CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

008372Orig1s045

Trade Name:	H.P. Acthar Gel (respository corticotropin injection)
Generic or Proper Name:	corticotropin
Sponsor:	Questcor Pharmaceuticals, Inc.
Approval Date:	July 5, 2012
Indication:	• indicated as monotherapy for the treatment of infantile spasms in children less than two years of age. • 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:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 008372/S-045

SUPPLEMENT APPROVAL
REMS ASSESSMENT ACKNOWLEDGMENT
RELEASE REMS REQUIREMENT

Questcor Pharmaceuticals, Inc.
Attention: Sian Bigora, PharmD
Vice President, Regulatory Affairs
6011 University Blvd, Ste 260
Ellicott City, MD 21043

Dear Dr. Bigora,

Please refer to your Supplemental New Drug Application (sNDA) dated April 14, 2012, received April 14, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for H.P. Acthar Gel (respository corticotropin injection).

We acknowledge receipt of your amendment dated April 25, 2012. We also acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated April 20, 2012.

This sNDA proposes to eliminate the requirement for the approved REMS.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for H.P. Acthar Gel (respository corticotropin injection) was originally approved on October 15, 2010. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

You propose that FDA no longer require a REMS for H.P. Acthar Gel (respository corticotropin injection).

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of H.P. Acthar Gel (respository corticotropin injection) outweigh its risks, and a REMS is no longer required.

We remind you that the Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208.

REPORTING REQUIREMENTS

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

If you have any questions, call Stephanie Parncutt, PharmD, Regulatory Project Manager, at (301) 796-4098.

Sincerely,

{See appended electronic signature page}

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

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/s/

RUSSELL G KATZ
07/05/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

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OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	**May 17, 2012**
To:	Russell Katz, MD Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Medication Guide (MG)
Drug Name (established name):	H.P. ACTHAR GEL (repository corticotropin)
Dosage Form and Route:	Injection
Application Type/Number:	NDA 008372 sNDA 022432
Supplement Number:	S-045
Applicant:	**Questcor Pharmaceutical, Inc.**

1 INTRODUCTION

On March 14, 2012 Questcor Pharmaceuticals, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS) for H.P. ACTHAR GEL (repository corticotropin) Injection, indicated for the treatment of infantile spasms in children less than two years of age. This supplement proposes the elimination of the approved Risk Evaluation and Mitigation Strategy (REMS) for H.P. ACTHAR GEL (repository corticotrophin) Injection. On April 19, 2012, the Division of Neurology Products (DNP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for H.P. ACTHAR GEL (repository corticotropin) Injection.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed Medication Guide (MG) for H.P. ACTHAR GEL (repository corticotropin) Injection.

The REMS is being reviewed by the Division of Risk Management (DRISK) and will be provided to DNP under separate cover.

2 MATERIAL REVIEWED

- Draft H.P. ACTHAR GEL (repository corticotropin) MG submitted May 17, 2012.
- H.P. ACTHAR GEL (repository corticotropin) MG approved October 15, 2010.

3 CONCLUSIONS

In our review, we performed a side-by-side review of the Applicant's proposed MG against the currently approved H.P. ACTHAR GEL (repository corticotropin) MG dated October, 2010, and find the Applicant's proposed MG is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
05/17/2012

MELISSA I HULETT
05/17/2012

LASHAWN M GRIFFITHS
05/17/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

008372Orig1s045

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 Compliance

REMS Memorandum

TO: Russell G. Katz, MD, Director
Division of Neurology Products

THROUGH: Tamika White, Acting Branch Chief
Post Marketing Safety Branch
Division of Safety Compliance
Office of Compliance (OC)

FROM: Kendra Biddick, Consumer Safety Officer
Post Marketing Safety Branch, REMS Compliance Team
Division of Safety Compliance
Office of Compliance (OC)

SUBJECT: Risk Evaluation and Mitigation Strategy (REMS) Modification and Assessment Review

APPLICATION NDAs 008372, 022432

This memorandum serves as the OC review of the H.P. Acthar Gel (repository corticotropin injection) NDA 008372 REMS modification submitted to the Food and Drug Administration (FDA) on March 14, 2012 by Questcor Pharmaceuticals, Inc.

BACKGROUND

FDA approved H.P. Acthar Gel (repository corticotrophin) on April 29, 1952 for multiple indications. In 1972 FDA expanded the label to include multiple sclerosis. FDA added the indication of infantile spasms in pediatric patients on October 25, 2010. As part of the October 15, 2010 approval, FDA required a REMS consisting of a Medication Guide and a timetable for submission of assessments. FDA required the REMS because the known risks of infections, blood pressure elevation and the risk of adrenal insufficiency are important potential serious adverse events in the pediatric population. On June 29, 2011 FDA emailed Questcor inquiring whether the firm had considered submitting a proposed REMS modification to request removal of the Medication Guide from the product's REMS. FDA noted that removal of the Medication Guide would effectively eliminate the REMS for H.P. Acthar Gel.

On March 14, 2012 Questcor submitted a request for removal of Medication Guide from REMS. On April 19, 2012, Questcor submitted the 18-month REMS assessment report for H.P. Acthar Gel. The assessment report was four days late. On April 24, 2012 Questcor submitted an amendment to the request for removal of the Medication Guide from the REMS for Acthar Gel which stated Questcor has no ongoing PMC or PMR studies.

Review date: June 18, 2012

The assessment plan should include, but not be limited to, an evaluation of patients' understanding of the serious risks of H.P. Acthar Gel (repository corticotropin).

The April 19, 2012 H.P. Acthar Gel REMS Survey Report, referenced below, addresses the required assessment.

