical significant difference between the two arms for this combined endpoint.

Why was there a lower response rate for the high dose arm in this supportive study compared to the pivotal study? There may have been differences in the patient population although the inclusion/exclusion criteria are similar. The most likely explanation seems to be that the pivotal study used a BID dosage for the high dose Acthar Gel which would be expected to give a more sustained ACTH levels and a greater cortisol response

Assuming that the BID dosage accounts for the higher response rate for the high dose (150 U/m2/day) seen in the pivotal study (CSR 222017-01) in comparison to the supportive study (CSR 222017-05) and also assuming that the CSR 222017-05 secondary endpoint of spasm control response indicates greater efficacy from the high dose arm compared to that of the low dose arm, the use of the high dose dosage given BID (as in the pivotal study can be considered to be supported over the use of a lower dose or a QD dose. However, the data is not as definitive as it would have been in a prospective contemporaneous dose response study of several doses in a single randomized population of infants with IS.

Additional Data Analysis to Assess Acthar Efficacy: CSR 222017-04 (Hrachovy, 1983)

Questcor was also able to obtain the primary study data from a second clinical trial by Dr. Hrachovy and colleagues entitled, “Double-blind Study of ACTH versus Prednisone Therapy in Infantile Spasms.” This study was a randomized, controlled, double-blind study that compared Acthar at a dose of 20 to 30 U/day administered as a single daily (20 to 30 U/QD) IM dose (Acthar low-dose) to prednisone at a dose of 2 mg/kg/day PO in patients with IS (CSR 222017-04).

Eligibility Criteria: Patients enrolled in the study were diagnosed with IS (clinical spasms with hypsarrhythmic EEG patterns). All study patients were under the age of 4 years, had onset of spasms prior to age 12 months, and had spasms ongoing at the time of entry into the study. An infant previously treated with any steroid or ACTH or Acthar treatment was not eligible for the study. Informed consent was obtained from each patient’s parent or guardian.

Evaluations: Before the initiation of treatment, patients were monitored for 24 to 48 hours to confirm the presence of IS and to establish a baseline seizure frequency. Patients were monitored at 2 weeks and at 6 weeks after discontinuation of therapy. Patients were evaluated throughout the study for safety.

Treatment Protocol: Patients were randomly assigned to receive Acthar 20 U/QD IM and a prednisone placebo PO or prednisone 2 mg/kg/day PO and an Acthar placebo IM, for 2 weeks. Acthar and matching placebo were administered as a single dose/day. Prednisone and matching placebo were administered as 2 mg/kg/day.

If the patient responded to therapy within the first 2 weeks, the dosage of the drug was tapered to zero over a 1- to 2-week period. Then, the patient was monitored at 2 weeks and 6 weeks after discontinuation of therapy to substantiate a continued response. If a patient did not respond after the first 2 weeks, therapy was either changed to the other study drug (Acthar 30 U/QD or prednisone 2 mg/kg/day) or the originally assigned treatment was continued; this treatment was continued for an additional 4 weeks, after which study drug was tapered to zero over a 2-week period. Nonresponders to the initial 2 weeks of therapy or to the additional 4 weeks of therapy as were then crossed over to the other drug after a 1-week washout period and the protocol was repeated. Efficacy Measures: The primary response to therapy in this study was defined as total cessation of spasms and disappearance of the hypsarrhythmic EEG pattern. Spasms and hypsarrhythmic EEG pattern were assessed by serial 24-hour video and EEG monitoring.

Reviewers of the serial long-term EEG and video monitoring studies were unaware of patients' treatment group assignment. Secondary endpoints included in the analysis included EEG changes in nonresponders and changes in mental and developmental status.

Results: Twenty-four patients were enrolled in the study; 12 patients were randomly assigned to Acthar low-dose and prednisone placebo, and 12 patients were randomly assigned to prednisone and an Acthar placebo. A total of 19 patients (19/24, 79.2%) had symptomatic etiology of IS and 5 patients (5/24, 20.8%) had cryptogenic etiology of IS.

Questcor's analysis of the efficacy data demonstrated that the overall response rates in the initial treatment phase were 5/12 (41.7%) for Acthar low-dose and 4/12 (33.3%) for prednisone. The 95% 2-sided confidence intervals for the initial phase overall response were (15.2%, 72.3%) and (9.9%, 65.1%), respectively. Overall response rates were greater than the historical comparator rate of 5% for spontaneous remission through 3 months and 11% through 6 months (Hrachovy 1991) and were better than the placebo rate of 5% reported in a placebo-controlled, randomized, controlled trial of vigabatrin comparing the response rate (complete elimination of spasms and hypsarrhythmia) (Appleton 1999).

The overall response rates reported in this study, suggest that both therapies have some efficacy in the treatment of this disorder.

Conclusions: The overall response seen in these analyses to both Acthar low-dose and prednisone was similar between the 2 treatments. The response rates were higher than the reported spontaneous remission rates for this disease. These data indicated that both therapies provide some degree of efficacy for the treatment of patients with IS.

Reviewer Note:

There was no statistical difference between the two arms of the study. Although the comparison to the historical placebo spontaneous remission rate and to the placebo arm of the Appleton vigabatrin study (which had a different primary outcome) is interesting and somewhat reassuring, it is not conclusive. Therefore, the Sponsor is correct in considering this study as "additional data" rather than a pivotal or supportive study.

Safety Studies

See section 7.1.1 of this review for a discussion of the studies used for safety analysis.

6 Review of Efficacy

6.1 Indication

Infantile Spasms

6.1.1 Methods

Because only one study was presented as pivotal, only one study as supportive, and only one study as additional evidence of efficacy, the three studies' results are presented individually. Each study is discussed in detail in section 5.3 of this review.

6.1.2 Demographics

See section 5.3 for each study

6.1.3 Subject Disposition

See section 5.3 for each study

6.1.4 Analysis of Primary Endpoint(s)

Table 1 Comparison of Response Rates across All Three Studies

(from the Agency's Statistical Review by Dr. Zhang)

	Acthar Gel						prednisone		
	High dose			Low dose					
Study	overall response rate (%)	EEG response rate (%)	clinical response rate (%)	overall response rate (%)	EEG response rate (%)	clinical response rate (%)	overall response rate (%)	EEG response rate (%)	clinical response rate (%)
222017-01	86.7	86.7	93.3	NA	NA	NA	28.6	28.6	28.6
222017-05*	62.5	66.7	79.2	48.1	51.9	51.9	NA	NA	NA
222017-04**	NA	NA	NA	41.7	75.0	41.7	33.3	41.7	33.3

* Based on mITT population defined by the sponsor

** The response rates are calculated using initial stage only

6.1.5 Analysis of Secondary Endpoints(s)

See section 5.3 for each study

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

The small number of patients did not allow for a meaningful comparison of the response of patients with cryptogenic vs. symptomatic infantile spasms.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No dose response study was performed.

The "additional evidence" efficacy study, CSR 222017-04, studied Acthar low-dose 20 U/day (the same daily dose of Acthar Gel studied in CSR 222017-05) compared to the prednisone 2 mg/kg/day (the same daily dose of prednisone studied in CSR 222017-

01). The data from CSR 222017-04 revealed no difference in the overall response between the patients randomized to Acthar low-dose compared to the patients randomized to prednisone. Of interest in this CSR 222017-04 study is that the response rate for the Acthar low-dose group of 5/12 (41.7%) was approximately the same response rate as was reported for the Acthar low-dose patients in the CSR 222017-05 mITT Population of 13/27 (48.1%). Similarly, the overall response for the prednisone patients in CSR 222017-04 of 4/12 (33.3%) is approximately the same response rate as was reported for the prednisone patients in CSR 222017-01 of 4/14 (28.6%). The concordance of the response rates of the two arms of CSR 222017-04 to the results seen with similar treatment arms in the two other studies, CSR 222017-01 and CSR 222017-05, provides some confirmation of the conclusions reached in the pivotal (CSR 222017-01) and supportive (CSR 222017-05) efficacy studies.

However, the data is not as definitive as it would have been in a prospective contemporaneous dose response study of several doses in a single randomized population of infants with IS.

6.1.9 Discussion of Persistence of Efficacy (Relapse) and/or Tolerance Effects

Given the relatively short-term treatment of 4 weeks (2 weeks of high dose with a two week taper) proposed in this NDA, it is important to consider what the relapse rate is after treatment is stopped. Unfortunately, the relapse data is very limited.

CSR 222017-01 (Baram 1996)

The publication and the clinical study report with protocol from the pivotal study CSR 222017-01 (Baram 1996) do not indicate how relapses were determined. The Sponsor was asked about method of recurrence detection on March 19, 2010 and replied that this could not be determined. For the purpose of my review, it is assumed that detection of a recurrence of spasms was based on caretakers notifying the investigators who may or may not have verified the recurrence with a video-EEG study. The fact that recurrence of spasms would be an “all-or-none” phenomenon suggests that the caretakers would be reasonably likely to detect a recurrence of spasms which would recur in clusters rather than subtle isolated spasms. Table 2 of the Baram publication shows that two of the 13 patients who responded to Acthar gel relapsed (a symptomatic female infant treated at 3 months of age and followed-up for 2 months; a symptomatic male infant treated at 6 months of age and followed-up for 17 months). This suggests a relapse rate of at least 2/13 (15%) but there is no indication as to how many months after treatment the recurrence was observed. Of the remaining 11 infants who responded to Acthar gel, 3 had no reported recurrence but were only followed for 1 month after treatment and 8 had no reported recurrence after being followed for 6 months or more (mean 17 months, range 6-37 months). Thus, it is possible that the

recurrence rate was higher if one assumes that one or more of the infants with short follow-up times had a recurrence occurring after the time of follow-up with the investigators.

CSR 222017-05 (Hrachovy 1994)

The supportive efficacy study CSR 222017-05 (Hrachovy 1994) relied on caregiver report to detect relapse after the treatment period. If the caregiver reported relapse, this was verified with video-EEG monitoring. In the completed patient population, 13/26 high dose patients responded and 14/24 low dose patients responded. The relapse rate for the high dose arm responders was 2/13 patients (15%). In the published article, the relapse rate for the low dose arm responders was 3/14 patients (21%). There was no statistical difference between these relapse rates. Questcor re-analyzed the data using the response data for the mITT population and found similar relapse rates: 3/15 (20%) of responders in the high dose arm relapsed and 2/13 (15%) of the responders in the low dose arm relapsed.

Reviewer Note:

Although very limited, the relapse rate data suggests a relapse rate in the range of 15 to 30%. This is similar to the relapse rate range observed in studies of oral vigabatrin presented at the FDA Advisory Committee of January 2009.

Additional Discussion submitted by the Sponsor on June 8, 2010

In response to the Agency's request following the Advisory Committee meeting (section 9.3 of this review), the Sponsor submitted a paper entitled (b) (4)

The Sponsor addressed issues concerning relapse rates and possible retreatment with Acthar Gel:

The Sponsor concluded that the relapse rate is between 15-21% for patients who have a combined response of cessation of spasm and elimination of hypsarrhythmia on EEG. This is based on the studies summarized in the following table from the June 8 submission.

Study	Type of Study: Treatments	Acthar/Comparator Dose	# of Patients	Response Rate	Relapse Rate	Average±SD (Range) Time of Follow-Up [months]
Baram 96	RCT: Acthar vs.	150 U/m^2 /d (75U/m^2 BID)	15	87%	15%	15.1±13.66 (2-48)
	Prednisone	2mg/kg (1 mg BID)	14	27%	NR	16.9±14.39 (2-46)
Snead 83	Retrospective: Acthar	150 U/m^2 /d (75U/m^2 BID)	30	97%	20%	24.6
	vs. Prednisone	3 mg/kg/d	22	50%	15%	47.1
Snead 89	Prospective: Acthar	150 U/m^2 /d (75U/m^2 BID)	15	93%	14%	43.3
Hrachovy 94*	RCT: Acthar Low Dose	20 U QD (≈50U/m^2 QD)	26	58%	21%	1.9±0.47 (0.5-2.6)
	vs. Acthar High Dose	150 U/m^2 QD	24	50%	15%	3.1±1.55 (1.4-9.5)
Hrachovy 83#	RCT: Acthar vs.	20 U QD (≈50U/m^2 QD)	12	42%	33%	12-33
	Prednisone	2 mg/kg QD	12	33%	28%	12-33
		Acthar Patients	122	89/122 (73%)	18/89 (20%)	

NR = Not reported
* Time to follow-up data was not included in the publication: this data was calculated based on Questcor's analyses (CSR 222107-05)
# The complex design of this study and the data provided did not allow Questcor to calculate a relapse rate or even confirm these published relapse rates

Reviewer Note:

The Baram 96, Hrachovy 94, and Hrachovy 83 studies in the table correspond to Studies 01, 05, and 04 respectively as discussed in this review. The table is essentially the same as slide CE-10 presented as a PowerPoint presentation at the Advisory Committee.

As the Sponsor points out, only Study 05 (Hrachovy 95) has the relapse data in the publication based on the mITT population who had achieved the combined response). The Sponsor comments that Dr. Baram (pivotal study -01) did not have data on relapse in the clinical study report data-base; however, a relapse rate of 15% is given apparently based on the same criteria I used at the beginning of this section o my review which was available in draft to the sponsor just prior to the Advisory Committee. As noted above, the recurrence rate for the Baram study -01 could be higher given that 3 of the infants only had a 1 month follow-up after responding to therapy

The Sponsor notes that the relapse rate for study -04 (Hrachovy 83) is higher (33%). The Sponsor suggests this may be due to the ;lower dose of Acthar Gel used in this study compared to the pivotal Baram study (although the dose is the same as in Hrachovy 94 study -05 and although the prednisone relapse rate is also higher despite being the same as in the Baram study). An alternative explanation may be that all patients in this study had at least 12 months of follow-up whereas some of the patients in studies -01 and -05 only had as little as 1-2 months of follow-up as indicated in the range of follow-up in the last column of the table.

In spite of the shortcomings of the data in the table, it seems reasonable to conclude with the Sponsor that the relapse rate is about 15-33% in patients who had a combined response.

The Sponsor notes that the time to relapse cannot be determined form the study data. However, the sponsor states that their consultants'' experience indicates that relapse occurs typically within 2-3 months after response and that recurrence after 6 months is rare. This also reflects the experience of the pediatric neurologist members of the Advisory "committee expressed during discussion.

The Sponsor concluded that lower relapse rates and improved long-term outcome are related to how quickly a patient achieves Overall Response on Acthar after a diagnosis of Infantile Spasms.

Reviewer Note:

The Sponsor reviews the medical literature that supports the current clinical practice consensus that infants treated within 1 month of appearance of the spasms have a somewhat higher response rate and somewhat improved prognosis. As previously discussed this data is suggestive but not conclusive.

The Sponsor concludes that "(b) (4)".

Reviewer Note:

This seems reasonable, but is not conclusive. As discussed above, this is not based on study data but on the clinical experience of the Sponsor's consultants.

The Sponsor concludes that retreatment with Acthar Gel after a recurrence should be a decision made by the physician and parent. Ther sponsor concludes that the following factors should be taken into account in assessing the risk/benefit o retreatment:

(b) (4)

Reviewer Note:
The Sponsor addresses several clinical scenarios. The Sponsor notes that no trials or cohort studies directly address this issue. Some studies allowed for retreatment and this data is cited as supportive of the conclusion. The conclusion is based largely on their consultants' experience rather than adequate data; although it seems reasonable given our current state of knowledge, it is not conclusive. Therefore, this particular approach to clinical practice should not be included in the labeling to the exclusion of other reasonable approaches.

6.1.10 Additional Efficacy Issues/Analyses
The Sponsor concludes that the evidence presented in this Complete Response from the independent analyses of the data obtained in studies conducted by Drs. Baram (CSR 222017-01) and Hrachovy (CSR 222017-05 and CSR 222017-04), together with the AAN Practice Parameter recommendation (Mackay 2004) and the published literature, all support Acthar as an effective treatment for patients with IS. These data, when considered in their entirety, support the approval of Acthar for the IS indication.

The pivotal efficacy study, CSR 222017-01, demonstrated that Acthar at a dose of 150 U/m2/day administered as 75 U/m2/bid IM for 2 weeks followed by a 2-week taper was superior to prednisone 2 mg/kg/day administered as 1 mg/kg/bid in patients with IS as determined by the overall response of spasm cessation and resolution of the hypsarrhythmia pattern on EEG (13/15, 86.7% versus 4/14, 28.6%, respectively, P=0.0015). This study also showed a statistically significant difference in the spasm cessation response alone (P=0.0015) and in the resolution of the hypsarrhythmia pattern on EEG (P=0003) in favor of the patients randomized to receive Acthar compared to those randomized to receive prednisone. These significant differences, seen in such a small study, provide convincing and clear-cut evidence of the efficacy of Acthar at the studied dose of 150 U/m2/day administered IM in 2 divided doses for 2 weeks followed by a 2-week taper in the treatment of IS patients.

The supportive efficacy study, CSR 222017-05 studied 2 doses of Acthar in patients with IS. The Acthar high-dose regimen consisted of treatment with Acthar as a single daily dose of 150 U/m2/QD for 3 weeks, followed by a 9-week taper. The Acthar low-dose regimen consisted of treatment with Acthar as a single daily dose of 20 U/QD for 2 weeks. Patients in the Acthar high-dose arm were not assessed for efficacy using an EEG assessment until the full 12 weeks of treatment whereas patients in the Acthar low-dose group had an EEG after 2 weeks of treatment with an upward dose adjustment to 30 U/QD for 4 additional weeks if spasms and/or the hypsarrhythmic EEG pattern persisted or the dose was tapered if the patient had responded to the Acthar low-dose treatment based on both spasms cessation and resolution of the hypsarrhythmic EEG pattern. It is likely that the study design difference in the timing of

the post treatment EEG assessment (patients who received Acthar high-dose regimen in this study were not to be re-assessed for EEG response until the full 12 weeks of Acthar therapy, whereas patients in the Acthar low dose arm had their first post treatment EEG assessment 2 weeks after starting treatment) had negatively impacted the ability for the Acthar high-dose patients to meet the primary efficacy endpoint in this study, the Overall Response (cessation of spasms and resolution of the hypsarrhythmic EEG pattern). The fact that this study demonstrated a statistically significant difference in the Spasm Control Response in the mITT Population (the primary study population) as well as the Spasms Population with a trend toward this result in the other 2 supportive populations, the ITT Population (used for the sensitivity analysis) and the Completed Patients Population, demonstrate that the Acthar high-dose treatment was more efficacious than the Acthar low-dose treatment, particularly when taking into account the EEG measurement issues described above.

The additional efficacy study, CSR 222017-04, studied Acthar low-dose 20 U/day (the same daily dose studied in CSR 222017-05) compared to the prednisone 2 mg/kg/day (the same daily dose studied in CSR 222017-01). The data from CSR 222017-04 revealed no difference in the overall response between the patients randomized to Acthar low-dose compared to the patients randomized to prednisone. Of interest in this study is that the response rate for the Acthar low-dose group of 5/12 (41.7%) was approximately the same response rate as was reported for the Acthar low-dose patients in the mITT Population CSR 222017-05 of 13/27 (48.1%). Similarly, the overall response for the prednisone patients in CSR 222017-04 of 4/12 (33.3%) is approximately the same response rate as was reported for the prednisone patients in CSR 222017-01 of 4/14 (28.6%). The concordance of the response rates of the two arms of CSR 222017-04 to the results seen with similar treatment arms in the two other studies, CSR 222017-01 and CSR 222017-05, provides some confirmation of the conclusions reached in the pivotal (CSR 222017-01) and supportive (CSR 222017-05) efficacy studies in this NDA.

7 Review of Safety

Safety Summary

Reviewer Note: The Sponsor notified the Agency in a teleconference on March 22 that it intended to revise the "treatment groups" (dose categories based on the maximal daily dose of Acthar Gel received) used to integrate the safety data across safety studies in their NDA submission (see 7.1.3 and 7.2.1 of this review). This means that the safety summary tables concerning the 319 patients (see section 7.1.1 of this review) in the Sponsor's briefing document for the Advisory

Committee differ slightly from the summary tables presented in their NDA submission and reviewed in this review.

7.1 Methods

This section reviews the safety data presented by the Sponsor in the integrated summary of safety, in the clinical study reports from the individual studies cited in section 7.1.1 below, and from the published articles from the three studies discussed in the efficacy section of this review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Questcor could not obtain safety data from the pivotal study (CSR222-017-01, Baram) although these patients are presumed to be among the patients evaluated in the retrospective chart review by Partikian and Mitchell discussed below as CSR 222017-02.

Questcor obtained source safety data from the following 4 studies:

A study conducted by Partikian and Mitchell (Partikian 2007). Questcor's analyses of these safety data are presented in this Complete Response as CSR 222017-02. This study presumably contained the safety data for the patients treated in the randomized controlled trial conducted by Baram and reported in this submission as CSR 222017-01.

Questcor also conducted its own protocol to obtain safety data from patients treated at 4 clinical sites in the United States. These data are presented in this Complete Response as CSR QSC007-ACT-002.

Questcor obtained source data from the 2 of the RCTs conducted and published by Hrachovy and colleagues (Hrachovy 1994, Hrachovy 1983); Questcor's independent analyses of these data are presented in this Complete Response as CSR 222017-05 and CSR 222017-04, respectively.

These four studies are shown in the table below.

Study	Description	Number of Acthar Gel-treated patients contributed to Integrated Safety Tables
CSR 222017-02	Partikian and Mitchell retrospective chart review	84

CSR QSC007-ACT-002	Questcor retrospective chart review at 4 sites	178
CSR 222017-05	Hrachovy 1994 Study of Acthar Gel High vs Low Dose (charts reviewed retrospectively for safety data)	57
CSR 222017-04	Hrachovy 1983 study of ACTH vs Prednisone (patients on Acthar gel not identifiable in retrospective chart review)	None
Total patients in Integrated Safety Tables		**319**

The division of the 319 patients into three dosage categories (Questcor Recommended Dose, Other High Dose, and Low Dose) is discussed in section 7.2.1 of this review.

These four studies are summarized in the following paragraphs.

CSR 222017-02

Clinical study report CSR 222017-02, entitled, "Retrospective Analysis of Adverse Events Associated with Treatment of Infantile Spasms with Acthar Gel," was a retrospective chart review. The primary objective of this study was to analyze retrospective data provided by Drs. Partikian and Mitchell to assess the safety and tolerability of Acthar administered using a standard treatment schedule consisting of a treatment phase followed by a taper phase. The secondary objective was to report the safety data from patients reported in the pivotal efficacy study that compared Acthar to prednisone in patients with IS (CSR 222017-01); safety data from these patients were likely contained within the data obtained from Drs. Partikian and Mitchell for this analysis based on the dates of treatment. Questcor obtained the safety data from the investigators, and with the investigators' permission, Questcor performed an independent analysis for submission in this sNDA; these analyses are presented in CSR 222017-02.

Study Design: Drs. Partikian and Mitchell reviewed the charts of all patients with IS (International Classification of Diseases code 345.6) admitted to Children's Hospital of Los Angeles (CHLA) between January 1990 and August 2006 (Partikian 2007). In addition, they identified outpatients from Neurology Division records of patients with IS whose treatment was initiated without hospital admission. Data from the chart review were collected on data collection forms developed by the Investigators. Drs. Partikian

and Mitchell provided these completed forms to Questcor; Questcor then performed its own independent analysis of these data.

Patients were included in the study based on the diagnosis of IS, with spasms confirmed by either clinical observation or on video-EEG, with EEG evidence of classical or modified hypsarrhythmia or multifocal independent spike discharges. Patients with an atypical EEG pattern were included if an attending pediatric neurologist intended to treat the child as having IS based on clinical criteria of spasms with psychomotor regression.

Demographic characteristics and baseline variables included sex, age at onset of spasms and onset of treatment, lag time from onset of spasms to initiation of treatment, etiology, IS history, developmental status, previous treatment with antiepileptic drugs (AEDs), and pre-existing medical conditions. Treatment variables included initial treatment type, drug dosage, and schedule of administration.

Treatment Protocol: Not all patients received Acthar Gel. Treatment choice was made by the attending child neurologist for the individual patient and not by randomization. When Acthar Gel treatment was chosen, Acthar treatment was administered by IM injection according to a standard protocol. The treatment schedule started with 150 U/m2/day divided into 2 daily doses for the first 1 to 2 weeks, and then tapered beginning with 75 U/m2/day for 1 week, then tapered rapidly to an alternate-day schedule for the next 3 to 4 weeks, which was followed by taper-off treatment. Treatment intervals could not be confirmed from the data provided.

Safety Measures: Assessments of safety and tolerability were collected from patient charts at baseline and at 3 follow-up intervals. The first follow-up interval included all visits that occurred 1 to 3 weeks after initiation of treatment. The second follow-up interval included all visits that occurred 4 to 8 weeks after the start of therapy. The third follow-up interval included visits that occurred 3 or more months after treatment initiation. Safety measures included AEs (parent-reported, major, and serious AEs [SAEs], changes in weight and blood pressure [BP]), changes in medication, and development of new seizure during the treatment period.

Results: The Questcor database had data from 130 patients (each receiving either Acthar Gel or an alternative therapy) from the original published study (Partikian 2007), consisting of patients treated at CHLA between January 1990 and August 2006 for IS, and also data from 29 additional patients, consisting of patients with IS treated at CHLA since the end of the original study through April 2008. The 130 patients from the original published study included **20** patients who received Acthar as initial treatment for IS in the era of the Baram 1996 study (Era 1) and **45** patients who received Acthar as initial treatment for IS after the era of the Baram 1996 study (Era 2). Of the 29 additional patients, **19** received Acthar as initial treatment for IS (Era 3).

Therefore, a total of 84 patients (20 + 45 + 19) received Acthar as initial treatment for IS (Overall: Eras 1, 2, and 3, combined). The analysis of safety for patients who received Acthar as initial treatment for IS in this retrospective data review is as follows:

• Parent-reported AEs consisted largely of irritability, excessive appetite, infections, and sleep difficulties. These tended to be reported during the first follow-up interval, when the patients were on the highest dose of drug, and decreased over time as the drug was tapered and discontinued.

• More than 33% (28/84) had at least 1 potentially significant systolic BP (SBP) measurement during the first follow-up interval compared with only 17.9% (15/84) at baseline. The number of patients with potentially significant SBP measurements decreased to 21.4 % and 3.6% during the second (18/84) and third (3/84) follow-up intervals, respectively. The results for diastolic BP (DBP) were similar, where 23.8% (20/84) had potentially significant measurements during the first follow-up interval compared with 14.3% (12/84) of patients at baseline. The number of patients noted to have potentially significant DBP measurements decreased to 10.7% and 4.8% during the second (9/84) and third (4/84) follow-up intervals, respectively.

• The most common SAEs included nervous system disorders, infections, and hospitalizations. The nervous system disorders were all seizure-related, but it was not possible to separate new seizures from exacerbations of the IS or progression of IS to other seizure disorders.

• Common laboratory abnormalities reported included white blood cell elevation, low serum potassium, elevated liver function tests, and low hemoglobin.

Mean change from baseline for weight averaged 11.6%, 17.8%, and 25.7% over the first, second, and third follow-up intervals, respectively. The increases in weight over time may have been due to both background growth in infants as well as to Acthar-induced weight gain.

• Safety results for patients who received Acthar during Era 1, representing patients previously evaluated for efficacy by Questcor (CSR 222017-01), were consistent with the safety findings for the patients who received Acthar in Era 2 and Era 3.

• There were no SAEs reported for patients who received prednisone in Era 1 of this study. This may be related to the fact that these patients appeared to have a shorter duration of therapy when compared to Acthar, possibly due to lack of efficacy of the prednisone treatment for IS.

Sponsor's Conclusions: The AEs reported in this study in patients treated with Acthar are well known to occur with this therapy. None of the findings from this retrospective chart review were unexpected. The AEs reported are readily recognized and managed by routine clinical care and medical interventions. In particular, blood pressure elevations that may occur with Acthar may be managed, if medically necessary, with antihypertensive drug therapy.

CSR QSC007-ACT-002

Clinical study report CSR QSC007-ACT-002, entitled, “Determination of the Adverse Effect Profile for Patients with Infantile Spasms Treated with H.P. Acthar Gel (ACTH): A Retrospective Review,” was a retrospective chart review study to determine the AE profile of patients with IS treated with Acthar. Patients were included in the study based on the diagnosis of IS and age at first treatment with Acthar.

The primary objective of this study was to assess the AE profile in patients with IS treated with Acthar high-dose (approximately 150 U/m2/day [range from 125 to 175 U/m2/day]) given in 2 divided doses administered to patients from January 2000 to 01 May 2008 at 4 participating clinical centers.

Study Design: Data review and capture was planned for the period January 2000 to 01 May 2008. Potential cases were identified by querying the hospital, pharmacy, and/or clinical records for patients from the years 2000 through 2008. The data were extracted from clinic and/or hospital charts including the treating doctors’ notes, EEG reports, magnetic resonance imaging reports, and other clinical information.

For the data analysis, patients were categorized into 1 of 3 treatment groups based on the maximum daily dose of Acthar administered as shown below:
• Questcor Recommended Dose: 150 U/m2/day (Dose range within the range ≥ 135 and ≤ 160 U/m2/day), divided, bid
• Other High Dose: Dose ≥ 80 U/m2/day but outside the Recommended Dose (included patients with a maximum dose ≥ 80 U/m2/day but outside the Recommended Dose range and patients with a maximum dose within the Recommended Dose range that was not administered divided bid)
• Low Dose: Dose < 80 U/m2/day

Treatment Protocol: Acthar treatment was administered by IM injection according to clinical practice at each study site.

Data Methods: Procedures used to collect, to analyze, and to ensure the integrity of study data are provided in the final study report (see CSR QSC007-ACT-002).

Safety Measures: For assessment of AEs, data were collected from patient charts at baseline, at subsequent visits for evaluation of Acthar treatment, and at a final visit. The final visit was defined as any clinic visit that occurred at least 2 weeks following the final dose of Acthar or the last recorded visit at or near 2 weeks.

Results: One hundred and seventy-eight (178) patients were included in the analysis data set. Analysis of data from this retrospective study of patients who received Acthar as treatment for IS demonstrated the following:

- Over half of all patients (59.0%, 105/178) experienced 1 or more AEs during the study. The proportions of patients with 1 or more AE were similar in the Other High Dose and Recommended Dose groups (67/105, 63.8% and 31/50, 62.0%, respectively). The Low Dose group had the smallest proportion of patients with 1 or more AEs (7/23, 30.4%).
- The most common AEs in all groups combined were: irritability (16.3%), Cushingoid appearance (9.6%), hypertension (9.6%), and increased appetite (6.2%). The most common AEs (occurring in >5% of all patients) in the Recommended Dose group were hypertension (18.0%), irritability (12.0%), and left ventricular hypertrophy (LVH) (8.0%). In the Other High Dose group, the most common AEs were irritability (19.0%), Cushingoid appearance (13.3%), increased appetite (10.5%) and hypertension (6.7%). The most common AEs in the Low Dose group were irritability (13.0%), Cushingoid appearance (4.3%), and hypertension (4.3%).
- There were 20 patients overall who experienced 1 or more SAEs during the study, most of which were judged to be related (possibly, likely) and were consistent with the known pharmacology of Acthar. Most patients required no treatment or were adequately treated with medication for the resolution of their SAE.
- One death, due to aspiration pneumonia, was reported in the Other High Dose group and considered to be possibly due to Acthar treatment.
- The most common parent-reported AEs in all patients were irritability, upper gastrointestinal irritability or gastroesophageal reflux disease, infections, drowsiness, sleep difficulties, reduced appetite, respiratory difficulties, excessive appetite, fever, and increased secretions/drooling.
- During the first follow-up interval, 14.0% (25/178) of patients had a planned downward titration of Acthar and 3.9% (7/178) of patients had Acthar decreased prematurely due to an AE. In the second follow-up interval, 73.6% (131/178) of patients had a planned downward titration of Acthar and 0.6% (1/178) of patients had Acthar decreased prematurely due to an AE.
- There were multiple patients with abnormal laboratory values throughout the study; very few resulted in an action being taken by the investigator.
- There were reversible increases in SBP, DBP, and potentially significant BPs during Acthar treatment, which returned to baseline following discontinuation of treatment. These tended to be more frequent in the Recommended Dose group and Other High Dose group compared to the Low Dose group, but the differences between treatment groups were not significant.

Sponsor's Conclusions: Analysis of data from this retrospective study of patients who received Acthar as treatment for IS demonstrated the following:

- The AEs reported in this study are well known to occur with Acthar administration in patients with IS. None of the findings from this retrospective chart review were unexpected.
- The AEs reported were readily recognized and managed by routine clinical care and medical interventions. In particular, blood pressure elevations that occurred with Acthar were readily managed, if medically necessary, with antihypertensive drug therapy.

CSR 222017-05

"High-dose, Long-duration versus Low-dose, Short-duration Corticotropin Therapy for Infantile Spasms" was a prospective, controlled, randomized, single-blind study that compared an Acthar high-dose regimen to Acthar low-dose regimen in patients with IS.

The Acthar high-dose regimen consisted of Acthar given at a dose of 150 U/m2/day as a single IM dose for 3 weeks followed by a 9-week taper; the Acthar low-dose regimen consisted of Acthar 20 U/day as a single IM dose for 2 weeks followed by a 2-week taper in responders or a dose escalation to 30 U/day in nonresponders. The principal investigator, Dr. Hrachovy and his colleagues had previously published the study results from their analyses of the data (Hrachovy 1994). Questcor obtained the source data from the investigators, and with the investigators' permission, Questcor performed an independent analysis for submission in this sNDA; these analyses are presented in the clinical study report CSR 222017-05.

Study Design: Patients enrolled in the study were diagnosed with IS defined by both the presence of clinical spasms and a hypsarrhythmic EEG pattern. All study participants were under the age of 4 years, had onset of spasms prior to the age of 12 months, and continued to have spasms at the time of entry into the study. Patients who had previously received ACTH or Acthar or corticosteroid therapy for their spasms were not eligible for the study. Informed consent was obtained from each patient's parent or guardian.

Prior to the initiation of treatment, patients were monitored using a video-EEG for up to 24 hours in order to confirm the presence of IS and to establish a baseline seizure frequency. Patients were monitored with video-EEGs 2 to 3 times during the treatment period; the treatment period was 12 weeks for the high-dose and 6 weeks for low-dose. As per the study protocol, the 2 dosing groups had different schedules as to when the post-Acthar EEGs were to be performed. The patients randomly assigned to the Acthar low-dose group were scheduled to have their first post-Acthar EEG performed 2 weeks after the start of treatment, whereas patients in the Acthar high-dose group did not have their first post-Acthar EEG performed until after the Acthar was tapered to zero, a full 12 weeks after the initiation of therapy and 9 weeks after the maintenance dose of 150

U/m2/qd had been administered. Patients were evaluated throughout the study for spasm cessation and safety.

Treatment Protocol: Eligible patients were first stratified as having either cryptogenic or symptomatic IS and then randomized to receive treatment with either high-dose Acthar (150 U/m2/day administered as a single daily dose IM for 3 weeks, followed by 80 U/m2/day IM for 2 weeks, then 80 U/m2/qod IM for 3 weeks, then 50 U/m2/qod IM for 1 week, and then Acthar was tapered to zero over 3 weeks) or Acthar low-dose (a single daily dose of 20 U/day IM for 2 weeks). Nonresponders to the high-dose Acthar regimen were treated with prednisone 2 mg/kg/day orally (PO) for 4 to 6 weeks, and then followed in a routine clinical manner. Nonresponders to low-dose Acthar had their Acthar increased to 30 U/day for an additional 4 weeks followed by a taper to zero over a 2-week period.

There were 57 patients in the Safety Population (patients who received at least one dose of Acthar Gel).

Data Methods: Procedures used to collect, to analyze, and to ensure the integrity of study data are provided in the final study report (see CSR 222017-05).

Safety Measures: Patients were monitored for safety throughout the study. Adverse events were recorded to the patient charts as were the results of clinical laboratory evaluations (complete blood count [CBC], blood glucose, electrolytes, urinalysis), vital signs (BP, height, weight, pulse and respiratory rates), concomitant medications, physical examination findings, chest x-rays, and other imaging studies (computed tomography [CT], magnetic resonance imaging [MRI]), as required.

Results:

- The majority of patients (51/57, 89.5%) had 1 or more AEs during the study. The rate of AEs in the Acthar high-dose group (26/28, 92.9%) was similar to that in the Acthar low-dose group (25/29, 86.2%).
- The most frequently reported (≥ 10% of patients) AEs in Acthar-treated patients (high-dose and low-dose) were candidiasis (10/28, 35.7% and 11/29, 37.9%), Cushingoid appearance (8/28, 28.6% and 6/29, 20.7%), otitis media (7/28, 25.0% and 6/29, 20.7%), irritability (4/28, 14.3% and 5/29, 17.2%), pyrexia (5/17.9% and 4/29, 13.8%), acne (6/21.4% and 3/29, 10.3%), diarrhea (6/28, 21.4% and 2/29, 6.9%), blood pressure increase (5/28, 17.9% and 2/29, 6.9%), and vomiting (3/28, 10.7% and 3/29, 10.3%).
- The most frequently reported (≥ 10% of patients) parent-reported AEs in Acthar-treated patients (high-dose and low-dose) at any time during the entire follow-up period were drowsiness (5/28, 17.9% and 3/29, 10.3%), irritability (23/28, 82.1% and 20/29, 69.0%), sleep difficulties (13/28, 46.4% and 10/29, 34.5%), excessive appetite (14/28, 50.0% and 7/29, 24.1%), reduced appetite (12/28, 42.9% and

9/29, 31.0%), infections (11/28, 39.3% and 12/29, 41.4%), fever (8/28, 28.6% and 9/29, 31.0%), and respiratory difficulties (7/28, 25.0% and 3/29, 10.3%).

- The most frequently reported (≥ 10% of patients) physical examination findings in Acthar-treated patients (high-dose and low-dose) at any time during the entire follow-up period were facial rash (15/28, 53.6% and 10/29, 34.5%), thrush (oral) (12/28, 42.9% and 10/29, 34.5%), skin (other rashes, hyperpigmentation) (17/28, 60.7% and 7/29, 24.1%), Cushingoid features (12/28, 42.9% and 10/29, 34.5%), muscular abnormality (7/28, 25.0% and 0/29, 0.0%), and dysmorphic feature (5/28, 17.9% and 2/29, 6.9%).
- There was 1 death in the study. Patient 90-004 was a 3.3 month-old male infant with a history of IS, microcephaly, and severe developmental delay at the start of treatment who was repeatedly hospitalized with severe respiratory symptoms, developed pulmonary edema, respiratory failure, and died of cardiac arrest at 4.5 months of age. The patient was treated with Acthar doses of 20 to 40 U/qd over several weeks.
- Nine (9) patients (4 Acthar high-dose, 5 Acthar low-dose) had 1 or more SAEs during the study. Serious AEs in the Acthar high-dose group were dehydration, bronchopneumonia, increased blood pressure, skin discoloration, and decreased appetite. Serious AEs in the Acthar low-dose group were bronchiolitis, acute respiratory distress syndrome, pneumonia, pulmonary edema, respiratory failure, and cardiac arrest, status epilepticus, otitis media, dyspnea, and cellulitis.
- There was no difference between the 2 dose groups in the number of patients who discontinued the study early due to AEs. Four (4) patients (1 Acthar high-dose, 3 Acthar low-dose) had 1 or more AEs leading to discontinuation during the study. The AEs were increased blood pressure and skin discoloration in the patients in the Acthar high dose group, and pyrexia, increased blood pressure, and otitis media in the patients in the Acthar low-dose group.

Sponsor's Conclusions: The AEs in this study reported in patients assigned to the Acthar high-dose regimen are well known and are readily managed by routine clinical care and routine medical intervention. Acthar high-dose has an acceptable benefit-risk profile for the treatment of patients with IS, particularly given the catastrophic nature of this disorder if left untreated.

CSR 222017-04

Questcor was also able to obtain the primary study data from a second clinical trial by Dr. Hrachovy and colleagues entitled, "Double-blind Study of ACTH [Acthar] versus Prednisone Therapy in Infantile Spasms." This study was a randomized, controlled, double-blind study that compared Acthar at a dose of 20 to 30 U/day given IM as a single daily dose (Acthar low-dose) to oral prednisone 2 mg/kg/day in patients with IS.

Reviewer Note: As discussed below under "Results" of this study, the safety data from these CSR 222017-04 patients could not be included in the integrated safety tables since the treatment arm to which each patient had been assigned could not be determined during the retrospective chart review for safety data.

Eligibility Criteria: Patients enrolled in the study were diagnosed with IS (clinical spasms with hypsarrhythmic EEG patterns). All study patients were under the age of 4 years, had onset of spasms prior to age l2 months, and had spasms ongoing at the time of entry into the study. An infant previously treated with any steroid, Acthar or ACTH treatment was not eligible for the study. Informed consent was obtained from each patient's parent or guardian.

Evaluations: Before the initiation of treatment, patients were monitored for 24 to 48 hours to confirm the presence of IS and to establish a baseline seizure frequency. Patients were monitored at 2 weeks and at 6 weeks after discontinuation of therapy. Patients were evaluated throughout the study for safety.

Treatment Protocol: Patients were randomly assigned to receive Acthar low-dose 20 U/day IM and a prednisone placebo PO or prednisone 2 mg/kg/day PO and an Acthar placebo IM, for 2 weeks. Acthar low-dose and matching placebo were administered as a single dose/day. Prednisone (2 mg/kg/day) and matching placebo were administered as a single dose/day. If the patient responded to therapy within the first 2 weeks, the dosage of the drug was tapered to zero over a 1- to 2-week period. Then, the patient was monitored at 2 weeks and 6 weeks after discontinuation of therapy to substantiate a continued response. If a patient did not respond after the first 2 weeks, therapy was either changed to the other study drug (Acthar 30 U/day or prednisone 2 mg/kg/day) or the originally assigned treatment was continued; this treatment was continued for an additional 4 weeks, after which study drug was tapered to zero over a 2 week period. Nonresponders to the initial 2 weeks of therapy or to the additional 4 weeks of therapy as were then crossed over to the other drug after a 1-week washout period and the protocol was repeated.

Safety Measures: Safety was evaluated throughout the study. The Questcor analysis, however, only included the safety measures that were reported in the study publication, specifically, the incidence of sustained high BP > 140/90 mmHg and cerebral shrinkage. **When the patient charts were obtained for a retrospective chart review for safety data (as had been done with CSR 222017-05), there was no method to determine into which treatment arm the patients had been assigned.**

Results: Twenty-four patients were enrolled in the study; 12 patients were randomly assigned to Acthar low-dose and prednisone placebo, and 12 patients were randomly assigned to prednisone and an Acthar placebo. A total of 19 patients (19/24, 79.2%) had symptomatic etiology of IS and 5 patients (5/24, 20.8%) had cryptogenic etiology of IS.

With respect to safety, limitations of the data available from the chart review did not permit confirmation of published results. Specifically, the data on adverse findings were not attributable to one arm of the study versus the other (low dose ACTH vs oral prednisone). Therefore, this data from CSR 222017-04 was not integrated into the integrated safety results of the three other studies [CSR 222017-02, the Questcor Retrospective Safety Study (CSR QSC007-ACT-002), and CSR 222017-05].

Questcor's analysis of the safety data demonstrated the following:
- Isolated instances of elevated BP >140/90 mmHg occurred during the study but no information was available to confirm that there were sustained elevations in BP.
- The numbers of patients with CT scans showing evidence of brain shrinkage were too few in number to draw any conclusions regarding the effect of treatment.

Sponsor's Conclusions: With respect to safety, limitations of the data available from the chart review did not permit confirmation of published results.

- Patients treated with Acthar or prednisone showed evidence of increased ventricular size or increased subarachnoid space, or both. The numbers of patients with CT scans showing evidence of brain shrinkage were too few in number to draw any conclusions regarding the effect of treatment.
- Hypertension developed with both Acthar and prednisone treatment. Isolated instances of elevated BP >140/90 mmHg occurred during the study but no information was available to confirm that there were sustained elevations in BP.

Reviewer's comment:

NDA submissions usually have blinded prospective safety data from pivotal trials collected during the study according to a prospective protocol. This quality of safety data is not available for this submission.

Supportive study CSR 222017-05 was a prospective efficacy study but the safety data was collected by an unblinded retrospective chart review of the participating patients according to a retrospective protocol for collection for safety data. A similar retrospective chart review was not possible for pivotal study CSR 222017-01 or for study CSR 222017-04 as discussed above.

Studies CSR 222017-02 and CSR QSC007-ACT-002 are retrospective chart reviews of larger numbers of patients the majority of which were not enrolled in a clinical study. They offer a larger, arguably more representative sample of the proposed treatment population.

7.1.2 Categorization of Adverse Events

Serious adverse events were those adverse evetns that required that the patient have an emergency room visit and/or hospitalization.
Significant adverse events were those occurring in ≥ 2% of the total patients (319 patients).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The study population in the analysis of safety integrated across clinical studies included patients from 3 of the 4 clinical studies from which safety data were available [CSR 222017-02, the Questcor Retrospective Safety Study (CSR QSC007-ACT-002), and CSR 222017-05].

Safety data from CSR 222017-04 were not included in the integrated safety summary because of the inability to clearly identify and link the AEs to the specific study treatments evaluated in this particular trial, i.e., Acthar low-dose or prednisone; consequently, these data are presented separately at the end of section 7.1.1 of this review.

Integration of safety data from the above-mentioned 3 studies was performed based on the maximum daily dose of Acthar received by patients at the start of treatment. Patients were categorized into treatment groups based on the maximum daily dose of Acthar received regardless of any prior treatment received before Acthar initiation. Dose categories corresponded with Acthar dose in the proposed label for the treatment of IS (Questcor Recommended Dose) as well as with other dose categories commonly reported in the literature (Other High Dose and Low Dose) as follows:

- Questcor Recommended Dose: Acthar dose of 150 U/m2/day (dose range within the range ≥ 135 to ≤ 160 U/m2/day), divided, bid, administered for 2 weeks
- Other High Dose: Acthar dose ≥ 80 U/m2/day (included patients with a maximum dose ≥ 80 U/m2/day and patients within the Questcor Recommended Dose range where Acthar was not administered as a divided, twice-daily dose)
- Low Dose: Acthar dose <80 U/m2/day (this includes patients who received Acthar 20 U/day in CSR 222017-05)

The designation of the dosing categories, “Other High Dose” and “Low Dose,” was established by Questcor to define Acthar dosing schedules that were different from the Questcor proposed dosing schedule. These designations, “Other High Dose” and “Low Dose,” were based on an arbitrary daily dose of 80 U/m2/day. In addition, patients included in the “Other High Dose” category received a daily Acthar dose that may have been 150 U/m2/day, but the drug was administered as a single daily dose instead of as 2 divided doses, the Questcor recommended dosing schedule.

In all cases where the dose administered to the patient was presented as U/day, Questcor did calculations to present the dose as U/m2/day. These calculations were based upon the data provided in the patient charts. Questcor calculations revealed that patients who received the Questcor proposed dosing schedule of 150 U/m2/day revealed an actual dose range of 135 to 160 U/m2/day (likely due to practical issues around the withdrawal of the actual Acthar dose from the drug vial). Therefore, for this integrated safety summary, the Recommended Dose group of 150 U/m2/day dosing schedule included patients whose actual dose ranged from 135 to 160 U/m2/day administered IM in 2 divided doses.
All safety data presented in this section reflect data integrated from 3 of the 4 studies.

7.2 Adequacy of Safety Assessments

See discussion in section 3.1 of this review concerning safety data quality.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The number of patients from each study that contributed data to each treatment group is shown in Sponsor’s Table

1.1.

Table 1.1 Numbers of Patients from Clinical Safety Studies Contributing Data to Integrated Analysis

Study	Questcor Recommended Dose[a] n=134	Other High Dose[a] n=133	Low Dose[a] n=52	All Patients[a] N=319
CSR 222017-02	84	0	0	84
CSR QSC007-ACT-002	50	105	23	178
CSR 222017-05	0	28	29	57

a. Dose groups are defined in Section 1.4.5.

NOTE: Safety data from the Hrachovy Acthar versus prednisone study (CSR 222017-04) were not included in the integrated summary because of the inability to identify and link the AEs resulting from Acthar or prednisone therapies for the majority of patients.

Source: CSR 222017-02, CSR QSC007-ACT-002, CSR 222017 05

Demographics

Demographics and other baseline characteristics are summarized by treatment group in the sponsor's Table 1.2.
The mean (± standard deviation [SD]) age of all 319 patients at IS diagnosis was 7.7 months (± 5.04 months) and was similar across the 3 treatment groups. Consistent with the known epidemiology of IS, there was a slight preponderance of male patients (187/319, 58.6%).
The mean (± SD) weight of patients was 8.2 kg (± 1.92 kg) and mean (± SD) height of patients was 68.9 cm (± 7.78 cm). The mean (± SD) body surface area (BSA) was 0.397 m2 (± 0.0665 m2). In most patients, information concerning race was not available for analysis (135/319, 42.3%). In those patients with data, the majority were Caucasian (White) (122/319, 38.2%), or African-American (Black) (49/319, 15.4%).

As has been the case in all reported studies, the majority of patients had a symptomatic etiology of IS (189/319, 59.2%). There were, however, a substantial number of cryptogenic cases (122/319, 38.2%) in the study population, which allowed assessment of safety in this group as well.

Table 1.2 Overall Summary of Demographic and Baseline Characteristics by Treatment

Characteristic	Questcor Recommended Dose[a] (n=134)	Other High Dose[a] (n=133)	Low Dose[a] (n=52)	All Patients[a] (N=319)
Age at start of IS treatment (m)				
N[b]	133	126	46	305
Mean	8.2	8.5	9.0	8.4
SD	5.09	5.33	5.78	5.29
Median	7.0	7.5	7.1	7.2
Min, Max	0, 33	1, 36	2, 28	0, 36
Gender, n (%)				
Male	77 (57.5)	74 (55.6)	36 (69.2)	187 (58.6)
Female	57 (42.5)	59 (44.4)	15 (28.8)	131 (41.1)
Race, n (%)				
White	29 (21.6)	70 (52.6)	23 (44.2)	122 (38.2)
Black or African-American	13 (9.7)	27 (20.3)	9 (17.3)	49 (15.4)
Asian	2 (1.5)	4 (3.0)	1 (1.9)	7 (2.2)
Other	2 (1.5)	3 (2.3)	1 (1.9)	6 (1.9)
Unknown	88 (65.7)	29 (21.8)	18 (34.6)	135 (42.3)
Ethnicity, n (%)				
Hispanic or Latino	25 (18.7)	23 (17.3)	11 (21.2)	59 (18.5)
Non-Hispanic or Non-Latino	21 (15.7)	83 (62.4)	19 (36.5)	123 (38.6)
Unknown	88 (65.7)	27 (20.3)	22 (42.3)	137 (42.9)
Height, cm				
N[b]	130	110	42	282
Mean	69.0	68.4	69.8	68.9
SD	7.56	7.63	8.87	7.78
Median	68.3	68.7	69.8	68.7
Min, Max	52, 91	49, 97	55, 90	49, 97
Weight, kg				
N[b]	133	133	51	317
Mean	8.3	8.0	8.5	8.2
SD	1.85	1.83	2.29	1.92
Median	8.4	7.9	8.3	8.2
Min, Max	4, 13	5, 14	4, 14	4, 14

Characteristic	Questcor Recommended Dose[a] (n=134)	Other High Dose[a] (n=133)	Low Dose[a] (n=52)	All Patients[a] (N=319)
Body Surface Area, m^2				
N[b]	134	133	51	318
Mean	0.398	0.392	0.409	0.397
SD	0.0633	0.0640	0.0798	0.0665
Median	0.397	0.389	0.409	0.397
Min, Max	0.24, 0.57	0.25, 0.61	0.26, 0,60	0.24, 0.61
Etiology Category, n (%)				
Cryptogenic	44 (32.8)	57 (42.9)	21 (40.4)	122 (38.2)
Symptomatic	89 (66.4)	71 (53.4)	29 (55.8)	189 (59.2)
Unknown	1 (0.7)	5 (3.8)	2 (3.8)	8 (2.5)

a. Dose groups are defined in Section 1.4.5
b. The number of patients with data available are provided where data were missing for some patients.
Source: Section 1.12.3, Table 6.12.1: CSR 222017-02, CSR QSC007-ACT-002, CSR 222017 05

7.2.2 Explorations for Dose Response

The absence of a formal dose response study is discussed in section 6.1.8 of this review with respect to efficacy.

The integrated safety tables have been formulated with three dose categories discussed in section 7.2.1 of this review.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

Included vital signs, physical and neurological assessment, clinical laboratory assessment as available from retrospective chart review.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Sponsor summarized selected Adverse effects expected from clinical experience with ACTH and steroid medications in Sponsor's Table 1.5 reproduced below.

Table 1.5 Overall Summary of Selected Adverse Events by Treatment Group

Selected Adverse Event	Questcor Recommended Dose[a] (n=134) n (%)	Other High Dose[a] (n=133) n (%)	Low Dose[a] (n=52) n (%)	All Patients[a] (N=319) N (%)
Patients with at least 1 AE	**36 (26.9)**	**77 (57.9)**	**25 (48.1)**	**138 (43.3)**
Patients with No AEs	**98 (73.1)**	**56 (42.1)**	**27 (51.9)**	**181 (56.7)**
Infections	25 (18.7)	32 (24.1)	16 (30.8)	73 (22.9)
Irritability	8 (6.0)	26 (19.5)	8 (15.4)	42 (13.2)
Cushingoid	3 (2.2)	25 (18.8)	8 (15.4)	36 (11.3)
Hypertension	13 (9.7)	16 (12.0)	5 (9.6)	34 (10.7)
Increased appetite	0 (0.0)	12 (9.0)	1 (1.9)	13 (4.1)
Weight gain	1 (0.7)	7 (5.3)	0 (0.0)	8 (2.5)
Cardiac hypertrophy	4 (3.0)	1 (0.8)	0 (0.0)	5 (1.6)
Hyperglycemia	1 (0.7)	2 (1.5)	0 (0.0)	3 (0.9)
Hypokalemia	0 (0.0)	2 (1.5)	0 (0.0)	2 (0.6)

a. Dose groups are defined in Section 1.4.5.
Source: Section 1.12.3, Table 6.12.5,: CSR 222017-02, CSR QSC007-ACT-002, CSR 222017 05

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in the publication (Baram, 1996) of the pivotal efficacy study (CSR 222017-01). Safety data on the patients from this study are presumed to be included in the retrospective safety study by Partikian (CSR 222017-02) which reported only one death. This infant had not been part of the data analysis since the infant did not meet the criteria of being treated for infantile spasms at the author's institution but was subsequently admitted to this institution while being treated with a prolonged 4 month course of Acthar Gel combined with 6 weeks of valproate therapy. This child died of pneumonia attributable to prolonged ACTH therapy.

One death was reported from CSR 222017-05. This infant had a history of microcephaly and severe developmental delay and was randomized at age 3.3 months to the low dose arm of Acthar Gel (20-40 U QD). After repeated hospitalizations with severe respiratory symptoms, the infant died at 4.5 months of age form respiratory failure and cardiac arrest.

One death was reported in the retrospective chart review (QSC007-ACT-002) from aspiration pneumonia possibly related to the "Other High Dose" dose category of Acthar Gel.

Postmarketing surveillance revealed eight other deaths. See 8.3 below.

7.3.2 Nonfatal Serious Adverse Events

Serous adverse events (SAEs) are defined as those requiring an emergency room visit and/or hospitalization. When the chart review of the patient did not indicate the spediifci condition requiring the emergency room visit or hospitalization, the SAE was coded as "emergency care examination" or "hospitalization" in the Sponsor's Table 1.6 reproduced below.

Table 1.6 Overall Summary of Serious Adverse Events by Treatment Group

Serious Adverse Event	Questcor Recommended Dose[a] (n=134) n (%)	Other High Dose[a] (n=133) n (%)	Low Dose[a] (n=52) n (%)	All Patients[a] (N=319) N (%)
Patients with at least 1 SAE	**48 (35.8)**	**10 (7.5)**	**6 (11.5)**	**64 (20.1)**
Patients with No SAEs	**86 (64.2)**	**123 (92.5)**	**46 (88.5)**	**255 (79.9)**
Convulsion	17 (12.7)	1 (0.8)	0 (0.0)	18 (5.6)
Infections	11 (8.2)	2 (1.5)	3 (5.8)	16 (5.0)
Hypertension	10 (7.5)	2 (1.5)	0 (0.0)	12 (3.8)
Hospitalization	6 (4.5)	0 (0.0)	0 (0.0)	6 (1.9)
Pyrexia	3 (2.2)	0 (0.0)	0 (0.0)	3 (0.9)
Diarrhea	1 (0.7)	1 (0.8)	0 (0.0)	2 (0.6)
Vomiting	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.6)
Emergency care examination	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.6)
Decreased appetite	1 (0.7)	1 (0.8)	0 (0.0)	2 (0.6)
Grand mal convulsion	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.6)
Myoclonic epilepsy	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.6)
Dyspnea	1 (0.7)	0 (0.0)	1 (1.9)	2 (0.6)
Pneumonia aspiration	0 (0.0)	2 (1.5)	0 (0.0)	2 (0.6)
Respiratory failure	1 (0.7)	0 (0.0)	1 (1.9)	2 (0.6)
Cardiac arrest	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)
Cardiac hypertrophy	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Diarrhea hemorrhagic	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)

Serious Adverse Event	Questcor Recommended Dose[a] (n=134) n (%)	Other High Dose[a] (n=133) n (%)	Low Dose[a] (n=52) n (%)	All Patients[a] (N=319) N (%)
Gastroesophageal reflux disease	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Irritability	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Hepatomegaly	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Herpes zoster	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Shunt infection	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Compression fracture	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Biopsy liver	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Acidosis	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Dehydration	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Osteoporotic fracture	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Complex partial seizures	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Partial seizures	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Status epilepticus	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)
Acute respiratory distress syndrome	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)
Pulmonary edema	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)
Skin discoloration	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Exposure to communicable disease	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Brain operation	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)

a. Dose groups are defined in Section 1.3.

Source: Section 1.12.3, Table 6.12.6, CSR 222017-02, CSR QSC007-ACT-002, CSR 222017 05

7.3.3 Dropouts and/or Discontinuations

The Sponsor provided very limited data concerning drop-outs and discontinuations, presented only in the format of narratives from the four clinical studies discussed in section 7.1.1 of this review.

There was no safety data from pivotal study CSR 22017-01.

The narratives (derived from retrospective chart reviews) from study CSR 22017-02 are often not clear as to whether discontinuations were planned or due to noncompliance or an adverse effect. Most of these patients were not in a clinical study,

The narratives (derived from retrospective chart reviews) from study CSR 22017-05 (Hrachovy 1994) indicated that two of the original 59 patients randomized dropped out before receiving any Acthar Gel (as discussed previously, the safety population was 57). Of the 57 patients, only two narratives indicated discontinuation due to an adverse effect: patient 098-50 (increased blood pressure on high dose).and patient 090-008 (pyrexia on low dose). One patient (090-002) moved to Ohio. One patient (090-007) was lost to follow-up after one dose of low dose. It is not clear why the other three other patients discontinued the study.

The narratives (derived from retrospective chart reviews) from study CSR QSC007-ACT-002 are often not clear as to whether discontinuations were planned or due to noncompliance or an adverse effect. Most of these patients were not in a clinical study,

Patients from study CSR 22017-04 were not included in the integrated summary as previously discussed.7.3.4 Significant Adverse Events

The Sponsor's Table 6.12.4 (reproduced below) shows treatment-emergent adverse effects with an incidence greater than or equal to 2%.

Integrated Summary of Safety for HP Acthar Gel
NDA Supplement for the Treatment of Infantile Spasms

Table 6.12.4 Summary of Treatment-Emergent Adverse Events with Incidence Greater than or Equal to 2%
by MedDRA System Organ Class by Preferred Term by Treatment Group

	Recommended Dose (N=134)	Other High Dose (N=133)	Low Dose (N=52)	All Patients (N=319)
CARDIAC DISORDERS	5 (3.7%)	1 (0.8%)	1 (1.9%)	7 (2.2%)
ENDOCRINE DISORDERS	3 (2.2%)	25 (18.8%)	8 (15.4%)	36 (11.3%)
CUSHINGOID	3 (2.2%)	25 (18.8%)	8 (15.4%)	36 (11.3%)
GASTROINTESTINAL DISORDERS	8 (6.0%)	21 (15.8%)	7 (13.5%)	36 (11.3%)
DIARRHOEA	3 (2.2%)	7 (5.3%)	2 (3.8%)	12 (3.8%)
VOMITING	4 (3.0%)	5 (3.8%)	3 (5.8%)	12 (3.8%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	12 (9.0%)	34 (25.6%)	11 (21.2%)	57 (17.9%)
IRRITABILITY	8 (6.0%)	26 (19.5%)	8 (15.4%)	42 (13.2%)
PYREXIA	6 (4.5%)	8 (6.0%)	4 (7.7%)	18 (5.6%)
INFECTIONS AND INFESTATIONS	27 (20.1%)	32 (24.1%)	17 (32.7%)	76 (23.8%)
INFECTIONS	25 (18.7%)	32 (24.1%)	16 (30.8%)	73 (22.9%)
INVESTIGATIONS	8 (6.0%)	11 (8.3%)	2 (3.8%)	21 (6.6%)
WEIGHT GAIN	1 (0.7%)	7 (5.3%)	0 (0.0%)	8 (2.5%)
METABOLISM AND NUTRITION DISORDERS	9 (6.7%)	22 (16.5%)	4 (7.7%)	35 (11.0%)
INCREASED APPETITE	0 (0.0%)	12 (9.0%)	1 (1.9%)	13 (4.1%)
DECREASED APPETITE	3 (2.2%)	4 (3.0%)	1 (1.9%)	8 (2.5%)
NERVOUS SYSTEM DISORDERS	22 (16.4%)	8 (6.0%)	1 (1.9%)	31 (9.7%)
CONVULSION	17 (12.7%)	4 (3.0%)	0 (0.0%)	21 (6.6%)

Treatment groups defined by maximum dose: Recommended Dose = 150 Divided range from 135 through 160 U/m2/day divided, BID; Other High Dose (>= 80 U/m²/day) excludes the Recommended Dose; and Low Dose (<80 U/m²/day).
All Patients group = (Recommended Dose) + (Other High Dose) + (Low Dose).

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Integrated Summary of Safety for HP Acthar Gel
NDA Supplement for the Treatment of Infantile Spasms

Table 6.12.4 Summary of Treatment-Emergent Adverse Events with Incidence Greater than or Equal to 2% by MedDRA System Organ Class by Preferred Term by Treatment Group

	Recommended Dose (N=134)	Other High Dose (N=133)	Low Dose (N=52)	All Patients (N=319)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (3.7%)	14 (10.5%)	7 (13.5%)	26 (8.2%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.7%)	24 (18.0%)	6 (11.5%)	31 (9.7%)
ACNE	0 (0.0%)	10 (7.5%)	3 (5.8%)	13 (4.1%)
RASH	0 (0.0%)	7 (5.3%)	2 (3.8%)	9 (2.8%)
SURGICAL AND MEDICAL PROCEDURES	6 (4.5%)	0 (0.0%)	1 (1.9%)	7 (2.2%)
VASCULAR DISORDERS	13 (9.7%)	17 (12.8%)	5 (9.6%)	35 (11.0%)
HYPERTENSION	13 (9.7%)	16 (12.0%)	5 (9.6%)	34 (10.7%)

Treatment groups defined by maximum dose: Recommended Dose = 150 Divided range from 135 through 160 U/m2/day divided, BID; Other High Dose (>= 80 U/m²/day) excludes the Recommended Dose; and Low Dose (<80 U/m²/day).
All Patients group = (Recommended Dose) + (Other High Dose) + (Low Dose).

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7.3.5 Submission Specific Primary Safety Concerns

See discussion of limitations of the safety data quality in section3.1 of this review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

See Section 7.3.4 of this review.

7.4.2 Laboratory Findings

The Sponsor did not provide an integrated summary of laboratory findings. These are discussed in section 7.1.1 of this review under the individual safety studies.

7.4.3 Vital Signs

The Sponsor did not provide an integrated summary ofvital signs. These are discussed in section 7.1.1 of this review under the individual safety studies.

7.4.4 Electrocardiograms (ECGs)

ECGs were not routinely done in this infant population.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not evaluated. No adverse reactions attributable to immunogenicity were reported.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See section 7.2.2 of this review

There is a trend for increased adverse effects for higher doses of Acthar Gel especially when given for a treatment period exceeding two weeks with a two week taper. However, dose dependent studies with a prospective collection safety data has not been done.

7.5.2 Time Dependency for Adverse Events

The Partikian (CSR 222017-02) study suggests that some of the steroid-related adverse effects (risk of serious infection, osteopenia) are more likely in treatment courses longer than 2 weeks treatment with 2 weeks for tapering. This is part of the rationale for the proposed dosage. However, the limited data available does not definitively establish the proposed dosage (high dose, short duration) as the optimal one.

7.5.3 Drug-Demographic Interactions

See current labeling.

7.5.4 Drug-Disease Interactions

See current labeling.

The safety data suggest that pre-existing hypertension, congenital infection, other chronic infection or impaired immune status, and some metabolic disorders may be relative contra-indications to the use of Acthar Gel for infantile spasms.

7.5.5 Drug-Drug Interactions

See current labeling.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See current labeling.

7.6.2 Human Reproduction and Pregnancy Data

See current labeling

7.6.3 Pediatrics and Assessment of Effects on Growth

Infantile spasms is a pediatric indication. No assessment of effects on growth has been done.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The sponsor reports there have been no reports of death or symptoms from an acute overdose of Acthar in clinical studies or in the published literature.

There are no systematic studies on the optimal taper period and whether or not there is acute withdrawal and/or rebound from Acthar in the treatment of patients with IS. Like all drugs in the corticosteroid class, it is common practice to taper patients receiving Acthar for the treatment of IS to reduce the possible occurrence of AEs that might be related to abrupt Acthar withdrawal.

The taper regimen suggested by Questcor in the proposed product label is as follows: Taper the dose for 3 days 30 U/m2 in the morning; for 3 days 15 U/m2 in the morning; for 3 days 10 U/m2 in the morning; for 6 days 10 U/m2 every other morning.

8 Postmarket Experience

From 1.5 of ISS

Questcor reviewed and summarized postmarketing surveillance records for Acthar gel including AEs, SAEs, and deaths reported to New Drug Application (NDA) 08-372 from 29 April 1952, when Acthar was approved, through June 2009. This review included all annual reports, periodic AE reports, 15-day alerts, and all follow-up reports submitted to FDA and any other NDA communications and submissions. A summary of the findings related to the safety of Acthar in treating IS reported in postmarketing surveillance records can be found in Section 1.5.2.

Safety data provided in this submission include data from postmarketing surveillance records for Acthar used to treat infants (Questcor Safety Database).

In support of this Complete Response, Questcor thoroughly reviewed in-house safety data for Acthar and AEs reported to NDA 08-372 from 29 April 1952, when the NDA for Acthar was approved, through June 2009. This review included all annual reports, periodic AE reports, 15-day alerts, and follow-up reports submitted to the FDA. Other NDA communications and submissions were also reviewed.

A review of all identified AEs was conducted for patients who had been treated with Acthar or unidentifiable ACTH for the indication of IS, and patients identified as infants by age (28 days through 24 months). In addition to IS, the terms implying the same disorder or a similar condition, such as hypsarrhythmia and myoclonic seizures, were included, in order to obtain the relevant postmarketing information. In these AE reports, the terms originally used to report the AEs were reproduced verbatim or were coded to the preferred term.

8.1 Postmarketing Surveillance Adverse Events Reported for Patients Treated with Acthar

Postmarketing surveillance records (Questcor Safety Database) show a total of 76 patient reports received by the manufacturers and submitted to the FDA for infants treated with Acthar, who experienced 1 or more AE(s).

The most commonly occurring AEs (>2 patients) observed in the postmarketing use of Acthar for the treatment of IS are summarized in the Sponsor's Table 1.8. This table is derived from a tabular summary of all postmarketing AEs provided in Appendix 1.12.5, Table 1.19. A detailed listing of patients and AEs can be found in Appendix 1.12.5, Table 1.18; the list is organized by the date the case was submitted to the NDA.

Table 1.8 Most Common (>2 Patients) AEs Reported to Manufacturer in Infants Treated with Acthar

Body System/Adverse Events (verbatim term)	No. of Patients Reporting AE
Endocrine disorders	
Cushing's syndrome	4
Facial edema	2
Gastrointestinal disorders	
Abdominal distention	2
Vomiting	2
General disorders and administration site conditions	
Drug withdrawal reaction	2
Edema	2
Fever	4
Ineffective therapy	3
Lethargy	2
Infections and infestations	
Oral thrush	2
Sepsis	4
Investigations	
Weight gain	2
Metabolism and nutrition disorders	
Appetite suppression	2
Dehydration	3
Fluid retention	2
Hypokalemia	3
Metabolic alkalosis	3
Nervous system disorders	
Insomnia	2
Seizure	4
Psychiatric (psychic) disorders	
Crying	2
Irritability	5
Respiratory disorders	
Cough	2
Pneumocystis carinii pneumonia	5
Respiratory distress	2

Body System/Adverse Events (verbatim term)	No. of Patients Reporting AE
Skin and subcutaneous tissue disorders	
Acne	2
Rash	6
Vascular disorders	
Hypertension	6

Notes: One patient may have more than one AE. Only one occurrence of an AE was counted for each patient. Adverse events were retrieved verbatim. No recoding was performed.

8.2 Postmarketing Surveillance Serious Adverse Events Reported for Infants Treated with Acthar

Thirty-three of the AE reports received by the manufacturers concerning the use of Acthar in infants were considered serious; these events were submitted to the FDA in 15-day alert reports (serious and unexpected or unlabeled events) or in periodic ADE reports (serious and expected or labeled events). A summary of the SAEs can be found in The Sponsor's Table 1.9.

Table 1.9 Serious Adverse Events Spontaneously Reported for Infants Treated with Acthar

Control No.	Dosing	Serious Adverse Events
M-335	80 U/d	Sepsis[a]
M-339	80 U/d	Sepsis[a]
M-340	80 U/d	Sepsis[a]
M-341	80 U/d	Sepsis[a]
M-342	80 U/d	Hypertension, metabolic alkalosis[a]
M-343	80 U/d	Hypertension, metabolic alkalosis[a]
M-344	80 U/d	Hypertension, metabolic alkalosis[a]
01-001174	150 U/m^2/d –IM Treatment Duration: 3 d Total Dose: 100.8 U	Pyruvate carboxylase deficiency, catastrophic metabolic acidosis, death[b]
01-001652	10 U/kg/d Treatment Duration: 21 d Total Dose: 1764 U	Cushing's ulcer, small fontanel, toxic appearance, abdominal distention, emesis, respiratory distress, fever[b]
01-000941	60 U/d Treatment Duration: 45 d Total Dose: 2700 U	Hypertension, weight gain, motor development delayed
01-008741	50 U/d to 25 U/d Treatment Duration: 30 d Total Dose: 1125 U	Soft/white gums, fever, respiratory failure, seizure, sore throat, death[b]

Control No.	Dosing	Serious Adverse Events
US01-08623/01-011039	56 U/day –IM Treatment duration: 68 d Total dose: 3808 U	Drug withdrawal reaction, appetite suppression, dehydration
US01-08028/01-011040	56 U/day –IM Treatment duration: 81 d Total dose: 4536 U	Drug withdrawal reaction, appetite suppression, dehydration
US01-19053	18 U/day –IM Treatment duration: 7 d Total dose: 126 U	Fever, seizures
US01-19351	20 U/d x 14 d 40 U/d x 14 d 80 U/d x 7 d 40 U/d x 7 d 40 U/qod x 10 d Treatment duration: 52 d Total dose: 1880 U	*P. carinii* pneumonia, septic shock, fluid retention, weight gain, acute tubular necrosis, hypernatremia, hypokalemia, urinary tract infections
US01-19376	70 U/day –IM Treatment duration: 120 d Total dose: 8400 U	*P. carinii* pneumonia, tachypnea, dyspnea, Cushing's syndrome, oral thrush[b]
US01-19380	40 U/day –IM Treatment duration: 90 d Total dose: 3600 U	Cough, respiratory distress, Cushing's syndrome, oral thrush, *P. carinii* pneumonia[b]
US01-19381	80 U/qod – IM Treatment duration: 210 d Total dose: 8400 U	Cough, rhinorrhea, decreased appetite, lethargy, Cushing's syndrome (obesity with acne, hirsutism, purple striae, respiratory distress, hypotonia), *P. carinii* pneumonia, death[b]
US01-19689	80 U/qod x 60 d 80 U/d x 90 d Treatment duration: 150 d Total dose: 9600 U	Mucocutaneous candidiasis, hypertension, bilateral severe pneumonia. (Pneumocystis organisms observed at autopsy), death[b]
US01-20092	20 bid to 30 bid, tapering Treatment duration: 32 d Total dose: 1640 U	Adrenal insufficiency, hypokalemia, cardiac arrest, anoxic brain injury
US01-20137	60 U/d x 21 d 40 U/d x 21 d 20 U/d x 14 d Treatment duration: 21 d to AE + 35 days Total dose: 1260 U to AE + 1120 U	Cardiac hypertrophy, hypertension, right upper lobe pneumonia, pulmonary edema, death[b]
US01-22284	80 U/day – IM Treatment duration: 42 d Total dose: 3360 U	Lethargy, decreased oral intake, rapid respiratory rate, *P. carinii* pneumonia[c]

Control No.	Dosing	Serious Adverse Events
US01-24280	80 U/d x 14 d 120 U/d x 14 d 80 U/d x 14 d 60 U/d x 35 d Treatment duration: 77 d Total dose: 4420 U	Respiratory syncytial virus infection, shortness of breath, fever, interstitial pneumonitis
2000-20713US	40 U bid Treatment duration: 153 d Total dose: 12240 U	Brain shrinkage[c], hydrocephalus
ACT-S0001	30 IU/mL qod – IM Treatment duration: NR	Hypertension, cardiomyopathy
03-ADE-SU-0001-ACT	32 - 16 U/mL qod – IM Treatment duration: NR	Seizure, death
03-ADE-SU-0002-ACT	40 U/d to 20 U/d – IM Treatment duration: NR	Vomiting, respiratory arrest, death[b]
06-ADE-SU-0017-ACT	150 U/m^2/d IM x 2 wk, taper x 2 wk Treatment duration: NR	Encephalitis herpes, disease recurrence
06-ADE-SU-0020-ACT	NR	*P jirovecii* pneumonia
07-ADE-SU-0012-ACT	40 U IM qd Treatment duration: NR	Irritability, convulsions
08-ADE-SU-0003-ACT	40 U IM qd for 6 wks with taper Treatment duration: NR	Dehydration, oral intake reduced, fluid retention, acne
09-ADE-SU-0013-ACT	20 - 40 U IM qd Treatment duration: 43 d	Bronchiolitis, acute respiratory distress syndrome
09-ADE-SU-0011-ACT	NR	Leukemia

Notes:
Reference: Table 1.20 - Listing of SAEs Reported to the Manufacturer in Infants treated with Acthar
NR = Not Reported, IM =Intramuscular; d = day, qd = once/day

a. From 15-day alert and MedWatch forms submitted to FDA. By current reporting standards, these did not meet the current criteria for reportable events, because inadequate information was in the original reports sent to the manufacturer.

b. Report derived from a case described in the medical literature; deaths in literature not listed in Table 1.20: 01-001174, 01-008741, and 03-ADE-SU-0002-ACT.

c. The term brain shrinkage was used here, instead of cerebral atrophy.

8.3 Postmarketing Surveillance Deaths

Eight deaths were reported previously to NDA # 08-372 as part of ongoing postmarketing surveillance and are presented in the Sponsor's Table 1.10.

Table 1.10 Postmarketing Surveillance Summaries of Deaths Reported for Infants Treated with Acthar

Report Date	Control No.	Acthar Dose	Key Verbatim Excerpts from SAE Narratives[a]
13-Apr-90	01-001174[b]	150 U/m^2/day –IM Treatment duration: 3 d Total dose: 100.8 U[c]	The patient died at 12 weeks of age after recurrent episodes of profound acidosis. At autopsy, the brain manifested cystic degeneration and demyelination. According to the reporter, the dramatic rise in alanine levels coincident with ACTH therapy suggests that ACTH played a role in precipitating the catastrophic metabolic acidosis. The patient's physician stated that the infant was symptomatic before ACTH therapy and felt that ACTH may have exacerbated the reaction, but did not cause it. The event report included no opinion regarding a possible causal relationship between the events and Acthar treatment.
05-Oct-95	01-008741	50 U/day to 25 U/d Treatment duration: 30 d Total dose: 1125 U[d]	She experienced seizures while being treated with Acthar, the dose was decreased to 25 U daily and, according to the patient's father, the seizures worsened. The treatment duration at this time was 1 month. The patient was hospitalized with fever and a sore throat, administered oxygen through an oxygen tube, but without effect, and subsequently died. The cause of death reported by the pathologist was neurofibromatosis.
23-Jul-98	US01-19381[b]	80 U/qod – IM Treatment duration: 210 d Total dose: 8400 U	Because of rapid deterioration in respiratory status, trimethoprim-sulfamethoxazole 20 mg/kg/d was administered intravenously and mechanical ventilation started. Tissue from an open-lung biopsy showed severe alveolar damage with hyaline membranes, interstitial fibroblastic proliferation, and the presence of *P. carinii*. Cytomegalovirus was subsequently recovered from cultures of the lung specimen. The patient's condition continued to deteriorate, and he died 10 d after admission.
02-Sep-98	US01-19689[b]	80 U/qod x 60 d 80 U/d x 90 d Treatment duration: 150 d Total dose: 9600 U	Seizures ceased within 4 d. Two months later, seizures recurred, and the Acthar dosage was increased to 80 U/d. Seizure frequency declined, but the patient developed mucocutaneous candidiasis that responded poorly to topical therapy, and he became hypertensive. After 3 months, oral prednisone 1 mg/kg/d was substituted for Acthar with the intent of tapering. Clonazepam was used for seizure control. Two d later, the patient's mother thought he was "congested." The next day, the patient was found dead in his crib. The postmortem examination revealed bilateral severe pneumonia.

Report Date	Control No.	Acthar Dose	Key Verbatim Excerpts from SAE Narratives[a]
28-Oct-98	US01-20137[b]	60 U/d x21 d 40 U/d x 21 d 20 U/d x 14 d Treatment duration: 21 d to AE + 35 d, total treatment was 8 weeks. Total dose: 1260 U to AE + 1120 U	The seizures ceased within 24 hours. Three weeks later, examination revealed severe peripheral edema, tachypnea, hypertension (174 mm Hg systolic), hepatomegaly, and intermittent apnea. The Acthar dose was reduced to 40 U/d, and the systolic blood pressure gradually decreased to 110 mm Hg. An ECG conducted 6 weeks after institution of ACTH revealed no change in the degree of septal and left ventricular freewall hypertrophy, or systolic anterior motion of the mitral valve. The dose of Acthar was reduced to 20 U/d with no return of seizure activity. Cardiomegaly and edema persisted. 8 weeks after the start of Acthar, while at home, the infant became lethargic and pale and died during a nap. Postmortem examination revealed bilateral pulmonary edema, right upper lobe pneumonia, centrilobular hepatic congestion, and periventricular leukomalacia. The heart had severe asymmetric left ventricular hypertrophy without dilation of the chambers.
29-May-03	03-ADE-SU-0001-ACT	16 -32 U/mL qod – IM Treatment duration: NR	The medical history included hypertension. The patient was at home and had responded well to Acthar, with cessation of spasms. At the time of the event, the patient was on a tapering regimen of the drug. According to her family the patient had a uniquely new seizure, stopped breathing, and died suddenly. She could not be resuscitated. The treating physician did not think that Acthar was the cause of the event. The patient was severely neurologically impaired.
29-May-03	03-ADE-SU-0002-ACT	40 U alternating with 20 U qod – IM Treatment duration: NR	The patient was at home, and had responded well to a stable regimen of Acthar, with cessation of spasms. The patient became unresponsive after vomiting, had a respiratory arrest, and could not be resuscitated. The physician considered Acthar unrelated to the event. The patient was severely neurologically impaired. Preliminary verbal autopsy indicated impressive right ventricular hypertrophy, and the brain showed evidence of hypoxic ischemic changes before death. The final autopsy report included no information that would indicate relation of the event to treatment. The most likely cause of death was the patient's congenital cardiac and central nervous system abnormalities.

Report Date	Control No.	Acthar Dose	Key Verbatim Excerpts from SAE Narratives[a]
05 May 09[d]	09-ADE-SU-0013-ACT	20 - 40 U IM qd Treatment duration: 43 d	The patient was a 3.3-month-old male infant with a history of IS, microcephaly, and severe developmental delay at the time treatment with Acthar low-dose (20 U/qd) began on 21 February 1990. On 06 March 1990, the dose of Acthar was increased to 30 U/qd per protocol as the patient continued to have spasms. On (b) (6), the patient was admitted to the (b) (4) with bronchiolitis, acute respiratory distress syndrome, and pneumonia: a diagnosis of RSV was made. The patient improved and was discharged on (b) (6); the records of that admission show that the Acthar dose was 30 U/day. On (b) (6), the patient was readmitted with worsening respiratory symptoms; the records of this admission note the Acthar dose was 40 U/day. The patient improved and was discharged on (b) (6). On 03 April 1990, the dose of Acthar was scheduled to be tapered to 20 U/qd per a note in the patient chart at Baylor by the investigator; however, there is no documentation that this lower dose was ever administered. On (b) (6), the patient was again admitted to the (b) (4) with continuing respiratory symptoms. Despite aggressive care and antibiotic therapy, the patient developed pulmonary edema, respiratory failure, and died of cardiac arrest on (b) (6); the patient was 4.5 months of age at the time of death. The dose of Acthar at this last admission was not documented. The investigator did not assess the relationship of these SAEs to Acthar.

a. This column contains information excerpted verbatim from the SAE narratives of the events that had outcomes of death. Causes of death and physicians' comments about the causality relationships between the death and Acthar or ACTH are included when these data were available.

b. Report derived from a case described in medical literature.

c. Duration per regimen not reported. Total dose assumes 2 weeks at initial dose (50 U), 2 weeks at tapered dose (25 U)

d. Report documented in CSR 222017-05 and submitted via MedWatch.

9 Appendices

9.1 Literature Review/References

Baram TZ, Mitchell WG, Tournay A, Snead OC, Hanson RA, Horton EJ. High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study. *Pediatrics*. 1996;97:375-379

Hancock E, Osborne J. Treatment of infantile spasms. *The Cochrane Database Syst Rev.* 2002(2):CD001770.

Hrachovy RA, Frost JD, Jr, Kellaway P, Zion TE. Double-blind study of ACTH vs prednisone therapy in infantile spasms. *J Pediatr*. 1983;103(4):641-655.

Hrachovy RA, Glaze DG, Frost JD, Jr. A retrospective study of spontaneous remission and long-term outcome in patients with infantile spasms. *Epilepsia*. 1991;32(2):212-214.

Hrachovy RA, Frost JD Jr, Glaze DG. High-dose, long-duration versus low-dose, short duration corticotropin therapy for infantile spasms. *J Pediatr*. 1994 May;124(5 Pt 1):803-806.

Mackay MT, Weiss SK, Adams-Webber T, Ashwal S, Stephens D, Ballaban-Gill K, et al.American Academy of Neurology; Child Neurology Society. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. *Neurology*. 2004 May 25;62(10):1668 1681.

Partikian A, Mitchell WG. Major adverse events associated with treatment of infantile spasms. *J Child Neurol*. 2007 Dec;22(12):1360-1366.

9.2 Labeling Recommendations

The Division of Endocrine and Metabolic Products (DMEP) has primary responsibility for Acthar Gel and the conversion of the currently approved label to PLR format. The indications under the purview of DNP are the currently approved indication for the treatment of exacerbations of multiple sclerosis and the currently proposed indication for the treatment of infantile spasms, to eliminate spasms and hypsarrhythmia electroencephalogram pattern.

DMEP and DNP have worked together to prepare a revised draft using the Sponsor's April 28, 2010 draft labeling as a base document. Numerous changes have been proposed in this revised draft. The number of indications for Acthar Gel has been

greatly reduced to reflect current usage and evidence of effectiveness. Clarification of the dosing for treatment and tapering for infantile spasms has been requested. The Sponsor is asked to rewrite portions of the Adverse Reactions section (6). A reference to the MedGuide the has been added to the Patient Counseling Information (17). The MedGuide only addresses the infantile spasms indication because of the difficulty in recognizing and treating adverse effects in the infant population.

9.3 Advisory Committee Meeting of May 6, 2010

The Peripheral and Central Nervous System Drugs Advisory Committee met on May 6, 2010.

The vote regarding whether the Sponsor had provided substantial evidence of effectiveness from a single and adequate and well-controlled clinical investigation with confirmatory evidence was 22 affirmative and 1 negative. The effectiveness was in the dual endpoint of cessation of spasm and amelioration of the EEG but not prevention of other seizure types, improvement in long-term developmental outcomes, or any other outcomes.

The vote was more divided regarding whether the Sponsor had submitted evidence to support the view that a short course of treatment provides sustained effectiveness (16 affirmative, 7 negative). The discussion indicated that this vote reflected the committee's concern that data was not provided in order for them to determine if the drug product has been shown to provide sustained effectiveness. The committee recommended that the labeling should state which study the recommended regimen is based on. Other alternative dosing and tapering regimens should be considered for future study but should not delay approval.

The committee agreed that sufficient evidence of the safety of Acthar Gel at an effective dosing regimen had been submitted to allow approval. However discussion emphasized that use of ACTH should be closely monitored for toxicity and that ongoing monitoring and post-marketing surveillance are needed particularly with regard to long-term outcomes.

The committee further recommended:

Labeling should clearly state which adverse events should be monitored, such as blood pressure, relapse, adrenal insufficiency, and infection

The REMS may include: physician education prior to prescribing, patient registry, use of specialty pharmacy, and post-marketing studies to include data on second course outcomes with relapse reporting.

Follow-up to the Advisory Committee

A teleconference was held by the Agency with the Sponsor on May 13, 2010 to follow-up on the issues raised at the Advisory Committee. The Sponsor was asked to provide further data and discussion regarding relapse rates, early versus late initiation of treatment, and retreatment (multiple courses for refractory or relapsing patients) with Acthar Gel for infantile spasms.

In response to this teleconference, the Sponsor submitted on June 8, 2010 a paper entitled (b) (4) . This submission is discussed at the end of section 6.1.9 of this review.

In response to the discussion at the Advisory Committee, the Sponsor submitted on August 27, 2010 a four page paper entitled (b) (4) Sponsor concludes that it would not be practical to conduct a comparison study between these two treatments for four reasons. First, the response rates from the pivotal and supporting studies for Acthar Gel range from 42% to 87%, whereas the response rates for Sabril (from the Sabril label) are only in the range of 16% to 25%. This would make it unlikely that physicians and parents would consent to randomization when both treatments were approved for the infantile spasm indication. Second, physicians and parents would want to choose which treatment is most appropriate for the individual infant given the different profiles of adverse effects rather than allow the infant to undergo study randomization. Third, a noninferiority design study would require more patients than could be reasonably recruited; even a superiority design study would require a study population large enough to make recruitment difficult to complete for this relatively rare syndrome, and the superiority design would imply that equipoise does not exist. Fourth, a comparator study in the tuberous sclerosis population alone would be difficult given that the medical community has concluded that vigabatrin is the treatment of choice for infantile spasms secondary to tuberous sclerosis. Furthermore, extrapolation from the tuberous sclerosis population to all other infantile spasms patients would not be appropriate. After discussion within the Division, it was agreed that the Sponsor's overall point that it would be extremely difficult to recruit enough patients for even a superiority study is valid in light of the recruitment challenges of the studies which supported approval of these two treatments.

Given the Advisory Committee's interest in further studies of optimal dosage for Acthar Gel, (b) (4) (b) (4)

(b) (4)

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/s/

PHILIP H SHERIDAN
09/28/2010

NORMAN HERSHKOWITZ
09/28/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-432

H.P. Acthar® Gel
(repository corticotropin injection)

Questcor Pharmaceuticals

Martha R. Heimann, Ph.D.
Division of New Drug Quality Assessment 1

for the

Division of Neurology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-432

2. REVIEW #: 1

3. REVIEW DATE: June 1, 2010

4. REVIEWER: Martha R. Heimann, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
Original NDA (originally submitted as NDA 8-372/S-039)	23-Jun-2006
J. Brown review of claimed categorical exclusion (reviewed under NDA 8-372/S-039)	31-Oct-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Labeling/Package Insert	28-Apr-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Questcor Pharmaceuticals, Inc
Address:	3260 Whipple Road Union City, CA 94587
Representative:	David Young Chief Scientific Officer 8550 Stanford Blvd. Columbia, MD 21045
Telephone:	(410) 953-0336

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: H. P. Acthar® Gel
b) Non-Proprietary Name (USAN): corticotropin injection
c) Code Name
d) Chem. Type/Submission Priority:

- Chem. Type: 6
- Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOLOGICAL. CATEGORY: treatment of infantile spasms

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 80 USP Units/mL

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

__X__SPOTS product – Form Completed

_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: corticotropin

Structural formula:

H-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Try-Pro-Asp-Gly-Ala-Glu-Asp-Gln-Leu-Ala-Glu-Ala-Phe-Pro-Leu-Glu-Phe-OH

Molecular formula: not provided in NDA

Molecular weight: not provided in NDA

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: N/A

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Acthar® Gel NDA	NDA 8-372	Indication is for diagnostic testing of adrenocortical function.

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not required	---	---
EES	Not required	---	---
Pharm/Tox	Not required	---	---
Biopharmaceutics	Not required	---	---
LNC	Not required	---	---
Methods Validation	Not required	---	---
DMETS	Not applicable	---	---
EA	Claim for categorical exclusion is acceptable	01-JUN-2010	M. Heimann
Microbiology	Not required	---	---

The Chemistry Review for NDA 22-432

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry perspective, approval of this application is recommended.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No post-approval commitments are required.

II. Summary of Chemistry Assessments

Reviewer Note: The application was originally submitted as efficacy supplement S-039 to the approved application for Acthar® Gel (repository corticotropin injection), 80 USP Units/mL (NDA 8-372). The Agency issued a Not Approvable letter for NDA 8-372/S-039 on 10-May-2007. Upon resubmission, the supplemental application was reclassified as a Type 6 NDA.

A. Description of the Drug Products and Drug Substance

H. P. Acthar Gel (repository corticotropin injection) is marketed by Questcor Pharmaceuticals for diagnostic testing of adrenocortical function. The product is a sterile preparation of "highly purified" adrenocorticotropic hormone in 16% gelatin to provide a prolonged release after intramuscular injection. It also contains 0.5% phenol, not more than 0.1% cysteine (added), sodium hydroxide and/or acetic acid to adjust pH, and water for injection. The current labeling (approved under NDA 8-372) indicates that it has limited therapeutic value in conditions responsive to corticosteroid therapy. Several disorders for which the drug may be employed are identified in the current labeling.

B. Description of How the Drug Product is Intended to be Used

The applicant seeks approval of H. P. Acthar Gel for treatment of infantile spasms. The product is currently used "off-label" for this indication and the applicant estimates that approximately (b) (4)% of the current sales are for this indication. In the treatment of infantile spasms, the drug product may be administered intramuscularly at a daily dose of 150 U/m^2 divided into twice daily intramuscular injections of 75 U/m^2. After two weeks of treatment, dosing should then be tapered, gradually eliminating administration over a 2-week period.

C. Basis for Approvability or Not-Approval Recommendation

H. P. Acthar Gel is an approved product under NDA 8-372. The current application proposes use of the same product for a new indication. No CMC changes have been made to the approved drug substance or drug product.

The applicant claims categorical exclusion under the provisions of 21 CFR §25.31(a). because it will not increase use of the drug The request for categorical exclusion was reviewed under the original efficacy supplement and found acceptable. [J. Brown review for NDA 8-372/S-039 dated 31-Oct-2006]

The proposed product labeling provides for minor format changes to the How Supplied sections as part of the conversion to PLR as shown below. The additional instructions *"H.P. Acthar Gel (repository corticotropin injection) should be warmed to room temperature before using. Do not over pressurize the vial prior to withdrawing the product."* are also contained in the Dosage and Administration sections of both the approved and proposed labeling. Inclusion of this information in the How Supplied section of the labeling is acceptable from a CMC perspective.

Approved Labeling

HOW SUPPLIED
H.P. Acthar Gel
(Repository Corticotropin Injection)

Presentation	NDC
5 mL multi-dose vial containing 80 USP Units per mL	63004-7731-1

Storage: Store **H.P. Acthar Gel** (Repository Corticotropin Injection) under refrigeration between 2°-8°C (36°-46°F).

Product is stable for the period indicated on the label when stored under the conditions described.

Proposed Labeling

16 HOW SUPPLIED / STORAGE AND HANDLING

H.P. Acthar Gel (repository corticotropin injection) is supplied as 5 mL multi-dose vial (63004-7731-1) containing 80 USP Units per mL. H.P. Acthar Gel (repository corticotropin injection) should be warmed to room temperature before using. Do not over pressurize the vial prior to withdrawing the product.

Store H.P. Acthar Gel (repository corticotropin injection) under refrigeration between 2°-8°C (36°-46°F). Product is stable for the period indicated on the label when stored under the conditions described.

In view of the approved status of this product, it should also be approved under the current application.

III. Administrative

A. Reviewer's Signature

See electronic signature in DARRTS.

B. Endorsement Block

See electronic signatures in DARRTS.

C. CC Block

ONDQA/DNDQA-1/H. Patel
ONDQA/DNDQA-1/M. Heimann
ONDQA/DNDQA-1/T. Bouie
DNP/S. Daugherty
DMEP/J. Weber

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

MARTHA R HEIMANN
06/01/2010

HASMUKH B PATEL
06/01/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

PHARMACOLOGY REVIEW(S)

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

NDA No. 8-372/HP Acthar gel (Corticotropin) for infantile spasms/April 23, '07

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?			The reviewer cannot comment on the item because there is no pharmacology & toxicology sections.
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?			The reviewer cannot comment on the item because there is no pharmacology & toxicology sections.
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?			The reviewer cannot comment on the item because there is no pharmacology & toxicology sections.
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? **Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA** (None)			The reviewer cannot comment on the item because there is no pharmacology & toxicology sections.

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?			The reviewer cannot comment on the item because there is no pharmacology & toxicology sections.
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?			The reviewer cannot comment on the item because there is no pharmacology & toxicology sections.
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		

8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	x		

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	x		The reviewer cannot comment on the item because there is no pharmacology & toxicology sections.
10) Reasons for refusal to file:			

Herman Rhee, Ph.D.
Reviewing Pharmacologist

Karen Davis-Bruno, Ph.D.
Supervisory Pharmacologist

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/s/

Herman Rhee
8/10/2006 12:47:06 PM
PHARMACOLOGIST

Karen Davis-Bruno
8/10/2006 01:00:28 PM
PHARMACOLOGIST
NDA filing

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-432 / N_000
Drug Name:	H.P. Acthar Gel (repository corticotropin injection)
Indication(s):	Infantile Spasms
Applicant:	Questcor Pharmaceuticals
Date(s):	Date of Document: December 10, 2009
	PDUFA due date: June 10, 2010
Review Priority:	Priority
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Jialu Zhang, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D.
	Kooros Mahjoob, Ph. D.
Medical Division:	Division of Neuropharmacological Drug Products, HFD-120
Clinical Team:	Philip Sheridan, M.D.
Project Manager:	Susan Daugherty, Pharm.D.
Keywords:	Sample size, retrospective

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List of Tables

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor obtained source efficacy data from three published, randomized, controlled studies. Among three studies, Study 222017-01 showed that Acthar Gel was significantly better than prednisone in both EEG response and clinical seizure response as well as the overall response ($p<0.01$). Study 222017-05 had 59 patients enrolled in the trial but a number of patients did not complete the study protocol, which had a considerable impact on the results of the trial. Depending on the population used for analyses, the conclusion can vary. Study 222017-04 compared Acthar low-dose with prednisone and showed that the low dose did not differ much from prednisone numerically ($p>0.99$).

Even though Study 222017-01 showed highly significant treatment effect of Acthar Gel, it is somewhat concerning that the conclusion cannot be directly confirmed in the other two trials. The analyses are retrospective and the sample size in each trial is small. With such small sample size, the study sample may not be a good representation of the intended pediatric population. The data to draw a definitive conclusion are limited. The efficacy evidence from three trials needs to be weighted carefully.

1.2 Brief Overview of Clinical Studies

The sponsor presented the efficacy results based on 3 published, randomized controlled trials (RCTs) where Acthar was evaluated for the treatment of patients with infant spasms (Baram 1996, Hrachovy 1994, Hrachovy 1983).

Study 222017-01 (Baram 1996) is a single-blind study compared high dose Acthar (150 U/ m^2/day) administered twice daily and prednisone (2 mg/kg/day) administered twice daily in patients with IS. 15 patients were randomized to Acthar and 14 patients were randomized to prednisone.

Study 222017-05 (Hrachovy 94) is a prospective, controlled, randomized, single-blind study that compared an Acthar high-dose regimen (150 U/m^2/qd) to Acthar low-dose regimen (20 U/qd) in patients with IS. 59 patients were enrolled in the study. 9 patients did not complete the treatment protocol.

Study 222017-04 (Hrachovy 83) is a randomized, controlled, double-blind study that compared low dose Acthar (20 to 30 U/day) administered as a single daily dose to prednisone at a dose of 2 mg/kg/day in patients with IS. 12 patients were randomized to Acthar Gel and 12 were randomized to prednisone.

1.3 Statistical Issues and Findings

Unlike the conventional pivotal trials submitted for drug approvals, the efficacy evidence of Acthar gel in treating infantile spasms is based on three published randomized controlled trials. Although the sponsor obtained the source efficacy data of those three trials and re-analyzed them, there was no prospectively defined statistical analysis plan. The sample size of each trial is small. With such small sample size, the study sample may not be a good representation of the intended pediatric population. Therefore the efficacy data to draw conclusions are limited. Even though the sponsor used one study (222017-04) as the pivotal trial and the other two as supportive trials, this was not determined prospectively. All three studies should be weighted carefully. Furthermore, the so-called primary endpoint may not carry as much weight as the primary endpoint in the conventional clinical trials since it was not defined prospectively.

Study 222017-05 had a number of patients who did not complete the treatment protocol. Depending on the population used for analyses, the conclusion can vary. The analyses of overall response and EEG response showed no statistically significant differences between the 2 treatment groups. The analysis of the spasm control response by IS etiology showed a nominally significant difference between the Acthar high-dose and Acthar low-dose treatment groups in favor of Acthar high-dose. This is based on the sponsor-defined mITT population. The significance disappeared if some other defined population is used (e.g., ITT population, completed patients population). Study 222017-04 showed similar overall response rate in both Acthar low-dose group and prednisone group. It cannot be determined whether it suggests that the low dose Acthar has similar effect in treatment infantile spasms as prednisone, or it is likely due to the small sample size of the trial.

2. INTRODUCTION

2.1 Overview

Out of 5 published, randomized controlled trials (RCTs) where Acthar was evaluated for the treatment of patients with infant spasms, the sponsor was able to obtain source efficacy data from the following 3 studies:

- Questcor obtained source efficacy data from the study conducted by Dr. Baram (Baram 1996). Questcor's analyses of these data are presented as CSR 222017-01. CSR 222017-01 is designated as the pivotal efficacy study.

- Questcor obtained source efficacy data from the 2 additional RCTs conducted and published by Dr. Hrachovy and colleagues (Hrachovy 1994, Hrachovy 1983). Questcor's analyses of these data are presented as CSR 222017-05 and CSR 222017-04, respectively. CSR 222017-05 is presented as the supportive efficacy study. Additional efficacy data supporting the use of Acthar for the treatment of IS patients is presented in CSR 222017-04.

Pivotal study 222017-01 is a single-blind comparison of response to treatment. It compared Acthar 150 U/ m^2/day administered as 75 U/ m^2/bid IM for 2 weeks with a taper to zero for an additional 2 weeks and prednisone 2 mg/kg/day administered as 1 mg/kg/bid orally (PO) for 2 weeks with a taper to zero over 2 weeks in patients with IS. 15 patients were randomized to Acthar and 14 patients were randomized to prednisone.

The supportive efficacy study 222017-05 is a prospective, controlled, randomized, single-blind study that compared an Acthar high-dose regimen (150 U/ m^2/qd) to Acthar low-dose regimen (20 U/qd) in patients with IS. The study enrolled 59 patients (30 in high-dose, 29 in low-dose). Nine patients (4 in the high-dose group, 5 in the low-dose group) did not complete the treatment protocol.

Study 222017-04 is a randomized, controlled, double-blind study that compared Acthar at a dose of 20 to 30 U/day administered as a single daily (20 to 30 U/qd) IM dose (Acthar low-dose) to prednisone at a dose of 2 mg/kg/day PO in patients with IS. 12 patients were randomly assigned to Acthar Gel and 12 were randomly assigned to prednisone.

2.2 Data Sources

The sponsor's electronic submission is stored under the directory of
\\Fdswa150\nonectd\N22432\N_000\2009-12-10

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY 222017-01

3.1.1.1 Study Objectives

The objective of this study was to compare the efficacy of H.P.Acthar Gel (repository Corticotropin injection or ACTH) 150 U/m^2/day and prednisone (2 mg/kg/day), administered for 2 weeks, in suppressing clinical spasms and hypsarrhythmic electroencephalogram (EEG) in patients with infantile spasms (IS).

3.1.1.2 Study Design

The study was initially designed as a single-blind comparison of response to treatment, evaluating a single dose of ACTH 20 U/day compared to ACTH 150 U/m^2/day and to prednisone (2g/kg/day) in the treatment of infants with IS. Acthar 150 U/m2/day was administered as 75 U/m2/bid IM for 2 weeks and then tapered to zero for an additional 2 weeks. Prednisone 2 mg/kg/day was administered as 1 mg/kg/bid PO for 2 weeks, and then tapered to zero over 2 weeks. The study was amended to eliminate the 20 U/day ACTH dose. As a result of the amendment, the study was a single-blind comparison of response to treatment, evaluating 150 U/m2/day ACTH and 2mg/kg/day prednisone in the treatment of infants with IS. The investigators were unblinded to the treatment assignment but the interpreter of the video -EEG was blinded. Patients with persistent spasms or hypsarrhythmia after initial treatment were offered the alternative treatment.

Patients eligible for enrollment into this study were diagnosed with clinical IS. An infant previously treated with any steroid or Acthar treatment was not eligible for the study. All patients had a 24-hour video-EEG to ascertain the presence of hypsarrhythmia before initiation of treatment. Seizure frequency was monitored throughout the 2-week treatment period by parents who maintained seizure diaries. After 2 weeks of treatment, a repeat video-EEG was performed, and both clinical and EEG responses were assessed. Video-EEG monitoring was performed for a minimum of 4 hours and optimally, for 24 hours and included a minimum of 1 full sleep-wake cycle.

3.1.1.3 Efficacy Measures

(1) Primary Efficacy Endpoint

Since this is re-analysis of a published study, the sponsor did not specify primary or secondary endpoints. The endpoints were referred as efficacy endpoints. The efficacy measure of the study was a combined clinical (seizure) and video-EEG response, which was used to establish response to treatment. In addition, the sponsor also provided analysis of response adjusted for age as well as the analysis of response to crossover treatment.

(2) Secondary Efficacy Endpoints

Not applicable.

3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

Fifteen (15) patients were randomized to Acthar and 14 patients were randomized to prednisone.

Table 1 Summary of Demographic and Baseline Characteristics

	Prednisone N[a]=14	Acthar Gel N=15	All Patients N=29	*P*-value
Age, months[b]				0.0616
Mean	7.5	5.1	6.3	
SD	4.51	2.21	3.66	
Median	7.0	5.0	6.0	
Min, Max	3, 21	2, 11	2, 21	
Gender, n[a] (%)[c]				0.0959
Female	6 (42.9)	11 (73.3)	17 (58.6)	
Male	8 (57.1)	4 (26.7)	12 (41.4)	
Etiology Category, n (%)[c]				0.9408
Symptomatic	12 (85.7)	13 (86.7)	25 (86.2)	
Cryptogenic	2 (14.3)	2 (13.3)	4 (13.8)	

a. N/n is the number of patients.
b. The comparison of age distributions between treatment groups was performed with a Mann-Whitney test.
c. The comparisons of gender and etiology category frequencies by treatment were performed with a Pearson chi-square test.

[Source: Sponsor's clinical study report 222017-01 Table 11.1, confirmed by the reviewer]

3.1.1.5 Sponsor's Primary Efficacy Results

As mentioned previously in Section 3.1.1.3, the sponsor did not specify primary or secondary endpoints. So the reviewer also referred the analyses as efficacy analyses. For a patient to be considered a responder to treatment, both video-EEG and clinical (seizure) responses were necessary. The sponsor reported that the overall response (ie, EEG plus clinical response) indicated greater efficacy of Acthar Gel (13/15, 86.7%) compared to prednisone (4/14, 28.6%), *P*=0.0015.

Table 2 Analysis of Response to Treatment

	Prednisone N=14	**Acthar Gel N=15**	***P*-value**
Overall Response (EEG + Clinical), n (%)			0.0015
Yes	4 (28.6)	13 (86.7)	
No	10 (71.4)	2 (13.3)	
EEG Response, n (%)			0.0015
Yes	4 (28.6)	13 (86.7)	
No	10 (71.4)	2 (13.3)	
Clinical Response, n (%)			0.0003
Yes	4 (28.6)	14 (93.3)	
No	10 (71.4)	1 (6.7)	

* p-value is based on Pearson Chi-square test
[Source: Sponsor's clinical study report 222017-01 Table 11.2, confirmed by the reviewer]

The sponsor performed analyses of response to treatment adjusted for age group for the overall, EEG, and clinical response. Each analysis to evaluate the relative response rate (risk) for ACTH compared to prednisone was stratified by age at 2 levels. The analysis was performed for age groups defined by thresholds at 5, 6, 7, 8, 9, or 10 months. The sponsor reported that the differences between ACTH and prednisone for EEG and clinical responses remained statistically significant favoring the ACTH treatment group after adjusting for age group ($P<0.01$, for all comparisons).

Table 3 Analyses of Overall Response to Treatment Adjusted for Age

Age Groups (Months)	N	Response	Treatment: Prednisone (N=15)	Treatment: ACTH (N=14)	Weighted Relative Risk (95% CI)	P-value (d)
< 5	9	Yes	0 (0.0%)	5 (83.3%)	3.37 (1.32, 8.58)	0.0015
		No	3 (100%)	1 (16.7%)		
>=5	20	Yes	4 (36.4%)	8 (88.9%)		
		No	7 (63.6%)	1 (11.1%)		
< 6	14	Yes	0 (0.0%)	7 (77.8%)	3.81 (1.44, 10.09)	0.0006
		No	5 (100%)	2 (22.2%)		
>=6	15	Yes	4 (44.4%)	6 (100%)		
		No	5 (55.6%)	0 (0.0%)		
< 7	19	Yes	1 (16.7%)	11 (84.6%)	3.95 (1.26, 12.38)	0.0017
		No	5 (83.3%)	2 (15.4%)		
>=7	10	Yes	3 (37.5%)	2 (100%)		
		No	5 (62.5%)	0 (0.0%)		
< 8	21	Yes	2 (25.0%)	11 (84.6%)	3.27 (1.28, 8.37)	0.0021
		No	6 (75.0%)	2 (15.4%)		
>=8	8	Yes	2 (33.3%)	2 (100%)		
		No	4 (66.7%)	0 (0.0%)		

[Source: Sponsor's clinical study report 222017-01 Section 14.2 Table 3, confirmed by the reviewer]

The p-values in the tables were calculated based on Mantel-Haenszel test by controlling the age factor. The weighted relative risk is obtained from the Estimate of the Common Relative Risk (Row1/Row2) in SAS.

Assuming that the true prednisone response rate is 28.6%, as observed in the current study, the sponsor suggested that a future study, with 15 subjects randomized to Acthar Gel and 14 to prednisone would have at least 80% power to detect a treatment difference if the true Acthar Gel response rate is at least 84.4%. The study had only 10% power to detect a 20% difference in response rates compared between treatments.

Patients were also followed up for an average of 15 months (minimum of 1 month and maximum of 48 months).

3.1.1.6 Sponsor's Secondary Efficacy Results

Not applicable.

3.1.1.7 Reviewer's Results

The reviewer confirmed sponsor's analyses of response to treatment. Due to the small numbers in each cell, it would be more appropriate to use Fisher's Exact test instead of Chi-square test to compare the response rates between Acthar Gel group and prednisone group. The results based on Fisher's Exact test are shown in the following table (Table 4). The results do not differ much from the sponsor's results.

Table 4 Analysis of Response to Treatment using Fisher's Exact Test

	Prednisone	Acthar Gel	p-value
Overall response			0.0025
Yes	4	13	
No	10	2	
EEG response			0.0025
Yes	4	13	
No	10	2	
Clinical Response			0.0005
Yes	4	14	
No	10	1	

The median follow up time in this study is 11 months and mean follow up time is 15.3 months. The minimum and maximum follow up time for the 29 patients are 1 month and 48 months, respectively. 1 patient was recorded to have relapse in the sponsor's dataset.

3.1.1.8 Conclusions

Pivotal study 222017-01 appears to show that Acthar was superior to prednisone in infant spasms using twice-daily administration and 2-week high-dose regimen with a 2-week taper.

3.1.2 STUDY 222017-05

3.1.2.1 Study Objectives

The primary objectives of this study analysis were to compare the efficacy and safety of Acthar high-dose with that of Acthar low-dose in the treatment of patients with infantile spasms (IS). The secondary objective of this study analysis was to assess efficacy based on spasm cessation alone (Spasm Control Response) and by resolution of the hypsarrhythmic EEG pattern (Hypsarrhythmia EEG Pattern Response) alone between the 2 treatment groups.

3.1.2.2 Study Design

This is a randomized, controlled, single-blind study of Acthar high-dose (150 U/m2/once-daily [qd]), long-duration (3 weeks treatment plus 9 weeks taper) versus Acthar low-dose (20 U/qd), short-duration (2 to 6 weeks treatment plus 1 to 2 weeks taper) in patients with IS. Before initiation of treatment, each patient was monitored for up to 24 hours to confirm the presence of clinical spasms and to characterize the EEG pattern. At the end of the 12-week treatment period, patients returned for an EEG monitoring session to evaluate response to therapy. Developmental testing was repeated at this time. Nonresponders were treated with prednisone, 2 mg/kg/day for 4 to 6 weeks, and then followed in a routine clinical manner. Reviewers of the monitoring studies were unaware of the dosage of ACTH administered.

3.1.2.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary efficacy endpoint was the Overall Response. An Overall Response was defined as both cessation of spasms and resolution of the hypsarrhythmic EEG pattern at any time during the study.

(2) Secondary Efficacy Endpoints

The secondary efficacy endpoints were the assessment of efficacy based on spasm cessation alone (Spasm Control Response) and by resolution of the hypsarrhythmic EEG pattern (Hypsarrhythmia EEG Pattern Response) alone between the 2 treatment groups.

Note that the original publication (Hrachovy 1994) did not use primary and secondary endpoints.

3.1.2.4 Patient Disposition, Demographic and Baseline Characteristics

Fifty-nine (59) patients were enrolled in the study. In the original publication (Hrachovy 94), only 50 out of the 59 patients were included in the analysis. Nine patients (4 in the high-dose group, 5 in the low-dose group) were excluded because they did not complete the treatment protocol due to various reasons. Among the nine patients, information from eight patients was recovered. The sponsor subsequently included all patients in the analyses as requested by the Division.

Among the fifty-nine patients, thirty (30) patients were randomly assigned to the Acthar high-dose group and 29 were randomly assigned to the Acthar low-dose group. Twelve (12) patients were withdrawn from the study prior to completion of the protocol: 4 patients were withdrawn due to AEs, 1 patient was withdrawn due to death, and 7 patients were withdrawn due to another reason. The chart for 1 patient (90-999) could not be located; based on information provided by the investigator, this patient was randomly assigned to the Acthar low-dose group Two patients (90-005, 90-006) were randomized and assigned to treatment but did not receive any Acthar doses.

Table 5 Summary of Patient Disposition by Treatment Group (ITT Population)

Parameter	Acthar High Dose n=30	Acthar Low Dose n=29	Acthar All Patients N=59
Number of patients enrolled, n (%)	30 (100)	29 (100)	59 (100)
Number of patients completed, n (%)	25 (83.3)	21 (72.4)	46 (78.0)
Number of patients with no documentation, n (%)	0	1 (3.4)	1 (1.7)
Number of patients prematurely withdrew, n (%)	5 (16.7)	7 (24.1)	12 (20.3)
Number of patients withdrew due to AEs	1 (3.3)	3 (10.3)	4 (6.8)
Number of patients withdrew due to death	0 (0.0)	1 (3.4)	1 (1.7)
Number of patients withdrawn due to other reason	4 (13.3)	3 (10.3)	7 (11.9)

[Source: Sponsor's clinical study report 222017-05 Table 10.1, confirmed by the reviewer]

There are 4 efficacy analysis populations for this study. These were defined as follows:

The mITT Population (n=51) includes all patients who were randomized, received ≥ 1 dose of Acthar study medication, and had sufficient data to evaluate the Overall Response. This was sponsor's primary efficacy analysis population.

The ITT Population (n=59) includes all patients randomized to treatment. This population included the 1 patient who was randomized to Acthar low-dose whose chart was not able to be located by Dr. Hrachovy; this is the only population that includes this patient. The ITT Population was used to perform a sensitivity analysis of the treatment efficacy response. All patients with unknown Spasm Control Response or Hypsarrhythmic EEG Pattern Response were classified as responders if in the Acthar low-dose group, and as nonresponders if in the Acthar high-dose group.

The Spasms Population (n=55) includes all patients with sufficient data to evaluate the Spasm Control Response.

The Completed Patients Population (n=50) includes the 50 patients identified by the investigators as having completed the study protocol. The Completed Patients Population was analyzed for this report so that Questcor could perform an independent analysis of the same population of patients analyzed by the investigators. This population is identical to the one used in Hrachovy 94 publication. Note that the sponsor reported 46 patients who completed study in Table 5. The sponsor stated that it was unknown what criteria were used by Dr. Hrachovy in identifying the 50 patients in his analysis. No analysis was done on the 46 "completed patients" selected by the sponsor.

The Safety Population (n=57) includes all patients known to have been dosed with ≥ 1 dose of Acthar. Patients were classified by treatment. Safety summaries were based on the Safety Population.

Table 6 and Table 7 provide summary on analysis populations, as well as demographic and baseline statistics.

Table 6 Analysis Populations by Treatment Group

	Acthar High Dose n=30	**Acthar Low Dose n=29**	**Acthar All Patients N=59**
Populations for Analysis, n (%)			
ITT Population	30 (100.0)	29 (100.0)	59 (100.0)
mITT Population	24 (80.0)	27 (93.1)	51 (86.4)
Spasms Population	28 (93.3)	27 (93.1)	55 (93.2)
Completed Patients Population	26 (86.7)	24 (82.8)	50 (84.7)
Safety Population	28 (93.3)	29 (100)	57 (96.6)

[Source: Sponsor's clinical study report 222017-05 Table 10.2, confirmed by the reviewer]

Table 7 Summary of Demographic and Baseline Characteristics

Variable	Treatment Group: Acthar High Dose n=24	Acthar Low Dose n=27	Acthar All Patients N=51
Age at onset of spasms (months)			
n	24	26	50
Mean (SD)	8.05 (5.149)	9.07 (6.31)	8.58 (5.746)
Median	6.77	6.39	6.62
Min, max	1.9, 25.2	2.6, 28.2	1.9, 28.2
Age at start of treatment (months)			
n	24	26	50
Mean (SD)	8.25 (5.159)	9.31 (6.457)	8.8 (5.836)
Median	6.98	6.41	6.72
Min, max	1.9, 25.2	2.6, 28.2	1.9, 28.2
Sex, n (%)			
Male	12 (50.0)	19 (70.4)	31 (60.8)
Female	12 (50.0)	8 (29.6)	20 (39.2)
Race, n (%)			
White	9 (37.5)	11 (40.7)	20 (39.2)
Black or African-American	5 (20.8)	6 (22.2)	11 (21.6)
Unknown	9 (37.5)	7 (25.9)	16 (31.4)
Other	1 (4.2)	0 (0.0)	1 (2.0)
Etiology Category, n (%)			
Symptomatic	17 (70.8)	18 (66.7)	35 (68.6)
Cryptogenic	7 (29.2)	9 (33.3)	16 (31.4)

* one patient did not have data for age
[Source: Sponsor's clinical study report 222017-05 Table 10.3, confirmed by the reviewer]

3.1.2.5 Sponsor's Primary Efficacy Results

The Overall Response rate in the mITT Population (N=51) was 15/24 (62.5%) in the Acthar high-dose group and 13/27 (48.1%) in the Acthar low-dose group. The risk ratio was 1.318. However, the Overall Response rates between the 2 groups were not significantly different. The treatment comparison was *P*=0.2768.

The Overall Response rate in the ITT Population sensitivity analysis (N=59) was 15/30 (50.0%) in the Acthar high-dose group and 15/29 (51.7%) in the Acthar low-dose group. The risk ratio was 0.982. The Overall Response rates in the sensitivity analysis were not significantly different. The treatment comparison was *P*=0.9443.

The sponsor attributed the non-significant results of the trial to the once-daily administration of Acthar in this trial. In this study, Acthar was administered as a once-daily dose of 150 U/m^2. Although this daily dose was equivalent to the total daily dose in CSR 222017-01, the Acthar in the CSR 222017-01 was administered as 2 divided daily doses (ie, 75 U/m^2 per dose). The sponsor argued that this once-daily dosing could yield a lower ACTH accumulation when compared to the ACTH accumulation from twice-daily dosing.

3.1.2.6 Sponsor's Secondary Efficacy Results

The Spasm Control Response rate in the mITT Population (N=51) was greater in the Acthar high-dose group (19/24, 79.2%) than in the Acthar low-dose group (14/27, 51.9%). The risk ratio was 1.553 and the treatment comparison was *P*=0.0329.

The Hypsarrhythmic EEG Pattern Response rate in the mITT Population (N=51) was 16/24 (66.7%) in the Acthar high-dose and 14/27 (51.9%) in the Acthar low-dose groups. The risk ratio was 1.299 and the treatment comparison was *P*=0.2686.

The sponsor also performed a number of sensitivity analyses based on different populations as shown in Table 8, Table 9, and Table 10 (ITT population, spasm population, and completed patients population). The p-values were calculated based on Mantel-Haenszel test comparing response rates between treatments, stratified on etiology. The risk ratio is the common relative risk calculated by PROC FREQ procedure.

Table 8 Sensitivity Analyses in ITT Population (N=59)

Outcome	Acthar Treatment	n	Responders n (%)	Nonresponders n (%)	Risk Ratio	*P*-value
Overall Response	High Dose	30	15 (50.0)	15 (50.0)	0.982	0.9443
	Low Dose	29	15 (51.7)	14 (48.3)		
Spasm Control Response	High Dose	30	23 (76.7)	7 (23.5)	1.410	0.0691
	Low Dose	29	16 (55.2)	13 (44.8)		
Hypsarrhythmic EEG Pattern Response	High Dose	30	16 (53.3)	14 (46.7)	0.865	0.5209
	Low Dose	29	18 (62.1)	11 (37.9)		

[Source: Sponsor's clinical study report 222017-05 Table 11.4, confirmed by the reviewer]

There were 4 patients in the low dose group who did not have complete EEG data and were therefore assigned as EEG responders in the ITT analysis (Patients 90-007, 90-008, 90-999, and 97-068).

Table 9 Sensitivity Analyses in Spasms Populations (N=55)

Outcome	Acthar Treatment	n	Responders n (%)	Nonresponders n (%)	Risk Ratio	*P*-value
Overall Response	High Dose	28	15 (53.6)	13 (46.4)	1.133	0.6363
	Low Dose	27	13 (48.1)	14 (51.9)		
Spasm Control Response	High Dose	28	23 (82.1)	5 (17.9)	1.612	0.0126
	Low Dose	27	14 (51.9)	13 (48.1)		
Hypsarrhythmic EEG Pattern Response	High Dose	28	16 (57.1)	12 (42.9)	1.116	0.6580
	Low Dose	27	14 (51.9)	13 (48.1)		

[Source: Sponsor's clinical study report 222017-05 Table 11.5, confirmed by the reviewer]

Table 10 Sensitivity Analyses in Completed Patients Populations (N=50)

Outcome	Acthar Treatment	n	Responders n (%)	Nonresponders n (%)	Risk Ratio	*P*-value
Overall Response	High Dose	26	15 (57.7)	11 (42.3)	1.058	0.8225
	Low Dose	24	13 (54.2)	11 (45.8)		
Spasm Control Response	High Dose	26	21 (80.8)	5 (19.2)	1.374	0.0782
	Low Dose	24	14 (58.3)	10 (41.7)		
Hypsarrhythmic EEG Pattern Response	High Dose	26	16 (61.5)	10 (38.5)	1.050	0.8349
	Low Dose	24	14 (58.3)	10 (41.7)		

[Source: Sponsor's clinical study report 222017-05 Table 11.6, confirmed by the reviewer]

3.1.2.7 Reviewer's Results

The reviewer is able to confirm the results reported by the sponsor. The reviewer compared response rates across all three trials (Table 11). While the response rates in prednisone group and in ACTH low dose group vary in different trials, the response rates in ACTH high dose group differ the most across trials. The response rate in ACTH high dose group is much lower in Study 222017-05 than in Study 222017-01. One possible explanation of the rate difference could be due to the once-daily dosing versus the twice-daily dosing and this would be agreeable to the sponsor's argument.

3.1.2.8 Conclusions

The efficacy results in Study 222071-01 cannot be confirmed in this trial. The analysis of Overall Response (spasms cessation and resolution of the hypsarrhythmic pattern on EEG) showed no statistically significant differences between the 2 treatment groups in any of the 4 defined populations. The analysis of the Spasm Control Response by IS etiology, however, showed a nominal statistical significance between the Acthar high-dose and Acthar low-dose treatment groups in favor of Acthar high-dose (P=0.0329) based on the sponsor-defined mITT population.

Even though this is the largest study among three studies included in this application, the sample size is still small. The study can be underpowered. The different administration of ACTH (twice-daily in Study 222017-01 versus once-daily in Study 222017-05) may have effect on the outcome; however, it cannot be proven definitively. The efficacy results of this study remain inconclusive.

Table 11 Comparison of Response Rates across All Three Studies

	Acthar Gel						prednisone		
	High dose			Low dose					
Study	overall response rate (%)	EEG response rate (%)	clinical response rate (%)	overall response rate (%)	EEG response rate (%)	clinical response rate (%)	overall response rate (%)	EEG response rate (%)	clinical response rate (%)
222017-01	86.7	86.7	93.3	NA	NA	NA	28.6	28.6	28.6
222017-05*	62.5	66.7	79.2	48.1	51.9	51.9	NA	NA	NA
222017-04**	NA	NA	NA	41.7	75.0	41.7	33.3	41.7	33.3

* Based on mITT population defined by the sponsor

** The response rates are calculated using initial stage only

3.1.3 STUDY 222017-04

3.1.3.1 Study Objectives

The primary objective of this study was to compare the efficacy of H.P. Acthar Gel (repository corticotropin injection) (20 to 30 U/day) with prednisone (2 mg/kg/day) in treating infantile spasms (IS).

3.1.3.2 Study Design

This is a double-blind crossover study of Acthar Gel or prednisone therapy in patients with IS. After completion of a baseline 24 to 48-hour monitoring period to confirm the presence of IS and to establish a baseline seizure frequency, patients were randomly assigned to receive Acthar Gel 20 U/day intramuscularly (IM) and a prednisone placebo orally (PO) or prednisone 2 mg/kg/day PO and an Acthar Gel placebo IM, for 2 weeks. Acthar Gel and matching placebo were administered as a single dose/day. Prednisone and matching placebo were administered as 2/mg/kg/day.

If the patient responded to therapy within the first 2 weeks, the dosage of the drug was tapered to zero over a 1 to 2-week period. Then, the patient was monitored at 2 weeks and 6 weeks after discontinuation of therapy to substantiate a continued response.

If a patient did not respond after the first 2 weeks, therapy was continued (Acthar Gel 30 U/day or prednisone 2 mg/kg/day) for an additional 4 weeks, after which study drug was tapered to zero over a 2-week period.

Nonresponders to the initial 2 weeks of therapy or the additional 4 weeks of therapy were then crossed over to the other drug after a 1-week washout period, and the protocol was repeated. Patients who failed to respond to either Acthar Gel or prednisone were treated with clonazepam (0.03 to 0.18 mg/kg/day) over an 8-week period. Note that the so-called cross-over is not a typical cross-over design in the clinical trial. In this trial, the sponsor simply re-assigned the non-responders to the other treatment group. It did not involve all subjects in the trial.

The response to therapy was evaluated at specific times throughout the study by 24-hour video and polygraphic monitoring, developmental testing, and determination of serum cortisol concentrations.

3.1.3.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary response to therapy in this study was defined as total cessation of spasms and disappearance of the hypsarrhythmic EEG pattern. Spasms and hypsarrhythmic EEG pattern were assessed by serial 24-hour video and polygraphic monitoring.

(2) Secondary Efficacy Endpoints

Secondary endpoints included EEG changes in nonresponders and changes in mental and developmental status.

Note that again the original publication (Hrachovy 1983) did not use primary and secondary endpoints.

3.1.3.4 Patient Disposition, Demographic and Baseline Characteristics

Twenty-four infants with IS and hypsarrhythmic EEG patterns were enrolled in the study; 12 were randomly assigned to Acthar Gel plus prednisone placebo and 12 were randomly assigned to prednisone and an Acthar Gel placebo.

Table 12 Summary of Patient Disposition by Treatment Group

	Acthar Gel N=12 n (%)	Prednisone N=12 n (%)	All Patients N=24 n (%)
Number of patients enrolled	12 (100.0)	12 (100.0)	24 (100.0)
Number of patients completed initial phase[a]	9 (75.0)	12 (100.0)	21 (87.5)
Number of patients in the crossover phase	4 (33.3)	8 (66.7)	12 (50.0)
Number of patients prematurely withdrew	3 (25.0)	0 (0.0)	3 (12.5)
Number of patients withdrew due to AEs	2 (16.7)	0 (0.0)	2 (8.3)
Number of patients withdrew due to death	0 (0.0)	0 (0.0)	0 (0.0)
Number of patients withdrew due to other reason	1 (8.3)	0 (0.0)	1 (4.2)

[Source: Sponsor's clinical study report 222017-04 Table 10.1, confirmed by the reviewer]

The median age of all patients is 8.20 months (range: 3.5 to 24.4 months) at start of treatment. More patients are female (14/24, 58.3%) than male (10/24, 41.7%). Most patients are White (15/24, 62.5%). The majority of patients had symptomatic etiology of IS (19/24, 79.2%); 8 patients (8/24, 66.7%) were symptomatic in the Acthar Gel group and 11 patients (11/24, 91.7%) were symptomatic in the prednisone group.

3.1.3.5 Sponsor's Primary Efficacy Results

There is no difference in overall response rate between Acthar Gel and prednisone in patients who were non-responders in the initial phase of the study and who received these treatments as alternative therapy in the crossover phase of the study.

Table 13 Analysis of Response to Treatment

Treatment Phase	Treatment	N	Treatment Response			*P*-value[a]
			EEG Responder	Clinical Spasms Responder	Overall Responder	
Initial	Acthar Gel	12	9 (75.0%)	5 (41.7)	5 (41.7)	>0.9999
	Prednisone	12	5 (41.7)	4 (33.3)	4 (33.3)	
Crossover[b]	Acthar Gel	8	3 (37.5)	4 (50.0)	3 (37.5)	>0.9999
	Prednisone	7	4 (57.1)	3 (42.9)	3 (42.9)	
Final[c]	Acthar Gel	13	8 (61.5)	9 (69.2)	8 (61.5)	ND[d]
	Prednisone	11	8 (72.7)	7 (63.6)	7 (63.6)	

a. *P*-value based on the 2-sided Fisher's exact test for treatment effect on overall response rate.
b. Crossover was conditional, including only patients did not respond to initial treatment.
c. Count based on each patient's last treatment. If patient did not crossover to another treatment then final treatment was the initial treatment, if a patient did crossover then crossover treatment was the final treatment
d. Not done because final treatment was not randomly assigned but a mix of initial treatment randomization and crossover conditional on initial treatment response.

[Source: Sponsor's clinical study report 222017-04 Table 11.1]

3.1.3.6 Sponsor's Secondary Efficacy Results

There does not appear to be a relationship between treatment or treatment response and change in mental and developmental status. Complete disappearance of the hypsarrhythmic EEG pattern was reported in 1 nonresponder (1/9, 11.1%).

The sponsor argued that the trial was under powered to show a meaningful treatment difference.

3.1.3.7 Reviewer's Results

The reviewer is able to confirm the results reported by the sponsor.

Note that the so-called cross-over is not a typical cross-over design in the clinical trial. In this trial, the sponsor simply re-assigned the non-responders to the other treatment group. It did not involve all subjects in the trial. The reviewer would focus only on the initial stage as the result is much easier to interpret.

3.1.3.8 Conclusions

The sponsor argued that this study evaluated a dose that is below that being recommended by Questco. The overall response rates seen in these analyses to both Acthar low-dose and prednisone are similar between the 2 treatments. Again, the sample size is small and the efficacy data are limited. The results can be due to the small sample size or due to ineffectiveness of the low dose ACTH. Conclusion on efficacy of ACTH cannot be drawn based on this trial.

3.2 Evaluation of Safety

Please refer to the clinical review for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

Due to small number of patients enrolled in each of the trial, it is hard to reach any conclusion based on subgroup analyses. The reviewer provided summary statistics for each study.

Please refer to Table 3 for subgroup analysis by age in Study 222017-01. Table 14 shows the number of overall responses in each gender. Ethnicity information is not available in Study 222017-01.

Table 14 Summary of Overall Responses by Gender in Study 222017-01

	Acthar Gel		Prednisone	
Gender	N	responses	N	Responses
female	11	9	6	1
male	4	4	8	3

Table 15 Summary of Overall Responses by Subgroups in Study 222017-05

	Acthar High Dose		Acthar Low Dose	
	N*	Responses	N	Responses
White	10	6	11	4
Other	17	9	13	8
Female	14	5	8	4
Male	14	10	19	9
Age>7 month	16	9	13	7
Age<=7 month	12	6	14	6

* Total number of patients may not add up across subgroups due to some missing information

Subgroup analyses in study 222017-04 are based on initial stage before non-responders were crossed over to the other treatment group.

Table 16 Summary of Responses by Subgroups in Study 222017-04

	Acthar		Prednisone	
	N	Responses	N	Responses
White	7	3	8	2
Other	5	2	4	2
Female	7	3	7	3
Male	5	2	5	1
Age>7 month	7	3	9	3
Age<=7 month	5	2	3	1

4.2 Other Subgroup Populations

Other subgroup analyses are not performed in this review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Unlike the conventional pivotal trials submitted for drug approvals, the efficacy evidence of Acthar gel in treating infantile spasms is based on three published randomized controlled trials. Although the sponsor obtained the source efficacy data of those three trials and re-analyzed them, there was no prospectively defined statistical analysis plan. The sample size of each trial is small. With such small sample size, the study sample may not be a good representation of the intended pediatric population. Therefore the efficacy data to draw conclusions are limited. Even though the sponsor used one study (222017-04) as the pivotal trial and the other two as supportive trials, this was not determined prospectively. All three studies should be weighted carefully. Furthermore, the so-called primary endpoint may not carry as much weight as the primary endpoint in the conventional clinical trials since it was not defined prospectively.

Study 222017-05 had a number of patients who did not complete the treatment protocol. Depending on the population used for analyses, the conclusion can vary. The analyses of overall response and EEG response showed no statistically significant differences between the 2 treatment groups. The analysis of the spasm control response by IS etiology showed a nominally significant difference between the Acthar high-dose and Acthar low-dose treatment groups in

favor of Acthar high-dose. This is based on the sponsor-defined mITT population. The significance disappeared if some other defined population is used (e.g., ITT population, completed patients population). Study 222017-04 showed similar overall response rate in both Acthar low-dose group and prednisone group. It cannot be determined whether it suggests that the low dose Acthar has similar effect in treatment infantile spasms as prednisone, or it is likely due to the small sample size of the trial.

The reviewer compared response rates across all three trials for consistency (Table 11). While the response rates in prednisone group and in ACTH low dose group vary in different trials, the response rates in ACTH high dose group differ the most across trials. The response rate in ACTH high dose group is much lower in Study 222017-05 than in Study 222017-01.

5.2 Conclusions and Recommendations

The sponsor obtained source efficacy data from three published, randomized, controlled studies. Among three studies, Study 222017-01 showed that Acthar Gel was significantly better than prednisone in both EEG response and clinical seizure response as well as the overall response ($p<0.01$). Study 222017-05 had 59 patients enrolled in the trial but a number of patients did not complete the study protocol, which had a considerable impact on the results of the trial. Depending on the population used for analyses, the conclusion can vary. Study 222017-04 compared Acthar low-dose with prednisone and showed that the low dose did not differ much from prednisone numerically ($p>0.99$).

Even though Study 222017-01 showed highly significant treatment effect of Acthar Gel, it is somewhat concerning that the conclusion cannot be directly confirmed in the other two trials. The analyses are retrospective and the sample size in each trial is small. With such small sample size, the study sample may not be a good representation of the intended pediatric population. The data to draw a definitive conclusion are limited. The efficacy evidence from three trials needs to be weighted carefully.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIALU ZHANG
04/02/2010

KUN JIN
04/02/2010
I concur with this review.

KOOROS MAHJOOB
04/05/2010
I read this review and I discussed my views with the reviewer. My views are incorporated in this final version and I concur with that.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

Complete Response to 5/10/07 NA Letter

PRODUCT (Generic Name):	ACTH
PRODUCT (Brand Name):	H.P. Acthar® Gel
DOSAGE FORM:	Repository Injection
NDA:	22432/8372
SUBMISSION DATE:	12/11/2009
SPONSOR:	Questcor
INDICATION:	Infantile spasms
REVIEWER:	Ju-Ping Lai, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

BACKGROUND

In this submission, the sponsor provided the complete response to the Non-approvable letter of H.P. Acthar® Gel issued on May 7, 2007. In addition, the sponsor provided the updated version of the proposed label on 4/28/10.

The clinical pharmacology issue in the complete response is the appropriateness putting (b) (4) . The original clinical pharmacology review of NDA 08-372 s039 dated 4/20/2007 concluded that the proposal to include labeling language (b) (4) was not acceptable. During the meeting on 11/9/07 for discussing the deficiencies listed in the Not Approval Letter, the Agency asked the sponsor to obtain the original data of the publication and perform the analysis appropriately. Questcor tried to obtain these source data from the study authors but the data were no longer available.

Per the sponsor's meeting minutes, the discussion for this issue was summarized below.

DNP encouraged that all effort was to be made to obtain individual plasma data from each infant on any RCTs. The Agency also requested that Questcor attempt to obtain the pharmacokinetic/pharmacodynamic (PK/PD) subject records supporting the publication by Snead (1989) (Section 7, Appendices). However, if these data are not available and if the safety and efficacy data obtained are sufficient, it may be possible to gain approval without the PK data.

> *DNP recognized that it is not practical for Questcor to conduct a conventional PK/PD study in subjects being treated for IS. Questcor has confirmed that neither data nor samples are available in support of the publication by Dr. Snead. Dr. Snead and colleagues are no longer at the institution where the study was*

conducted. Interactions with (b) (4) *and* (b) (4) *in* (b) (4)*, also concluded that these data could not be located.*

Based on the meeting discussion and the fact that the individual data are not available, this NDA therefore was reviewed based on the efficacy and safety data.

These information has been addressed in the Clinical Pharmacology 2/12/2009 review.

(b) (4)

(b) (4)

Reviewer's comments:

To be consistent with previous review, using (b) (4) is considered inappropriate for the labeling language. Therefore, the proposed description for pharmacokinetics and

pharmacodynamics following a single H.P. Acthar Gel 75 units/m^2 should be removed from the sponsor's proposed labeling.

LABELING COMMENTS

The edits for the labeling are shown as the tracking change below.

12.1 Mechanism of Action

The mechanism of action of H.P. Acthar Gel in the treatment of infantile spasms is unknown.

H.P. Acthar Gel and endogenous ACTH stimulate the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a number of weakly androgenic substances. Although H.P. Acthar Gel and endogenous ACTH do stimulate secretion of aldosterone, the rate is relatively independent. Prolonged administration of large doses of H.P. Acthar Gel induces hyperplasia and hypertrophy of the adrenal cortex and continuous high output of cortisol, corticosterone and weak androgens. The release of endogenous ACTH is under the influence of the nervous system via the regulatory hormone released from the hypothalamus and by a negative corticosteroid feedback mechanism. Elevated plasma cortisol suppresses ACTH release.

H.P. Acthar is also reported to bind to melanocortin receptors.

The trophic effects of endogenous ACTH and H.P. Acthar Gel on the adrenal cortex are not well understood beyond the fact that they appear to be mediated by cyclic AMP.

ACTH rapidly disappears from the circulation following its intravenous administration; in man the plasma half-life is about 15 minutes. The pharmacokinetics of H.P. Acthar Gel has not been well characterized.

The maximal effects of a trophic hormone on a target organ are achieved when optimal amounts of hormone are acting continuously. Thus, a fixed dose of H.P. Acthar Gel will demonstrate a linear increase in adrenocortical secretion with increasing duration for the infusion.

(b) (4)

Ju-Ping Lai, Ph.D.
Division of Clinical Pharmacology I

Team Leader: Angela Men, M.D., Ph.D._____

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/s/

Ju Ping LAI
10/01/2010

YUXIN MEN
10/01/2010

Clinical Pharmacology/Biopharmaceutics Review
Completed Response to Not Approval Letter

PRODUCT (Generic Name):	ACTH
PRODUCT (Brand Name):	H.P. Acthar® Gel
DOSAGE FORM:	Repository Injection
NDA:	22432, 8372
SUBMISSION DATE:	11/26/08
INTERNAL MEETING:	12/11/08
SPONSOR:	Questcor
INDICATION:	Infantile spasms
REVIEWER:	Ju-Ping Lai, Ph.D.
ACTING TEAM LEADER:	Veneeta Tandon, Ph.D.
OCP DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

OBJECTIVES

In this submission, the sponsor submitted their second and final rolling submission for the completed responses to the Not Approval Letter issued on 5/10/07 regarding a supplemental NDA8372/s-039 for the indication of infantile spasms. The sponsor intended to address the deficiencies in the letter and gain approval for their product. This submission is not considered complete response due to inadequate electronic format.

BACKGROUND

The first rolling submission was received on 8/25/08 mainly addressing the efficacy issues while this second submission focused on the safety and labeling issues. The deficiencies in the Not Approval Letter were listed below.

(b) (4)

(b) (4)

The sponsor requested a meeting on 11/9/07 for discussing the deficiencies and intended to file an amendment to address these deficiencies. The sponsor asked 4 questions seeking agency's feedbacks. Only question #2 was related to clinical pharmacology and responded by OCP. This question and related communications are shown below.

Question 2: Considering all of the dose comparative safety data (low-dose versus high-dose) from the Hrachovy (1994) RCT, along with of all of the safety and efficacy data, presented in this submission that includes RCT data, relevant non-RCT data and the comprehensive retrospective chart review for safety data from Partikian and Mitchell (2007), does the FDA agree that these data are adequate to demonstrate that Acthar Gel can be safely and effectively administered according to the Acthar Gel label without the need to conduct a PK/PD study and that Questcor has adequately addressed the FDA's concerns?

FDA Preliminary Response:
The previous review of NDA 08-372 s039 concluded that the proposal to include labeling language (b) (4) **was not acceptable. The sponsor should obtain the original data of the publication and perform the analysis appropriately; otherwise, a clinical pharmacology study should be conducted. The study should define the pharmacokinetic parameters in this age group along with the effects of covariates (including demographics).**

If a clinical study is required, we recommend that the exposure response (including both effectiveness and safety) relationship be explored to provide information for selecting the appropriate dosing regimen. The currently available data demonstrate that, while the adverse events seem to be related to dose, the high dose group did not show more benefit over the low dose group.

Discussion:
The Division suggested that, in addition to the Baram and postmarketing safety data, the Sponsor should also obtain records from Physicians that have treated patients with Acthar Gel. The Sponsor stated that they would try to get the raw data to perform the analysis appropriately for the PK parameters.

The Sponsor stated that the incidence for IS 1,000/year and the prevalence is 1/10,000.

In addition to Agency's meeting minutes above, as the sponsor also summarized the primary outcomes from the meeting, below is the summary related to the PK/PD issue and stated in the submission #1 (p17).

DNP encouraged that all effort was to be made to obtain individual plasma data from each infant on any RCTs. The Agency also requested that Questcor attempt to obtain the pharmacokinetic/pharmacodynamic (PK/PD) subject records supporting the publication by Snead (1989) (Section 7, Appendices). However, if these data are not available and if the safety and efficacy data obtained are sufficient, **it may be possible to gain approval without the PK data**.

> **DPN recognized that it is not practical for Questcor to conduct a conventional PK/PD study in subjects being treated for IS.** Questcor has confirmed that neither data nor samples are available in support of the publication by Dr. Snead. Dr. Snead and colleagues are no longer at the institution where the study was conducted. Interactions with (b) (4) and (b) (4) in (b) (4), also concluded that these data could not be located.

RECOMMENDATION FROM CLINICAL PHARMACOLOGY

There are no comments regarding the response to the Not Approval issues from a clinical pharmacology perspective as long as the safety and efficacy are appropriately demonstrated. Although PK, PK/PD and/or exposure response studies might not be required for addressing the deficiencies, using (b) (4) for the labeling language is inappropriate. In addition, the reference cited in section 12.2 Pharmacodynamics is also incorrect.

Post Internal meeting conclusion:

This submission is not considered complete response due to inadequate electronic format submitted. The sponsor was informed that the review clock will not start until we receive a complete response. Based on this, the sponsor has proposed a resubmission plan on 1/7/2009.

Ju-Ping Lai, Ph.D.
Division of Clinical Pharmacology I

Acting Team Leader: Veneeta Tandon, Ph.D._____

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/s/

Ju-Ping Lai
2/12/2009 12:36:10 PM
BIOPHARMACEUTICS

Veneeta Tandon
2/12/2009 12:47:04 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: **September 27, 2010**

To: Susan Daugherty
Senior Regulatory Health Project Manager
DNP

CC: Mary Dempsey
Project Management Officer
OSE, DRISK

Sharon Mills
Acting Team Leader
OSE, DRISK

From: Sharon Watson, PharmD
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: Drug: H.P. Acthar® Gel (Repository Corticotropin)
NDA: 022432

DDMAC has reviewed the 9/24/10 DRISK review of the proposed Medication Guide (Med Guide) for H.P. Acthar Gel in comparison with the proposed FDA-approved product labeling (PI). DDMAC's comments are provided directly on the clean version of this proposed Med Guide document, attached below.

Thank you for the opportunity to comment on this proposed Med Guide.

If you have any questions or concerns regarding these comments, please contact me.

7 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

SHARON M WATSON
09/27/2010

Division of Drug Marketing, Advertisement, and Communications

Internal Consult

****Pre-decisional Agency Information****

To: Russell Katz, MD, Director, Division of Neurology Products (DNP)
Norman Hershkowitz, MD, Team Leader, DNP
Susan B Daugherty, Senior Regulatory Project Manager, DNP

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Reviewer, Division of Drug Marketing, Advertising, and Communications, (DDMAC)

CC: Andy Haffer, PharmD, Group Leader, DDMAC

Date: September 24, 2010

Re: Comments on draft labeling (Package Insert) for H.P. Acthar Gel (repository corticotropin) Injection

NDA 22-432

Thank you for the opportunity to review the proposed PI for H.P. Acthar Gel (FDA dated version 9/20/2010). Please see attached PI with our comments incorporated therein.

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/s/

QUYNH-VAN TRAN
09/27/2010

CLINICAL CONSULTATION

DATE CONSULT RECEIVED: Jan. 19, 2010

DATE CONSULT COMPLETED: May 26, 2010

FROM: William Lubas, MD-PhD, Medical Officer
Division of Metabolism and Endocrinology Products, HFD-510

THROUGH: Dragos Roman, MD, Team Leader, DMEP
Mary Parks, MD, Division Director, DMEP

TO: Susan Daugherty, RPM
Division of Neurology Products

SUBJECT: PLR review of H.P. Acthar Gel

MATERIAL EVALUATED IN THIS REVIEW

- The consult request from Division of Neurology Products
- Latest PLR version of submitted to the EDR on April 28, 2010
  \\FDSWA150\NONECTD\N22432\N_000\2010-04-28
- H.P. Acthar Gel and Cosyntropin Review: Clinical and Financial Implications.
  http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2697107/pdf/ptj34_5p250.pdf
- PLR version of Flo-Pred (prednisolone acetate) steroid class label
  http://darrts/darrts/ViewDocument?documentId=090140af801d4109

INTRODUCTION

H. P. Acthar Gel (Repository Corticotropin Injection) contains the full length 39-amino acid human native ACTH molecule in a 16% gelatin gel to provide for prolonged release after intramuscular or subcutaneous injection. Endogenous ACTH stimulates the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a number of weakly androgenic substances. It is presumed that the mechanism of action of H. P. Acthar Gel is most likely mediated by the relative increase in production of these individual steroid hormones, however, the exact mechanism of action for specific indications, such as treatment of infantile spasms, is not known.

Repository Corticotropin Injection was originally approved in 1952 for a variety of disorders and diseases that at the time were thought to benefit from steroid mediated immunosuppression including:

> COLLAGEN DISEASES - Acute Lupus Erythematosus; Psoriatic Arthritis; Rheumatoid Arthritis; Rheumatic Fever; Rheumatoid Spondylitis; Still's Disease.

HYPERSENSITIVITIES – Acquired Hemolytic Jaundice, Angioneurotic Edema, Contact Dermatitis, Drug Sensitivities, Severe Bronchial Asthma, Severe Hay Fever, Urticaria.

ACUTE INLFAMMATORY DISEASES OF THE EYE - Acute Secondary Glaucoma; Choroiditis; Conjunctivitis; Iritis; Keratitis; Optic Neuritis; Sympathetic Ophthalmia; Uveitis.

ACUTE INLFAMMATORY DISEASES OF THE SKIN – Acute Psoriasis unresponsive to usual treatment, Exfoliative Dermatitis, Severe Pemphigus.

NEPHROTIC SYNDROME

METABOLIC DISEASES – Acute Gouty Arthritis, Congenital Idiopathic Hypoglycemia.

ULCERATIVE COLITIS

ALCHOLISM AND DELIRIUM TREMENS

BURNS

BURSISTIS; TENOSYNOVITIS

PANHYPOPITUITARISM

OTHER USES – ACTHAR (Corticotropin) preparation have also been used in numerous other disease states, such as: Diagnosing adrenal cortical insufficiency and Addison's disease, Acute Leukemia and Chronic Lymphatic Leukemia; Acute Overwhelming Infections; Agranulocytosis; Beryllium Poisoning; Guillain-Barre Syndrome; Hodgkin's Disease; Loeffler's Syndrome; Stevens-Johnson Syndrome; Radiation Sickness, and Vasomotor Rhinitis.

The initial approval of H.P. ACTH gel occurred prior to the Kefauver-Harris amendment to the Federal Food, Drug and Cosmetic Act of 1962, which introduced the requirement of "substantial evidence" of two adequate and well controlled trials. At the time of the original approval drug manufacturers only had to show the drug was safe for use in humans. The original data included case reports from a few physicians describing patients with conditions originally treated with Acthar powder that were transferred to treatment with Acthar Gel and gave dosing guidance for treatment of these individual conditions. A few patients had improvements in hematology data and improvement in symptoms (decreased diarrhea, improved appetite, sense of well being, etc.) reported to support the efficacy of treatment. Additional indications for sarcoidosis, anogenital pruritis, nonsuppurative thyroiditis, and nontropical sprue were added in 1954 using additional information from case reports in the literature. These data would be grossly

inadequate to support approval of a new drug or new indications by the Agency under current standards requiring evidence from adequate and well-controlled clinical trials.

A Drug Efficacy Study Implementation (DESI) review of corticotrophin injection was initiated in 1971 and finalized in 1977. Changes to the package insert as part of the initiation of the DESI review in 1971 included the following:

> H.P. ACTHAR® GEL (Repository Corticotropin Injection) is indicated for diagnostic testing of adrenocortical function.
>
> H.P. ACTHAR GEL® (Repository Corticotropin Injection) has limited therapeutic value in those conditions responsive to corticosteroid therapy; however, corticosteroid therapy is considered to be the treatment of choice. H.P. ACTHAR® GEL (Repository Corticotropin Injection) may be employed in the following disorders:
>
> > RHEUMATIC DISORDERS: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Psoriatic arthritis, Rheumatoid arthritis; Ankylosing spondylitis; Acute and subacute bursitis; Acute nonspecific tenosynovitis; Acute gouty arthritis.
> >
> > COLLAGEN DISEASES: During an exacerbation or as maintenance in selected cases of Systemic lupus erythematosus; Systemic Dermatomyositis (polymyositis); Acute Rheumatic carditis.
> >
> > DERMATOLOGIC DISEASES: Pemphigus; Bullous dermatitis herpetiformis; Severe erythema multiforme (Stevens- Johnson syndrome); Exfoliative dermatitis; Severe psoriasis.
> >
> > ALLERGIC STATES: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment— Seasonal or perennial allergic rhinitis; Bronchial asthma; Contact dermatitis; Atopic dermatitis; Serum sickness.
> >
> > OPHTHALMIC DISEASES: Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: Allergic conjunctivitis; Keratitis; Herpes zoster ophthalmicus Iritis; Diffuse posterior uveitis and choroiditis; Optic neuritis; Sympathetic ophthalmia.
> >
> > RESPIRATORY DISEASES: Symptomatic sarcoidosis; Loeffler's syndrome not manageable by other means; Berylliosis.
> >
> > HEMATOLOGIC DISORDERS: Acquired (autoimmune) hemolytic anemia.
> >
> > NEOPLASTIC DISEASES: For palliative management of: Leukemias and lymphomas in adults; Acute leukemia of childhood.

EDEMATOUS STATE: To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.

MISCELLANEOUS: Tuberculous meningitis with subarachnoid block or impending block when concurrently accompanied by appropriate antituberculous chemotherapy. Trichinosis of neurologic or myocardial involvement.

ACTHAR® (Corticotropin Injection) and H.P ACTHAR® GEL (Repository Corticotropin Injection) may also be useful in the following conditions:

METABOLIC DISORDER: Congenital idiopathic hypoglycemia.

ALLERGIC STATES: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment: Angioedema; Urticaria.

RESPIRATORY DISEASES: Pulmonary emphysema where bronchospasm or bronchial edema plays a significant role.

GASTROINTESTINAL DISEASES: To tide the patient over a critical period of the disease in: Ulcerative colitis; Crohn's disease; Intractable sprue.

HEMATOLOGIC DISORDERS: Infectious mononucleosis

The following additional indications were added in 1977 as part of S-016:

ENDOCRINE DISORDERS: Nonsupportive thyroiditis; Hypercalcemia associated with cancer.

RHEUMATIC DISORDERS: Post-traumatic arthritis; Synovitis of osteoarthritis; Epicondylitis.

DERMATOLOGIC DISEASES: Severe seborrheic dermatitis; Mycosis fungoides.

OPHTHALMIC DISEASES section: Iridocyclitis; Chorioretinitis; Anterior segment inflammation; Allergic corneal marginal ulcers.

RESPIRATORY DISEASES section: Fulminating or disseminated pulmonary tuberculosis when used concurrently with antituberculous chemotherapy; Aspiration pneumonitis.

HEMATOLOGIC DISORDERS section: Idiopathic thrombocytopenia purpura in adults (i.v. only; I.M. is contraindicated); Secondary thrombocytopenia in adults; Erythroblastopenia (RBC anemia); Congenital (erythroid) hypoplastic anemia.

GASTROINTESTINAL DISEASES section: Regional enteritis.

MISCELLANEOUS section: Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy. Trichinosis of neurologic or myocardial involvement.

An additional indication for the treatment of acute exacerbations of multiple sclerosis was added in 1979, S-018.

The indication for use in ITP was removed as part of S-024 in 1981.

(b) (4)

Supplement SLR-039 in June of 2006 again sought to add the indication for the treatment of infantile spasms. This time the sponsor submitted a literature review and a meta analysis of eight randomized controlled trials. A May 2007 review by Drs. Schrager, Kehoe and Parks in DMEP again concluded that (b) (4) (b) (4) H.P. Acthar gel and a Not Approvable letter was issued. It was recommended that the sponsor address these deficiencies with a resubmission to the Division of NeuroPharmacology Products.

A complete response to NDA 08-372, SLR-039 was submitted under NDA 22-432 in March 2009. This includes a reanalysis of the most relevant publication (Baram 1996) and a retrospective chart review to support their currently proposed dosing scheme for infantile spasms.

No specific questions were included as part of this consult request. DMEP was instead asked to review the latest PLR version of the label for clarity and correctness.

REVIEW

Diagnostic Testing of Adrenocortical Function

The current package insert recommends the use of H.P. Acthar Gel for diagnostic testing of adrenocortical function; however, there is no reference to support the proposed indication. The dosing recommendation suggests that doses of as much as 80 units as a

single injection, or more injections of a lesser dose, may be used but that dosage and frequency should be individualized without giving any recommendations on how that should be done. It also gives no information on how to interpret the test results.

A review of the PubMed literature by this medical reviewer failed to identify any current references that refer to the use of the ACTH Acthar Gel for adrenocortical function testing. A 1995 version of de Groot and Jameson did mention the use of an alternative 48hr ACTH Infusion Test, but concluded that "the test requires hospitalization to perform and mainly for that reason has become obsolete in the differential diagnosis of adrenal insufficiency." In addition, Acthar Gel is contraindicated for IV infusion and the ACTH Infusion Test would have required the use of Acthar Powder which is no longer marketed. Other current references such as: De Groot, William's, Harrison's, the Merck Manual and ACP PIER & AHFS DI, instead recommend the currently approved cosyntropin test for adrenocortical function testing. This test has the advantage that in most cases the result can be obtained 30 minutes after the IV injection. Even the diagnosis of secondary adrenal insufficiency which might benefit from a longer testing period is recommended to be performed by standard short-term cosyntropin testing after several days of short term priming of the adrenal. Therefore, it is this medical reviewer's conclusion that the current evidence to support the dose and testing of adrenocortical function with Acthar Gel is inadequate and that this indication should be removed during the PLR conversion. If the sponsor wishes to maintain this indication, they should submit data to support a validated testing procedure. These data must include information on how to determine the appropriate testing dose and how to interpret the study results to conclude a diagnosis of adrenal insufficiency.

Endocrine Disorders

The current package insert includes two endocrine disorders with indications for treatment with H.P. Acthar Gel: nonsuppurative thyroiditis and hypercalcemia associated with cancer. Neither of these is a common indication for the use of Acthar Gel in current clinical practice. Painful subacute thyroiditis is usually treated with NSAIDs and if that fails prednisone is an alternative. Hypercalcemia associated with cancer is treated with intravenous hydration, diuretics, bisphosphonates, and gallium nitrate. Steroids can be useful in cases of multiple myeloma and lymphoma but as previously discussed there is no benefit to the use of H.P. Acthar therapy over standard steroid treatment. The original approval of H.P. Acthar Gel did not include these specific indications, nonsuppurative thyroiditis and hypercalcemia associated with cancer, and they were added in a later supplement using case reports from that literature as the supportive evidence.

A search in PubMed by this medical reviewer for references supporting the use of ACTH/corticotrophin for these endocrine indications was unsuccessful. For example: A search using the keywords. "ACTH" and "nonsuppurative thyroiditis" retrieved three references: two foreign and one in English (from Nov. 1953) but none had abstracts available on line for review. A search for the keywords "ACTH" and "hypercalcemia" and "cancer" identified 84 references, none of which referred to ACTH as a potential treatment for hypercalcemia associated with cancer. As there is inadequate evidence to support the safe and effective use of H. P. Acthar Gel for these specific endocrine

indications, DMEP would recommend removal of these indications from the package insert during the PLR conversion.

Use in Children over 2 years of Age and Adults for Indications Other than Infantile Spasms and Multiple Sclerosis

The question arises whether there is sufficient evidence to support the other potential indications in the following categories: nervous system, rheumatic, collagen, dermatologic, allergic states, ophthalmic, respiratory, hematologic, neoplastic, edematous, gastrointestinal, and miscellaneous, which are currently part of the H.P. Acthar Gel package insert. A search of Pubmed using the keyword "acthar" identified only 11 references of which only three reports dealt specifically with possible treatment indications: infantile spasms[1], hay fever[2] and sarcoidosis[3]. A recent review of the clinical utility of H.P. Acthar Gel, by Gettig et al.[4], which included an extensive search of the literature, confirmed that there are currently only three potential common uses for this medication despite the extensive list of potential uses included in the package insert. They include adrenocortical function testing, treatment of infantile spasms and treatment of multiple sclerosis. As the PLR conversion of the package insert offers an opportunity to reassess the quality of the evidence used to support the current indications it seems reasonable to recommend removal of these unsupported indications. The sponsor should be encouraged to submit evidence of adequate and well controlled trials to support any of these indications that they wish to retain. Consideration of the evidence in support of these other indications should be directed to the appropriate review division which has expertise in the particular medical condition (e.g., severe seborrheic dermatitis should be reviewed by the Division of Dermatalogy and Dental Products).

Use in Adults for Multiple Sclerosis

The current package insert recommends daily intramuscular injections of 80 -120 Units for 2-3 weeks for the treatment of acute exacerbations of multiple sclerosis. It is recommended that the Division of NeuroPharmacology review the PLR conversion for this indication.

---

[1] Discharge planning for the child with infantile spasms. Kongelbeck SR. J Neurosci Nurs. 1990 Aug;22(4):238-44.

[2] Comparison of a low and high dose ACTH gel in the treatment of hay fever. Parr EJ, Davies BH. Clin Allergy. 1980 Mar;10(2):195-202.

[3] Effect of Acthar-c (ACTH) in sarcoidosis. MILLER MA, BASS HE. Ann Intern Med. 1952 Oct ; 37(4):776-84

[4] H.P. Acthar Gel and Cosyntropin Review: Clinical and Financial Implications. Gettig J, Cummings JP, Matuszewski K. P T. 2009 May;34(5):250-257.

LABELING RECOMMENDATIONS

Highlights Section
INDICATIONS AND USAGE

Delete the initial indication for [redacted] (b) (4)

Replace the second paragraph:

- [redacted] (b) (4)

with the following:

- H.P. Acthar Gel may be used for the treatment of acute exacerbations of multiple sclerosis.

DOSAGE AND ADMINISTRATION

Delete the first two paragraphs describing [redacted] (b) (4) .

WARNINGS AND PRECAUTIONS

Revise to more closely resemble recent PLR class labeling for steroids.

USE IN SPECIFIC POPULATIONS

Delete the section on nursing mothers.

1 INDICATIONS AND USAGE

Delete the second paragraph describing [redacted] (b) (4) .

Replace the third paragraph:

[redacted] (b) (4)

with the following:

Use in Adults: H.P. Acthar Gel (repository corticotropin injection) is indicated for the treatment of exacerbations of multiple sclerosis.

Delete sections 1.1 to 1.15

2 DOSAGE AND ADMINISTRATION
Section 2.1- delete all but the last paragraph describing use in the treatment of exacerbations of multiple sclerosis, and revise according to Neuropharmacology recommendations.

Section 2.2- recommend revision by Neuropharmacology which is reviewing the infantile spasms indication.

5 WARNINGS AND PRECAUTIONS
Recommend revising this section to more closely resemble steroids class labeling (see recent PLR conversion for Flo-Pred). For example there is currently no mention of GI perforation, negative effects on bone density, negative effects on growth and development in pediatric patients, behavioral or mood disturbances, hypothalamic-pituitary-adrenal axis suppression, risk for fetal harm, Cushing's syndrome and hyperglycemia in the current WARNINGS AND PRECAUTIONS section.

8 USE IN SPECIFIC POPULATIONS
Renumber sections: Nursing Mother to 8.3 and Pediatric Use to 8.4 as per labeling guidance.

14 CLINICAL STUDIES
Recommend that Neuropharmacology revise this section to support the two revised indications: infantile spasms and multiple sclerosis.

15 REFERENCES
Delete this section as per recent labeling guidance.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

WILLIAM A LUBAS
05/28/2010

DRAGOS G ROMAN
05/28/2010

MARY H PARKS
05/28/2010

505(b)(2) ASSESSMENT

Application Information		
NDA # 022432	NDA Supplement #: S- n/a	Efficacy Supplement Type SE- 1
Proprietary Name: H.P. Acthar Gel Established/Proper Name: (repository corticotropin injection) Dosage Form: injection Strengths:		
Applicant: Questcor Pharmaceuticals		
Date of Receipt: June 23, 2006		
PDUFA Goal Date: June 11, 2010	Action Goal Date (if different):	
Proposed Indication(s): Infantile Spasms		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

H.P. Acthar Gel (repository corticotropin injection) is a highly purified sterile preparation of the adrenocorticotropic hormone, however, this product is regulated as a drug per 21 CFR 3.5.

YES ☒ NO ☐

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

N/A

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4©.*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: September 24, 2010

To: Russell Katz, MD, Director
Division of Neurology Products (DNP)

Through: Claudia B. Karwoski, PharmD, Director
Division of Risk Management (DRISK)

From: Mary Dempsey BS, Risk Management Programs Coordinator, DRISK
Sharon Mills Sharon R. Mills, BSN, RN, CCRP, Patient Product Information Reviewer, DRISK

Subject: Risk Evaluation and Migitation Strategy (REMS) Review

Drug Name: H.P. Acthar® Gel (Repository Corticotropin)

Application Type/ Number: NDA 022432 and NDA 008372

Applicant/Sponsor: Questcor Pharmaceuticals, Inc.

OSE RCM #: 2010-1794

1 Background

The Division of Neurology Products (DNP) requested the Division of Risk Management (DRISK) review the H.P Acthar Gel (Repository Corticotropin) proposed Risk Evaluation Mitigation Strategy (REMS) for New Drug Application (NDA) 022432 and 008372 submitted by Questcor Pharmaceuticals, Inc. September 20, 2010.

2 Material Reviewed

- July 21, 2010 REMS Notification Letter
- September 20, 2010 Questcor Pharmaceuticals email containing REMS documents

3 Proposed REMS Elements

- Medication Guide
- Timetable for Submission of REMS Assessment

4 Discussion and Recommendations

July 21, 2010 DNP sent Questcor a REMS Notification letter that included the following language:

> "H.P. Acthar Gel (repository corticotrophin) was approved on April 29, 1952, for multiple indications. The label was later expanded to include multiple sclerosis (MS) in 1972. We are now adding the indication of infantile spasms in pediatric patients. The known risks of infections and blood pressure elevation in MS patients have also been identified as risks in the pediatric population based on clinical trial data. Additionally, the risk of adrenal insufficiency seen in other patient populations is an important potential serious adverse event in the pediatric population. The extension of the indication to pediatrics changes the risk benefit profile of H.P. Acthar Gel (repository corticotrophin) and is considered to be "new safety information" as defined in section 505-1(b)(3) of the FDCA. In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for H.P Acthar Gel (repository corticotropin) to ensure that the benefits of the drug outweigh the risks of adrenal insufficiency, infections, and blood pressure elevation.
>
> Your proposed REMS must include the following:
>
> - Medication Guide
> - Timetable for Submission of REMS Assessment "

DRISK comments on the REMS and Medication Guide are provided in Attachment A and B.

The comments regarding the Instructions for Use in the MG section "How should I give H.P. Acthar Gel to my child?" are collaborative DRISK and DMEPA comments.

We defer comment on your REMS assessment until you submit a full protocol and survey instrument.

1. Submit for review the detailed plan you propose to use to evaluate patients' understanding about the safe use of Acthar Gel. You may submit the proposed plan after approval of the REMS, however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." Make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of Acthar Gel.
2. Recruit respondents using a multi-modal approach. For example, you might recruit respondents through physicians' offices, pharmacies, managed care providers, consumer panels, or on-line.

   Explain how often you perform non-respondent follow-up or reminders.

   If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.

   Explain how you select recruitment sites.

   Submit for review any recruitment advertisements.
3. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).
4. Define the expected number of people to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
5. Ensure the sample is demographically representative of the population who use the drug.
6. When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, socio-economic status, education level, and geographically.
7. List the inclusion criteria. For example, eligible caregiver respondents must be:
   - Age 18 or older
   - Currently administered Acthar Gel or administered the drug in the past 3 months

- Not currently participating in a clinical trial involving Acthar Gel
- Not a healthcare provider

Submit any screener instruments, and describe any quotas of sub-populations used.

8. Explain how you administer surveys and the intended frequency.

   Offer respondents multiple options for completing the survey. Be sure to include an option for the lower literacy population. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person.

   Explain how you train surveyors.

9. Explain how you control for limitations or bias associated with the methodology and survey instrument(s).

10. Submit for review the introductory text used to inform respondents about the purpose of the survey.

    Tell potential respondents that their answers will not affect their ability to receive or take the drug, and that their answers and personal information will be kept confidential and anonymous.

11. Clarify in your methodology that respondents are eligible for one wave of the survey only.

12. The assessment evaluates the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of the drug. The assessment does not evaluate consumer comprehension of the Medication Guide.

    According to regulation (21 CFR 208.24), patients receive the Medication Guide at the time the prescription is filled/dispensed. Do not offer respondents an opportunity to read or see the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.

13. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.

14. Ensure the patient knowledge survey includes questions that ask about the specific risks or safety information conveyed in the Medication Guide to determine if the patient understands the information and knows what to do if they experience an adverse event.

    Derive the risk-specific questions from information located in the "What is the Most Important Information I should know about Acthar Gel?" section of the Medication Guide.

    Ensure the risk-specific questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Ensure that each question has an "I don't know" answer option.

Randomize the order of the multiple choice responses on each survey.

15. Order questions so the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Collect demographic questions last or as part of any screener questions.

    Do not allow respondents the opportunity or ability to go back to previous questions in the survey.

    Explain if and when any education will be offered for incorrect responses.

16. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.

17. Prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,

    Now we are going to ask you some questions about the Medication Guide you may have received with Acthar Gel. The Medication Guide is a paper handout that contains important information about the risks associated with use of Acthar Gel and how to use Acthar Gel safely. Medication Guides always include the title "Medication Guide" followed by the word Acthar Gel and its pronunciation. The Medication Guide usually has sections titled "What is the most important information I should know about Acthar Gel," "What is Acthar Gel," and "Who should not take Acthar Gel."

18. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

    - Who gave you the Medication Guide for Acthar Gel? (Select all that apply)
        a) My doctor or someone in my doctor's office
        b) My pharmacist or someone at the pharmacy
        c) Someone else - please explain: _____
        d) I did not get a Medication Guide for Acthar Gel
    - Did you read the Medication Guide?
        a) All,
        b) Most,
        c) Some,
        d) None
    - Did you understand what you read in the Medication Guide?
        a) All,
        b) Most,
        c) Some,

d) None

- Did someone offer to explain to you the information in the Medication Guide?
    a) Yes, my doctor or someone in my doctor's office
    b) Yes, my pharmacist or someone at the pharmacy
    c) Yes, someone else – please explain: _____
    d) No
- Did you accept the offer? Yes or No
- Did you understand the explanation that was given to you?
    a) All,
    b) Most,
    c) Some,
    d) None
- Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

19. Analyze results on an item-by-item or variable-by-variable basis. You may present the date using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

    You may stratify the data by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments utilized.

Please send these comments to the sponsor with a request to re-submit the entire REMS for approval.

15 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY J DEMPSEY
09/24/2010

CLAUDIA B KARWOSKI
09/24/2010
concur

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: September 10, 2010

From: Norman Hershkowitz, HD,PhD
Division of Neurology Products, HFD-120

Subject: Acthar Gel (NDA 22432) REMS (MedGuide) Modification Memo

This division initially decided that a MedGuide was required for all indications proposed for Acthar Gel. This was expressed in our initial REMS memo and request letter (7/12/10). Upon further discussions within the division, this decision was changed as we concluded that the REMS will only be necessary for the treatment of the newly labeled indication of Infantile Spasms. The reasons for this were expressed in our REMS revision letter of 9/1/10 to the Sponsor where we noted that we believed this infant population is a uniquely vulnerable group. This determination was based upon two factors unique to this indication, age and cognitive/behavioral compromise. Thus, all other planned labeled indications are for older children and adults; indeed the predominant use for this agent, outside of Infantile Spasms, would likely be solely for adults with Multiple Sclerosis1. As per our present version of the label, the indication of Infantile Spasms is the only indication that allows for the treatment of children younger then 2 years. In fact, children as young as only a few months will be treated. One of the most worrisome side effects of ACTH is the lowering of immunologic resistance. As a child's immature immune system is already considered compromised, as a result of its immaturity2, the additional immuno–suppressive effect of ACTH is thought to add an additional risk to this population. It is also noteworthy that while it is generally difficult to identify whether a child at this very young age is infected, the cognitive/behavioral deficits associated with Infantile Spasms make it even more difficult[2]. Moreover, Acthar Gel may suppress normal signs of infection such as fever. Thus, parents would have to be educated to these facts and highly vigilant for any potential signs of infection that may be limited to changes in behavior (e.g. decreased responsiveness or feeding). Moreover, parents of children must also be educated and advised to monitor other symptoms of Acthar Gel toxicity (e.g. post treatment adrenal insufficiency). The

1 The initial label was to have only two indications, Infantile Spasms and Multiple Sclerosis. DMEP was planning on removing approximately 50 other indications, for which ACTH has been rarely, if ever, used in recent clinical practice because safer and more effective alternatives now exist. These other indications were based upon a DESI determination. However, after further negotiations with the Sponsor, only about half of these will be removed from the label.

2 Rudolph's Pediatrics – 21st Ed. (2003), Chapter 13 by Julie A. Jaskiewicz "Fever Without Localizing Signs In Infants And Children."

parents must also be educated as to the importance of adequate follow up for their children so that other potential serious adverse events (hypertension) can be monitored. It is noteworthy that some members of the advisory committee strongly recommended some form of patient education as a part of a REMS.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN HERSHKOWITZ
09/22/2010

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs I
Division of Neurology Products

NDA/BLA #s:	22-432
Products:	H.P. Acthar Gel (repository corticotropin injection)
APPLICANT:	Questcor Pharmaceuticals, Inc.
FROM:	Russell Katz, M.D.
DATE:	June 7, 2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for H.P. Acthar Gel (repository corticotropin injection) to ensure that the benefits of the drug outweigh the risks of adrenal insufficiency, infections, sepsis, and blood pressure elevation. H. P. Acthar Gel (repository corticotropin injection) is presently approved for diagnostic testing of adrenocortical function and acute exacerbations of multiple sclerosis (MS). Questcor seeks approval for the use of H. P. Acthar Gel (repository corticotropin injection) to treat infantile spasms (IS). We have determined that a REMS is necessary for H. P. Acthar Gel (repository corticotropin injection) only for indications in which the drug is administered for a period exceeding five days (MS and IS), and not for the indication of diagnostic testing of adrenocortical function, in which single doses are administered. In reaching this determination, we considered the following:

A. The estimated number of patients in the United States born with Infantile Spasms (IS) ranges from 1 per 2,250 to 1 per 6,000. Given that there are a little over 4,000,000 live births per year in the United States, there should be approximately 1,000 to 2,000 IS cases yearly. This incidence estimate is based upon a number of epidemiologic

articles published in peer-reviewed journals.[1] Even though H.P. Acthar Gel (repository corticotropin injection) is not presently indicated for use in the treatment of IS in the label, it is generally considered the treatment of choice in IS by many pediatric epileptologists. The Sponsor notes that there are presently (b) (4) to (b) (4) individual patients prescribed H. P. Acthar Gel (repository corticotropin injection) for IS each year. This accounts for (b) (4)% of IS patients. We suspect H. P. Acthar Gel (repository corticotropin injection) use will increase as a result of its approval and one may expect about (b) (4) patients treated yearly (approximately (b) (4)% to (b) (4)% of newly diagnosed cases).

The prevalence of MS in the United States is approximately 1 per 1000. A prevalence of 600,000 patients[2] in the United States has been estimated. H. P. Acthar Gel (repository corticotropin injection) is rarely used today to treat MS; however, a very small percentage of patients may still be treated with H. P. Acthar Gel (repository corticotropin injection).

B. Infantile Spasms is associated with frequent recurrent seizures (or spasms) and marked EEG (electroencephalogram) abnormalities. The disease is frequently associated with delayed development, permanent cognitive impairment and the occurrence of other seizure types upon maturation. Death may also occur. The long-term prognosis of infantile spasms is bleak. Fewer than 5% of patients are neurodevelopmentally normal. While there are no definitive data that treatment of the spasms will improve long term neurologic prognosis, there are limited data suggesting that this is the case.

MS is a chronic, often disabling disease that attacks the central nervous system (CNS). In Western societies, MS is second only to trauma as a cause of neurologic disability with onset in early to middle adulthood. MS can rapidly evolve to an incapacitating disease requiring profound lifestyle adjustments.[3] MS patients commonly have impaired ability to walk as well as weakness of the limbs, visual symptoms including decreased acuity and visual blurring, sensory symptoms including tingling, ataxia, bladder dysfunction, memory loss and impaired attention, depression, and fatigue. During acute exacerbations of MS, patients will lose neurologic function to varying degrees and may also be subject to injuries and other medical conditions associated with neurologic compromise (e.g., aspiration pneumonia and falls).

---

[1] Cowan LD, Hudson LS. The epidemiology and natural history of infantile spasms. *J Child Neurol.* 1991;6(4):355-364; Cowan LD. The epidemiology of the epilepsies in children. *Ment Retard Dev Disabil Res Rev*. 2002;8(3):171-181.

[2] See Neurologic Clinics, Neuroepidemiology, Editor J.E Riggs, W.B. Saunders company, Philadelphia, 1996; Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohammed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurological disorders? Neurology 2007;68;326-337

[3] Harrison's Principles of Internal medicine – 17th Ed. (2008)

C. The efficacy of H. P. Acthar Gel (repository corticotropin) for the treatment of infantile spasms was studied in three controlled trials. Data reviewed by the division indicate that H. P. Acthar Gel (repository corticotropin) results in complete resolution of spasms and EEG abnormalities in a majority of patients as compared to an active control (87% in the Acthar Gel arm vs. 29% in the prednisone arm). While the data are not definitive, it is generally believed that prognosis improves with early diagnosis and treatment.

   While there is some evidence that this drug appears to limit the duration of the MS exacerbations, there is no evidence that it can reduce accrued disability in MS.

D. If approved, H. P. Acthar Gel (repository corticotropin) would be labeled in IS as a two-week course of treatment, followed by a two-week taper. At present there is no plan to label more then one such course of treatment.

   The drug is labeled in MS as a single two- to three-week course of treatment at the time of each exacerbation.

E. As a result of combined prospective analysis of clinical IS data and IS literature review, the Sponsor determined that the two most likely drug-related serious adverse events include infections and hypertension which were observed in 7.4% and 8.2% of patients, respectively. In the aforementioned database of 300 patients, it was noted that at least one infection led to a death. Another potential serious adverse outcome is that of adrenal insufficiency resulting from adrenocorticotropic hormone (ACTH) treatment. No cases of adrenal insufficiency were identified in the Sponsor's database, likely because of the careful dosing regimen that includes a slow down-titration. However, this remains an important potential serious adverse event and was also of great concern to the Peripheral and Central Nervous System Advisory Committee. Other less common but potentially serious adverse events included hypokalemia, hyperglycemia, and cardiomyopathy.

F. H.P. Acthar Gel (repository corticotropin injection) is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for H.P. Acthar Gel (repository corticotropin). FDA has determined that H.P. Acthar Gel (repository corticotropin) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of H.P. Acthar Gel (repository corticotropin). FDA has determined that H.P. Acthar Gel (repository corticotropin) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use H.P Acthar Gel (repository corticotrophin), and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The elements of the REMS will be Medication Guide and a timetable for submission of assessments of the REMS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)
NDA-8372	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P. ACTHAR GEL
SAFETY-547	ORIG-1	NO FIRM	antiepileptic drugs

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN B DAUGHERTY
07/06/2010

RUSSELL G KATZ
07/13/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
008-372

NAME OF APPLICANT / NDA HOLDER
Questcor Pharmaceuticals, Inc.
3260 Whipple Rd.
Union City, CA 94587

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
H.P. Acthar® Gel

ACTIVE INGREDIENT(S)	STRENGTH(S)
Corticotropin	80 Units per mL

DOSAGE FORM
Injection, solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent

d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2 Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3 Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5 No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☒ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	June 16, 2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
David J Medeiros, VP Pharmaceutical Operations
Questcor Pharmaceuticals, Inc.

Address	City/State
3260 Whipple Rd	Union City, CA
ZIP Code 94587	Telephone Number 510-400-0772
FAX Number *(if available)* 510-400-0799	E-Mail Address *(if available)* dmedeiros@questcor.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 022432 SUPPL # type 6 NDA HFD # 120

Trade Name H.P.Acthar Gel

Generic Name recombinant corticotropin

Applicant Name Questcor Pharmaceuticals, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

H.P. Acthar Gel is a DESI upgrade product; however, the indication is not DESI.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 008372 parent NDA for H.P. Acthar Gel

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☒	NO ☐
Investigation #2	YES ☒	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

pivotal efficacy study
Study CSR 222017-01 titled “High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study”
(Questcor obtained source efficacy data from this study and conducted their own analyses.)

supportive efficacy study
Study CSR 222017-04 titled, “High-dose, Long-duration versus Low-dose, Short-duration Corticotropin Therapy for Infantile Spasms”
(Questcor obtained source efficacy data from this study and conducted their own analyses.)

supportive efficacy study
Study CSR 222017-05 titled, “Double-blind Study of ACTH versus Prednisone Therapy in Infantile Spasms”
(Questcor obtained source efficacy data from this study and conducted their own analyses.)

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

Investigation #3 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☒
! Explain:
Studies not conducted under an IND.

Investigation #2

IND # YES ☐ ! NO ☒
! Explain:
Studies not conducted under an IND.

Investigation #3		!
		!
IND #	YES ☐	! NO ☒
		! Explain: Studies not conducted under an IND.

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☒
Explain:	! Explain: Studies from published literature.

Investigation #2	!
	!
YES ☐	! NO ☒
Explain:	! Explain: Studies from published literature.

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Susan Daugherty

Title: Regulatory Project Manager
Date: 10/5/10

Name of Office/Division Director signing form: Russell Katz, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN B DAUGHERTY
10/21/2010

RUSSELL G KATZ
10/21/2010

QUESTCOR

DEBARMENT CERTIFICATION

Questcor Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

In addition, to the best of Questcor Pharmaceuticals, Inc.'s knowledge, no person affiliated with Questcor Pharmaceuticals that was responsible for the development or submission of this application has been convicted of an offense described in subsections (a) or (b) of the Generic Drug Enforcement Act of 1992.

David J. Medeiros
VP Pharmaceutical Operations
Questcor Pharmaceuticals, Inc.

June 16, 2006
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 022432 (type 6) BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type: SE-1
Proprietary Name: H.P.Acthar Gel Established/Proper Name: repository coticotropin Dosage Form: Gel for Injection		Applicant: Questcor Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Susan Daugherty		Division: Division of Neurology Products (DNP)

NDAs:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ If no listed drug, check box and explain:

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is October 30, 2010	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None NA May 6, 2007
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other talking points

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below* (Summary Reviews)*).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below* (Summary Reviews). *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[3]	included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval 10/15/10 Not Approvable Letter: 5/10/2007
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Agreed upon label 10/15/10
• Original applicant-proposed labeling	From resubmission: 12/10/09
• Example of class labeling, if applicable	None

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	See pg 5
• Original applicant-proposed labeling	See pg 5
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	N/A
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEPA ☒ DRISK 9/24/10 ☒ DDMAC 9/27/10 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	5/17/07
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2) 10/31/10
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes X No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Orphan Indication • Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	Pre IND advice: 3/27/2008 Correspondence: 4/21/2009 Correspondence: 6/1/2009 Inc. Resp. Ltr: 11/13/2009

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	Inc. Resp. Ltr: 12/10/2009 Inc. Resp. Ltr: 12/23/2009 Rev. Extension: 6/11/2010
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	End of Review conf: 11/9/2007
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	SPA response 3/27/08
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	May 6, 2010
• 48-hour alert or minutes, if available *(do not include transcript)*	Summary Minutes
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	X None
Division Director Summary Review *(indicate date for each review)*	☒ 05/10/07 and 10/15/10
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ 05/10/07 and 9/27/10
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	05/10/07 and 9/27/10
• Clinical review(s) *(indicate date for each review)*	04/24/07, 05/28/10, and 09/28/10
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	X None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	09/28/10 page 9 clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	DMEP PLR Review: 5/28/2010
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	X Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	9/29/10 7-21-2010 and 9-27-10 ☐ None 9/24/10 and 9/27/10
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	X None requested

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology	X None
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics	☐ None
❖ Statistical Division Director Review(s) *(indicate date for each review)*	See Primary Review
Statistical Team Leader Review(s) *(indicate date for each review)*	See Primary Review
Statistical Review(s) *(indicate date for each review)*	☐ None 4/5/2010
Clinical Pharmacology	☐ None
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	4/25/07, 11/19/07, 2/12/2009, and 10/01/10
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	X None
Nonclinical	☐ None
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 03/08/07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality	☐ None
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	none
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	6/1/2010
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	X Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	X None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☒ Review & FONSI *(indicate date of review)*	10/31/06
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022432
NDA 008372

REMS NOTIFICATION

Questcor Pharmaceuticals, Inc.
Attention: Sian Bigora, Pharm.D.
Vice President, Regulatory Affairs
3260 Whipple Road
Union City, CA 94587

Dear Dr. Bigora:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for H.P. Acthar® Gel (repository corticotropin) injection.

In addition, we refer to our Risk Evaluation and Mitigation Strategy (REMS) notification dated July 21, 2010, and your proposed REMS submitted on August 12, 2010.

According to our REMS notification letter dated July 21, 2010 and in accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for H.P Acthar Gel (repository corticotropin) to ensure that the benefits of the drug outweigh the risks of adrenal insufficiency, infections, and blood pressure elevation in pediatric patients being treated for infantile spasms.

Subsequent to our initial decision to require a REMS for H.P. Acthar® Gel (repository corticotropin), we have determined that the REMS for H.P. Acthar® Gel (repository corticotropin) should only apply to the infantile spasms indication for which you are seeking approval, and not to the multiple sclerosis indication or any of the existing approved indications. We have concluded that the patients who will be treated with H.P. Acthar® Gel (repository corticotropin) for infantile spasms are a uniquely vulnerable population, and that it is only for this indication that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. Our determination that this population is uniquely vulnerable is based upon both age and underlying disease suffered by patients with infantile spasms. These younger patients are more susceptible to infections and incapable of communicating symptoms associated with drug adverse reactions.

Therefore, amend your proposed REMS, including the Medication Guide, to address the infantile spasms population only.

Before we can continue our evaluation of this NDA, you will need to submit your amended proposed REMS.

Prominently identify your revised proposed REMS submission, with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022432 and NDA 008372
PROPOSED REMS-AMENDMENT

If you do not submit electronically, please send five copies of your REMS-related submissions.

If you have questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachments: REMS and REMS supporting document templates

Appendix A: Medication Guide REMS Template

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each [drug name] prescription in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, 18 months, three years and seven years from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix B:

REMS SUPPORTING DOCUMENT TEMPLATE
MEDICATION GUIDE REMS

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents

2. Background

3. Goals

4. Supporting Information on Proposed REMS Elements

    a. Medication Guide

    b. Describe in detail how you will comply with 21 CFR 208.24.
    c. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)

5. REMS Assessment Plan (for products approved under an NDA or BLA)

6. Other Relevant Information

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
09/27/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **CDER-DDMAC-RPM**			FROM: (Name/Title, Office/Division/Phone number of requestor)
REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)

NAME OF FIRM:	PDUFA Date:

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [Insert Date]

Labeling Meetings: [Insert Dates]

Wrap-Up Meeting: [Insert Date]

SIGNATURE OF REQUESTER	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN B DAUGHERTY
09/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **CDER-DDMAC-RPM**			FROM: (Name/Title, Office/Division/Phone number of requestor)
REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)

NAME OF FIRM:	PDUFA Date:

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:

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COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [Insert Date]

Labeling Meetings: [Insert Dates]

Wrap-Up Meeting: [Insert Date]

SIGNATURE OF REQUESTER	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN B DAUGHERTY
09/16/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:	August 31, 2010
TO:	NDA 22-432
FROM:	Colleen LoCicero, R.Ph. Associate Director for Regulatory Affairs Office of Drug Evaluation I
SUBJECT:	Change in regulatory classification of application from 505(b)(2) to 505(b)(1)
APPLICATION/DRUG:	NDA 22-432 for H. P. Acthar Gel (repository corticotropin injection)

Background:
This application for use of H.P. Acthar Gel in the treatment of infantile spasms, received by FDA on June 23, 2006, was submitted as an efficacy supplement by Questcor Pharmaceuticals to NDA 8-372, reviewed in the Division of Metabolism and Endocrinology Products (DMEP).

On May 10, 2007, DMEP issued a Not Approvable letter for this supplemental application. The Not Approvable letter advised Questcor that, henceforth, the Division of Neurology Products (DNP) should have regulatory and scientific oversight of the application.

On November 9, 2007, Questcor met with DNP for an end-of-review conference to discuss next steps. On January 29, 2008, Questcor submitted a request for clinical Special Protocol Assessment (SPA) under pre-IND (b) (4). On March 27, 2008, DNP responded to the questions in the SPA submission and in an April 24, 2008, teleconference, Questcor and DNP came to agreement on the protocol in the SPA submission. Subsequently, Questcor submitted a revised protocol (on June 20, 2008).

Questcor submitted a response to the May 10, 2007, Not Approvable letter to DNP on November 26, 2008, but DNP determined that the submission did not constitute a Complete Response. Questcor submitted three more responses to the May 10, 2007 Not Approvable letter, dated March 13, October 15, and November 25, 2009, that DNP determined not to be Complete Responses as well. On December 10, 2009, Questcor submitted to DNP (received December 11, 2009) a response to the May 10, 2007 Not Approvable letter that DNP determined to be a Complete Response to the Not Approvable letter. With the receipt of this Complete Response, the application was redesignated a Type 6 NDA* with a PDUFA goal date, for review of the Complete Response to the NDA, of June 11, 2010. This goal date was later extended to September 11, 2010 due to the receipt of a major amendment to the application.

Regulatory Classification:
Questcor designated the original efficacy supplement submitted to the Division of Metabolism and Endocrinology Products for this indication and the subsequent responses to the May 10, 2007, Not Approvable letter as submissions under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FFD&C Act). The original efficacy supplement, which relied upon published literature to support approval of the application, was considered and reviewed as a 505(b)(2) supplement. It has been determined, however, by the 505(b)(2) review staff** that, with the submission of the December 10, 2009 Complete Response, this application is a 505(b)(1) application, as the Complete Response contains source data from the investigator studies necessary to support approval of the application and does not rely on published literature.

As per Dr. Sheridan's review of this application, the clinical studies reviewed and relied upon by DNP to support the effectiveness of H.P. Acthar Gel in the treatment of infantile spasms are studies 222017-01, 222017-04 and 222017-05. All three studies were investigator-initiated studies. The data from these studies included in the Complete Response were obtained from the investigators' study records and from the charts of the patients included in the studies. The final study reports for these clinical studies that are included in the Complete Response were produced by Questcor, with the assistance of the study investigators.

The clinical studies reviewed and relied upon by DNP to support the safety of H.P. Acthar Gel in the treatment of infantile spasms are studies 222017-04, 222017-05, 222017-02, and QSC007-ACT-002. Studies 222017-02 and QSC007-ACT-002 provide new unpublished safety data obtained by Questcor from retrospective chart reviews.

In its review of this application, DNP relied upon the reports for these studies and their own analysis of the source data provided in the complete response. DNP did not rely on published literature or FDA's finding of safety and/or effectiveness of an approved application in reviewing the effectiveness and safety of H.P. Acthar Gel for the treatment of infantile spasms.

With respect to the nonclinical data that support this application, which is an efficacy supplement designated as a Type 6 NDA for administrative purposes, Questcor implicitly cross-references the nonclinical data in its previously approved 505(b)(1) application.

*A Type 6 NDA is an efficacy supplement that is designated in CDER's database as a new NDA and assigned a new NDA number for administrative purposes (e.g., to facilitate the review of a supplement for an indication for which the scientific expertise lies in a division different from the parent division for the original application).

**The 505(b)(2) review staff consists of representatives from CDER's Office of New Drugs (OND) Immediate Office, CDER's Office of Regulatory Policy, FDA's Office of Chief Counsel, and CDER's OND Associate Directors for Regulatory Affairs that meet on a regular basis to present and discuss pending 505(b)(2) applications and related issues.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

COLLEEN L LOCICERO
08/31/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022432
NDA 008372

REMS NOTIFICATION

Questcor Pharmaceuticals, Inc.
Attention: Sian Bigora, Pharm.D.
Vice President, Regulatory Affairs
3260 Whipple Road
Union City, CA 94587

Dear Dr. Bigora:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for H.P. Acthar® Gel (repository corticotrophin) injection.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

H.P. Acthar Gel (repository corticotrophin) was approved on April 29, 1952, for multiple indications. The label was later expanded to include multiple sclerosis (MS) in 1972. We are now adding the indication of infantile spasms in pediatric patients. The known risks of infections and blood pressure elevation in MS patients have also been identified as risks in the pediatric population based on clinical trial data. Additionally, the risk of adrenal insufficiency seen in other patient populations is an important potential serious adverse event in the pediatric population. The extension of the indication to pediatrics changes the risk benefit profile of H.P. Acthar Gel (repository corticotrophin) and is considered to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for H.P Acthar Gel (repository corticotropin) to ensure that the benefits of the drug outweigh the risks of adrenal insufficiency, infections, and blood pressure elevation.

Your proposed REMS must include the following:

> **Medication Guide**: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that H.P. Acthar Gel (repository corticotropin) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The

Medication Guide is necessary for patients' safe and effective use of H.P. Acthar Gel (repository corticotropin). FDA has determined that H.P. Acthar Gel (repository corticotropin) is a product for which patient labeling could help prevent serious adverse effects, that H.P. Acthar Gel (repository corticotropin) has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use H.P. Acthar Gel (repository corticotropin), and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed H.P. Acthar Gel (repository corticotropin).

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Once FDA finds the content of the REMS acceptable and determines that the application can be approved, we will include this document and the Medication Guide as attachments to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include but is not limited to the following:

a. An evaluation of patients' understanding of the serious risks of H.P. Acthar Gel (repository corticotropin)
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Before we can continue our evaluation of this NDA, you will need to submit the proposed REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication

Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend that you use one of the following two statements depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient." or
- "Dispense the accompanying Medication Guide to each patient."

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022432 and NDA 008372
PROPOSED REMS

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022432 and NDA 008372
PROPOSED REMS-AMENDMENT

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachments

Appendix A: Medication Guide REMS Template

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each [drug name] prescription in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, 18 months, three years and seven years from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix B:

REMS SUPPORTING DOCUMENT TEMPLATE
MEDICATION GUIDE REMS

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents

2. Background

3. Goals

4. Supporting Information on Proposed REMS Elements

    a. Medication Guide

    b. Describe in detail how you will comply with 21 CFR 208.24.
    c. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)

5. REMS Assessment Plan (for products approved under an NDA or BLA)

6. Other Relevant Information

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)
NDA-8372	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P. ACTHAR GEL

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/s/

RUSSELL G KATZ
07/21/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022432

REVIEW EXTENSION – EFFICACY SUPPLEMENT

Questcor Pharmaceuticals, Inc.
Attention: Sian Bigora, Pharm.D.
Vice President, Regulatory Affairs
3260 Whipple Road
Union City, CA 94587

Dear Dr. Bigora:

Please refer to your June 16, 2006 Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for H.P. Acthar® Gel (repository corticotropin injection).

We also refer to your December 10, 2009 submission containing a complete response to our May 10, 2007 action letter.

On June 9, 2010, we received your June 8, 2010, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 11, 2010.

If you have questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

JACQUELINE H H WARE on behalf of RUSSELL G KATZ
06/11/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Division of Metabolic and Endocrine Products
Attn: Jena Weber, RPM

FROM:
Division of Neurology Products
Susan Daugherty, RPM

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1-19-2010		22-432	PLR Converted labeling	12-10-09

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
H.P. Acthar® Gel (repository corticotropin injection)			5-7-2010

NAME OF FIRM: Questcor Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: PLR conversion review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: NDA 22-432 provides for the use of Acthar Gel to treat infantile spasms. The sponsor has submitted a Complete Response that contains PLR converted labeling (current and proposed labeling are attached). We request that DMEP conduct the PLR content review. This application will go to AC 5-6-10 and the PDUFA goal date is June 11, 2010. The application is in the EDR and may be accessed at: **\\FDSWA150\NONECTD\N22432\N_000\2009-12-10**

Thank you!

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Susan Daugherty, RPM 6-0878	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

29 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

SUSAN B DAUGHERTY
01/21/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-432

ACKNOWLEDGEMENT CLASS 2 RESPONSE

Questcor Pharmaceuticals, Inc.
Attention: David Young, Pharm.D., Ph.D.,
Chief Scientific Officer
3260 Whipple Road
Union City, CA 94587

Dear Dr. Young:

We acknowledge receipt on December 11, 2009 of your December 10, 2009 resubmission to your supplemental new drug application for H.P. Acthar® Gel (repository corticotropin injection).

We consider this a complete, class 2 response to our May 10, 2007 action letter. Therefore, the user fee goal date is June 11, 2010.

If you have any questions, call me at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Susan Daugherty
Senior Regulatory Health Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

SUSAN B DAUGHERTY
12/23/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-432

ACKNOWLEDGE INCOMPLETE RESPONSE

Questcor Pharmaceuticals, Inc.
Attention: Dave Medeiros
Sr. Vice President, Pharmaceutical Operations
Senior Vice President, Clinical and Regulatory Affairs
3260 Whipple Road
Union City, CA 94587

Dear Mr. Medeiros:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for H.P. Acthar® Gel (repository corticotropin injection).

We acknowledge receipt on November 25, 2009 of your November 25, 2009 submission to your supplemental new drug application for H.P. Acthar® Gel (repository corticotropin injection).

We do not consider this a complete response to our action letter because the definition file for the study 05 datasets is not entirely readable. Therefore, the review clock will not start until we receive a complete response.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

RUSSELL G KATZ
12/10/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-432

ACKNOWLEDGE INCOMPLETE RESPONSE

Questcor Pharmaceuticals, Inc.
Attention: Dave Medeiros
Sr. Vice President, Pharmaceutical Operations
Senior Vice President, Clinical and Regulatory Affairs
3260 Whipple Road
Union City, CA 94587

Dear Mr. Medeiros:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for H.P. Acthar® Gel (repository corticotropin injection).

We acknowledge receipt on October 15, 2009 of your October 15, 2009 submission to your supplemental new drug application for H.P. Acthar® Gel (repository corticotropin injection).

Please also refer to the teleconference between representatives of Questcor Pharmaceuticals and representatives from the Division of Neurology Products on November 4, 2009. During that teleconference we notified you that your submission was not a complete response to our action letter because the definition files do not provide enough detail for review and some of the links to case report forms (CRFs) are incorrect. Therefore, we will not start the review clock until we receive a complete response. The following deficiencies need to be addressed:

- Include an explanation in the definition file when the variable name in two different datasets is the same but does not represent the same data.
- Clearly define the variables. If a variable is for testing purpose rather than analysis, please clearly state that. If a variable is a derived variable, we recommend that you include a brief algorithm in the definition file.
- Correct links to the Case Report Forms.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

RUSSELL G KATZ
11/13/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-432

Questcor Pharmaceuticals, Inc.
Attention: Steven Halladay, Ph.D.
Senior Vice President, Clinical and Regulatory Affairs
3260 Whipple Road
Union City, CA 94587

Dear Dr. Halladay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for H.P. Acthar® Gel (repository corticotropin injection).

We also refer to the teleconference between representatives from Questcor Pharmaceuticals and the Division of Neurology Products on May 12, 2009, to discuss the resubmission of your NDA. We further refer to your electronic mail correspondences dated April 30, 2009 (containing an email from Dr. Hrachovy dated April 29, 2009), and May 7, 2009 (proposing a Statistical Report to supplement the 1994 Hrachovy study report) which are appended.

The following points were agreed upon during the May 12, 2009 teleconference:

- You will provide a new Statistical Report (serving as an addendum to the original Hrachovy [1994] study report). This will contain a new primary analysis of the primary endpoint that will examine the modified intent to treat (mITT) set, which will include all patients who received drug and have a recorded primary endpoint. Subset mITT analyses by gender, etc, must also be redone to include the previously missing patients. The Statistical Report will also repeat all the secondary endpoint analyses which had been previously done on the 50 patients now done on the revised mITT set.
- Newly recovered data must be incorporated into old datasets and must be presented as a single dataset.
- As a type of sensitivity analysis, an evaluation of the full ITT population of 59 patients must be performed. This analysis must include the mITT set and all remaining patients where there is no outcome data. A "worst case scenario" must be imputed for the patients where no outcome data exists such that the high-dose patients are considered to be nonresponders and the low-dose patients are to be considered responders.
- Patient narratives must be provided for patients #IX13, IX20, IX25, IX26 (including information about the infectious disease consultation report discussing the role of ACTH in the terminal illness), and IX 50.
- The original study report for the Hrachovy (1994) study, as previously submitted, does not have to be revised and will serve as a *per protocol* analysis of the 50 patients who completed the study.

- The new submission must have rewritten, comprehensive higher level summaries (ISE, ISS, and clinical summary) which should be revised so that the text and tables integrate the newly generated data on the missing patients with the efficacy and safety data previously submitted.
- The new submission must be submitted in the eNDA format as was done on March 13, 2009. There is no need to withdraw the March 13, 2009 submission.
- The new submission must be free-standing and comprehensive, incorporating all the previously submitted data and analyses (including those from the Baram and Hrachovy [1983] pivotal studies) as well as all the components detailed above.
- The Agency asks to be notified about one month prior to this resubmission

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Daugherty, Susan B (CSO)

From: [redacted]

Sent: Thursday, April 30, 2009 10:02 PM

To: Daugherty, Susan B (CSO)

Cc: DBailey@questcor.com; Medeiros, David; Dempsey, David; [redacted]; Choi, Young; [redacted]

Subject: NDA 22-432_Study-05_Analysis Ongoing and Letter from R Hrachovy

Attachments: R Hrachovy Ltr to QSC_4.29.09.pdf

Dear Susan,

In follow up to our recent emails and telephone discussions, we provide the attached letter from Dr. Richard Hrachovy from the Baylor University College of Medicine. This letter describes the diligence performed by him to locate the nine charts from patients who enrolled in the high dose-low dose Acthar study, but discontinued the study prior to study completion. Dr. Hrachovy was able to locate eight of the nine charts; further details are in his attached letter. As he indicated, Dr. Hrachovy is available to discuss these data with the Agency at your discretion.

Dr. Hrachovy did not recall until he reviewed these charts that one of these eight patients died after being enrolled into the study from complications thought unrelated to treatment with Acthar Gel. Questcor was informed of this finding on Tuesday, April 28, 2009, in a teleconference with Dr. Hrachovy. This was the first notification to Questcor of this event. Questcor is presently preparing the required expedited safety report (MedWATCH) and will submit this report as required.

Questcor is currently initiating a thorough review of these additional data. We will submit our plan to the Agency next week for updating the Complete Response; we would like to submit these to you via email. We would appreciate your feedback on our proposed plan by whichever mechanism is preferable to you (e.g., email, telephone discussion).

Please feel free to contact [redacted] for Questcor (at [redacted] mobile or via email at [redacted]), or me (at [redacted] mobile or reply to this email) if any additional information is needed.

Thank you,

[redacted]


(b) (4)

BCM
Baylor College of Medicine
PETER KELLAWAY SECTION
OF NEUROPHYSIOLOGY
Department of Neurology
ONE BAYLOR PLAZA, SUITE NB302
HOUSTON, TX 77030

713-798-0980 (Phone)
713-798-0984 (FAX)

April 29, 2009

Steven Halladay, Ph.D.
Senior Vice President, Clinical and Regulatory Affairs
Questcor Pharmaceuticals, Inc.
3260 Whipple Road
Union City, CA 94587

Dear Dr. Halladay:

I am writing this letter to Questcor following an inquiry by the U.S. Food and Drug Administration (FDA) regarding the availability of the charts for the 9 patients who withdrew from our study.[1] As was noted in our publication, these nine patients, four randomized to the high-dose group and five randomized to the low dose-group, "were excluded from final analysis because they did not complete the treatment protocol for various reasons, including compliance problems, moving from the area before the protocol was completed, or the development of medical problems unrelated to use of ACTH but, in, the opinion of the investigators, precluded the continued use of ACTH".[1] I also understand that FDA inquired as to whether we had performed any analyses that included more than the 50 patients in the publication, up to and including all 59 patients who enrolled into the trial or whether any other sources of study data (e.g., spreadsheets or other data sources) might still be available.

Regarding the availability of the patient charts, over the last week, I was able to secure several boxes; these boxes should have contained all of the study charts from Baylor

[1] Hrachovy RA, Frost JD, Glaze DG. High-dose, long-duration versus low-dose, short-duration corticotropin therapy for infantile spasms. J Pediatr 1994;124:803-806.

College of Medicine's storage facility. To my knowledge, this is the only possible source of the charts for these patients. I was pleased to find the study charts for 8 of these 9 patients who did not complete the study. These data have been photocopied and were sent to you by overnight delivery on April 28, 2009.

The following table summarizes the pertinent information for these 8 patients.

Pt #	Randomization (Low: ACTH 20 U/day; High: ACTH 150U/m2/day)	Study Treatment Duration	Reason for Study Discontinuation
IX-13	High	2 weeks	Parents refused to continue protocol
IX-20	High	Up to 3 weeks (Estimated)	Patient moved from state
IX-25	Low	6 weeks	Parents refused final monitoring
IX-26	Low	See narrative below	See narrative below
IX-34	High	None	Parents refused to start study treatment after randomization
IX- 42	High	None	Study treatment delayed due to medical condition. Spasms stopped before treatment started-spontaneous remission
IX-49	Low	None (Estimated)	Parents refused study treatment after randomization
IX-50	Low	1 day (Estimated)	Study treatment stopped because of fever and irritability
IX-58	Low	Unknown	Unknown

Regarding Patient IX-26, this was a 3 month old male with severe developmental delay and a history of seizures since 3 days of age. The patient was seen by Dr. (b) (4), a co-investigator, at the (b) (4) the patient was enrolled into the study and was randomized to the low dose ACTH regimen. Thereafter, the patient was treated by his local physician in (b) (4). Following 2 weeks of ACTH treatment (at a dose of 20 units/day), the patient returned to (b) (4) for EEG monitoring; at that time he still had spasms. His dose of ACTH was increased to 30 units/day and he returned to (b) (4) Shortly thereafter, he developed respiratory problems which were treated by physicians in (b) (4) Unfortunately, he did not recover from his illness and died from respiratory failure. At the time, Dr. (b) (4) and the infectious disease consultants did not believe that ACTH contributed to

the patient's death because of the severity of the patient's underlying medical problems. The patient's death was reported to the IRB. Subsequently, the patient's chart was inadvertently filed away with the charts of other patients who did not complete the protocol (listed above). When the publication of this study was being prepared several years later, we apparently did not remember this patient and consequently did not mention him in the paper.

Regarding the chart for patient IX-58, unfortunately, it was not contained in the archived boxes. This final chart, is, therefore, not locatable; its absence from the archival record storage facility means that the chart is lost. In addition, I also want to clarify that all original EEG records for the 59 patients enrolled in this study were stored in the basement of [redacted] (b) (4) and were destroyed when the basement was flooded during Tropical Storm [redacted] (b) (4) in 2001.

I would also like to confirm that there are no other known sources of data for this study. I am aware of no data files containing data from all 59 patients. In addition, no analyses were ever conducted that included all 59 patients who enrolled in the study. We did not conduct a Modified-Intent-To-Treat analysis or any other analyses that included all 59 patients randomized into the study.

I understand the importance of FDA's request for the additional data and would like to offer my continued assistance to them. Please let the officials at FDA know that I would be happy to discuss the details of this study with them, its conduct and data collection, as well as the analysis of the data and our conclusions.

Sincerely,

Richard A. Hrachovy MD

Richard A. Hrachovy, M.D.
Professor of Neurology
Head, Peter Kellaway Section of Neurophysiology
Baylor College of Medicine
One Baylor Plaza
Houston, Texas 77030
Telephone: 713-798-0980
Email-hrachovy@bcm.edu

Daugherty, Susan B (CSO)

From: (b) (4)

Sent: Thursday, May 07, 2009 8:13 PM

To: Daugherty, Susan B (CSO)

Cc: Bailey, Don; (b) (4); Medeiros, David; Dempsey, David; Choi, Young; (b) (4)

Subject: NDA 22-432_5.7.09_Acthar Gel: Proposal for Statistical Report: Study 222017-05B

Hi Susan,
Please forward this message to Dr. Katz:

Dear Dr. Katz:

Reference is made to our teleconference with your colleagues and you on 9 April 2009 and the subsequent efforts made by Dr. Hrachovy to locate the charts of the nine additional patients who enrolled into his study. (Hrachovy RA et al. High-dose, long duration versus low-dose, short duration corticotrophin therapy for infantile spasms. J Pediatr 1994;125:803-6.) Reference is also made to our submission of a letter from Dr. Hrachovy on 30 April 2009 where he describes his efforts to locate the nine charts from the patients, all of whom were reported to have discontinued the study prior to study completion. As he reported in his letter, eight of these nine charts were locatable.

Questcor has obtained redacted copies of the above-mentioned eight charts. The data are being processed in an identical fashion as the data from the first 50 patients from this study: the charts are undergoing transcription into Case Report Forms and the data will then be entered into the study database.
Questcor is, therefore, proposing the following:

- A Statistical Report (entitled, Questcor Statistical, #222017-05B) will be submitted to the Agency consisting of the following:
    - A Statistical Analysis Plan for a modified Intention to Treat (mITT) analysis of the entire patient dataset from the study
    - Tables and listings of the demographic, baseline and efficacy data for the mITT analysis
    - A listing of the adverse event data from the additional eight patients
    - SAS datasets of the mITT data (complete, baseline, efficacy and safety).
- A comprehensive safety update will be submitted to the sNDA to include the safety data from these additional patients as well as any additional safety data that Questcor may obtain through postmarketing surveillance or other means. Based on our earlier conversations with the Agency, this update will likely be submitted sooner than the traditional 120-day safety update. A discussion as to the date the Agency would like this update submitted would be appreciated.

Questcor believes that the submission of the Statistical Report will provide the full information on these additional patients, with data integration from the data from the other 50 study patients, via the mITT analyses. We believe this Report will enable the Agency to fully assess this study and, further, we believe this Statistical Report should allow the Agency to designate our sNDA submission to be a full Complete Response. This Statistical Report is scheduled to be available for transmission to the Agency on 22 May 2009 via email and/or electronic media. (b) (4) will communicate with Susan Daugherty on the particulars for the operational transmission of this submission.

Questcor is working to deliver this Statistical Report as described above concurrent with awaiting the Agency's concurrence with this plan. We respectfully request a brief telephone discussion with the Agency at your earliest convenience over the coming several business days, or, request a reply to this proposal in an expeditious manner. If you have any questions or need additional information, please contact either, (b) (4), at (b) (4) or (b) (4) to Questcor at (b) (4).

We appreciate your prompt attention.

Thank you.

(b) (4)

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/s/

Eric Bastings

6/3/2009 05:51:09 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-432

Questcor Pharmaceuticals, Inc.
Attention: Steven Halladay, Ph.D.
Senior Vice President, Clinical and Regulatory Affairs
3260 Whipple Road
Union City, CA 94587

Dear Dr. Halladay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for H.P. Acthar® Gel (repository corticotropin injection).

Please also refer to the teleconference between representatives of Questcor Pharmaceuticals and representatives from the Division of Neurology Products on April 9, 2009. During the April 9th teleconference we notified you that your submission was not a complete response to our action letter because data was missing for 9 patients in one of the pivotal studies. In order to correct this we ask you perform a thorough search for the missing data. If such data remains missing you must describe what efforts were made to search for the missing data and include a complete, and well documented, explanation of the reason the data is missing. This should include a formal detailed statement from the individual investigator.

Therefore, the review clock will not start until we receive a complete response.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz

4/21/2009 05:08:03 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-432

Questcor Pharmaceuticals, Inc.
Attention: Steven Halladay, Ph.D.
Senior Vice President, Clinical and Regulatory Affairs
3260 Whipple Road
Union City, CA 94587

Dear Dr. Halladay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for H.P. Acthar® Gel (repository corticotropin injection).

We do not consider this a complete response to our action letter, because we are not able to perform a review of your application in its present electronic format, and your application contains files that are not in conformance with FDA's specifications (e.g. .xls files or Zip files). Therefore, the review clock will not start until we receive a complete response.

Please re-submit your response in a format that is in conformance with FDA specifications. You may contact esub@fda.hhs.gov if you require assistance with the appropriate electronic formatting.

If you have any question, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz

12/23/2008 08:12:53 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Biometrics HFD-710			FROM: Division of Neurology Products, Susan Daugherty, (301 796-0878)	
DATE December 3, 2008	IND NO. (b) (4)	NDA NO. 22-432 (08-372/S-039)	TYPE OF DOCUMENT Complete Response to NA	DATE OF DOCUMENT November 26, 2008
NAME OF DRUG Acthar Gel	PRIORITY CONSIDERATION High		CLASSIFICATION OF DRUG AED – Infantile Spasms	DESIRED COMPLETION DATE May 28, 2008

NAME OF FIRM: Questcor

REASON FOR REQUEST

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☒ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ` PROTOCOL REVIEW OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

COMMENTS/SPECIAL INSTRUCTIONS: Please review and this Complete Response to NA

SIGNATURE OF REQUESTER Susan Daugherty, Regulatory Project Manager	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Susan B. Daugherty

12/3/2008 05:08:43 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 8, 2008

SUBJECT: Creating Type 6 NDA

NDA 08-372/S-039 was submitted to and reviewed by the Division of Metabolic and Endocrine Products. However, it should have been reviewed by the Division of Neurology Products as a type 6 NDA because the indication is for infantile spasms.

Therefore, sNDA 08-372/S-039 has been converted to the new NDA 22-432 for the 2nd cycle.

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/s/

Susan B. Daugherty
8/8/2008 02:45:50 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PIND (b) (4)

Questcor Pharmaceuticals, Inc.
Attention: Steven Halladay, Ph.D.
Senior Vice President, Clinical and Regulatory Affairs
3260 Whipple Road
Union City, CA 94587

Dear Dr. Halladay:

Please refer to your pre-Investigational New Drug Application (PIND) received on January 29, 2008, for Acthar® Gel. This submission contains a clinical Special Protocol Assessment request. The protocol is titled "Determination of the Adverse Effect profile for Patients with Infantile Spasms Treated with HP Acthar Gel (ACTH); A Retrospective Review."

We have completed our review and, based on the information submitted, have the following responses to your questions. Our responses are bolded and follow each question.

1. Disease: The protocol proposes to access the charts of patients diagnosed with infantile spasm (IS). Other diagnosed epileptic encephalopathies are not part of the intended population, or the Acthar Gel package insert. Does the Agency agree with this proposal to limit the charts to patients with IS?

Yes, because infantile spasm is the indication under consideration in supplemental new drug application NDA 08-372/S-039.

2. Patient Age: The protocol proposes to assess charts of patients in the age range of 3 months to 2 years old. The basis is that for patients aged below 3 months, there is often a different neurological syndrome involved and that may result in clinical outcomes and toxicities that are not representative of this condition. Acthar Gel is not intended for use in patients over 2 years old. Does the Agency agree with this proposal for the age range of minimum 3 months and maximum 2 years?

Yes, this age range would include the vast majority of infants presenting with infantile spasms. The protocol text needs to make explicit the minimum age of 3 months.

3. First Use of Acthar Gel: The protocol proposes to assess charts of patients who were naïve to treatment with Acthar Gel. This first use of Acthar Gel will provide information relevant to the proposed package insert. Experience other than first use will be included in discussion in the ISS in the Complete Response as available from literature and other sources. Does the Agency agree?

No, the Agency requests that the charts of patients who receive Acthar Gel other than first use (e.g. second course of therapy for partial responder to the first course) also be assessed as part of the retrospective study if their treatments occurred in the proposed 2002-2007 time period at the participating centers. The literature and other sources cannot be relied on for complete safety data in the "other than first use" patients just as they cannot be relied on for the first-use patients. This information will still be of interest even if you intend to label for a single course of treatment.

4. Dose of Acthar Gel: The prospective protocol plan will assess patients having the dosing schedule of approximately 150 lU/sq.m./day in equally-divided BID doses of 75 lU/sq m. This usage will most closely reflect the proposed package insert for Acthar Gel. A separate literature review of experience with Acthar Gel at other doses, including discussions on the overall efficacy and safety of Acthar Gel at various doses, will be included in the Complete Response. Does the Agency agree with this proposal for the dose of the retrospective safety study?

No, the Agency requests that the charts of patients who receive Acthar Gel by other dosing schedules (e.g. lower dose, higher dose, QD, etc.) also be assessed as part of the retrospective cohort study if their treatments occurred in the proposed 2000-2007 time period at the participating centers. The literature and other sources cannot be relied on for complete safety data in the "other dosing schedule" patients just as they cannot be relied on for the patients dosed at 150 lU/sq.m./day in equally-divided BID doses. The vast majority of patients however should be exposed to doses at or higher than the intended labeled daily dose. A separate analysis should be performed for patients that are exposed to the anticipated labeled dosage.

5. Denominator and Date Range for Charts: For the prospective safety analysis of this protocol, we propose to access charts in reverse chronological order beginning with 2007 and going back to 2002 with the objective to identify approximately100 applicable charts from patients fitting the inclusion criteria (approximately 150 IU/sq .m/day in equally divided BID doses of 75 lU/day) identified above. All applicable charts beyond the initial 100 will also be accessed and analyzed for inclusion with the applicable safety updates to the NDA. Does the Agency agree with these proposals for the denominator of N= 100 for the analysis, and the overall chart review plan?

The Agency requests that all charts fitting the inclusion criteria be accessed rather than stopping after the first 100 charts, as noted in the question. Then, continue on until 200 charts are accrued which meet the criteria and are considered evaluable. Please note there is an inconsistency in your present proposal: i.e. the protocol on page 6 [15] indicates a planned sample size of 150.

In addition, we have the following comments.

1. Please indicate whether both American and foreign centers will participate.

2. Please clarify in the exclusion criteria #2 (page 6 [15]) whether infants who previously received short-term steroids for asthma, bronchiolitis, etc. will be included. It would seem appropriate that they would be included.

3. The "final visit" for each patient is defined as the first visit after the last dose administered. The final visit should be at least 2 weeks after the last dose administered to allow assessment of late developing adverse effects.

4. The definition of serous adverse effect (page 9 [18]) should also include life-threatening AE, AE resulting in permanent disability, and AE requiring extension of hospitalization.

5. Complete patient narratives should be provided for patients with serious adverse effects or who discontinued the Acthar gel due to adverse events.

6. Analysis of all laboratory data (including EKGs when available) and vital signs should include shift tables (e.g. normal to abnormal shifts), central tendency analysis (e.g. mean and median) and analysis of marked outliers.

7. We note that you are evaluating adverse events through inferential statistics. This is acceptable, however, as this study is not powered for such an analysis and there are no corrections for multiple comparisons, we consider such an analysis as exploratory. We will largely rely on the descriptive statistical analysis.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the "*Guidance for Industry; Formal Meetings with Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cder/guidance/index.htm. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name
IND (b) (4)	QUESTCOR PHARMACEUTICALS INC	H.P. ACTHAR GEL

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/s/

RUSSELL G KATZ
03/27/2008

Weber, Jena M

From: Joffe, Hylton
nt: Tuesday, August 08, 2006 2:23 PM
Weber, Jena M
: Kehoe, Theresa
Subject: Acthar gel - comments for 45d filing letter

Hi Jena,

Here are my comments to Questcor:

1. We have been unable to locate the "define" file for the variables used in the dataset. Please send this document or let us know where we can find the information in the original submission.

2. Please provide a Microsoft Word version of the proposed labeling text as well as a Word version with tracked changes.

Thanks,

Hylton