REMS ELEMENTS REVIEWED

The OC reviewer read and reviewed the:

- October 15, 2010 approval letter for Acthar Gel.
- April 19, 2012 H.P. Acthar Gel REMS Survey Report
- March 14, 2012 request for removal of the Medication Guide from the Acthar Gel REMS
- April 24, 2012 amendment to the request for removal of the Medication Guide from the REMS.

OC RECOMMENDATIONS

OC has no comments and no objection to approval of Questcor's request to remove the Medication guide from the REMS for Acthar Gel.

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/s/

KENDRA A BIDDICK
06/21/2012

TAMIKA T WHITE
06/21/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Review of 18-Month Risk Evaluation and Mitigation Strategy (REMS) Assessment Report

Date:	June 19, 2012
Reviewer:	Kathryn O'Connell M.D., Ph.D. Medical Officer Mary Dempsey Risk Management Programs Coordinator Division of Risk Management
Team Leader:	Doris Auth, Pharm.D.
Associate Division Director:	Mary Willy, Ph.D.
Drug Name:	H.P. Acthar Gel (repository corticotropin injection)
Application:	NDA 22-432 and NDA 8372
Applicant/sponsor:	Questcor Pharma
OSE RCM#:	2012-957

1 BACKGROUND

This is a review of the first (18 month) assessment report for the H.P. Acthar Gel REMS. The REMS was approved on October, 15, 2010. The REMS consists of a Medication Guide and a timetable for submission of assessments[1]. 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.

H.P. Acthar Gel was first approved on April 29, 1952 for multiple indications. The label was later expanded to include multiple sclerosis (MS) in 1972. The October 2010 approval was for the indication of infantile spasms in pediatric patients. The extension of the indication to pediatrics changed the risk benefit profile of H.P. Acthar Gel and was considered to be "new safety information" as defined in section 505-1(b)(3) of the FDCA. Specifically, 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, and the risk of adrenal insufficiency seen in other patient populations is an important potential serious adverse event in the pediatric population. According to the sponsor website, Acthar Gel is available only through a specialty pharmacy.

The REMS assessment plan consists of an evaluation of patients' understanding of the serious risks of H.P. Acthar Gel, and information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. The timetable is 18 months, 3 years, and 7 years.

2 MATERIALS REVIEWED

- Sponsor's first (18month) assessment report April 19, 2012
- Acthar gel REMS Approval letter dated October 15, 2010
- Approved labeling per Drugs@FDA

[1] The sponsor submitted an amendment to remove the Medication Guide from the REMS on March 12, 2012.

3 RESULTS OF REVIEW

3.1 Patient/Caregiver Survey

The survey was pre-tested and underwent subsequent minor changes prior to conducting the survey, which was distributed to patients/caregivers of all patients with infantile spasms newly enrolled in the Acthar Support and Access Program (ASAP). The response rate was 247/597 (41.4%). Of the 247 surveys received, 31 (12.6%) did not meet criteria for eligibility, more than half because the respondent was a health care provider. All 244 with information regarding mode of survey completion were mailed in and 75% of these were returned after the first follow-up attempt (3 attempts were made to collect the surveys).

The "primary endpoint" is reported as the "fail rate". This is defined as "the number and percent of those [patients] answering the question who did not choose the correct answer choices, or who chose incorrect answer choices in addition to the correct ones, based on the information in the Medication Guide".

Reviewer comment: In other words, a result is included in the fail rate numerator if any correct answer is left unchecked or if any incorrect answer has been checked. The sponsor also reported on a "secondary endpoint"; a respondent is included in the "alternate fail rate numerator" if any correct answer is left unchecked, regardless of whether incorrect answers have been checked or not. The results using this endpoint are not included in this review, nor are the results stratified by the various reported variables such as income level, age, who gave them the MG, etc. None of these stratified analyses change the overall impression of patient knowledge, which is not surprising since the stratification appears to be by demographics of the young child (the patient), not the survey respondent.

Risk Topic*[&]	% choosing	No. missing
Are you aware that there may be side effects associated with Acthar?	100	3
Which of the following are possible while being treated with Acthar?		5
Increased risk of infection*	93	
Water retention/increased body salts/low blood potassium*	70	
Excessive urination and sweating	29	
Increased risk of liver disease	18	
Other important considerations when using Acthar include?		10
Your child (the patient) should not receive certain vaccines during treatment*	90	
Most of the possible side effects of Acthar are reversible after stopping *	73	
Acthar may make it easier for your doctor to diagnose other conditions	11	
Live vaccines are the best choice for children receiving Acthar	3	
While using Acthar		
Your child (or the patient) should keep away from people who are sick*	98	
Tell doctor right away if ...sign of infection/open cuts/sores on your child*	92	
It is not a problem if your child (or the patient) is around people who are sick	1	
Select any of the signs that you might see with an infection		2
Fever*	97	
Diarrhea*	83	
Vomiting*	81	
Cough*	62	
Bruising	23	
Nosebleed	14	
Dry scalp	3	
Hiccups	1	

* indicates a correct choice

[&] in interest of space, wording of topic is not necessarily verbatim

Reviewer comment: The inclusion of bruising as a foil answer is unfortunate, since a bruising rash can portend bacterial meningitis, especially important if earlier signs and symptoms are masked by corticosteroids. This response

garnered one of the two highest selection rates of the foils, suggesting that some participating parents/caregivers may have known this important fact. Less worrisome, but equally puzzling is use of excessive urination and sweating as a foil response. Sweating is specifically mentioned in the labeling and frequent urination is a well known side effect of cortisol which is released from the adrenal cortex upon stimulation by corticotropin. This "incorrect" response had the highest selection rate, presumably reflecting parents' actual experience. This underscores the importance of clinical input for selection of foil responses in medically oriented surveys.

3.2 Medication Guide

Less than 3% of respondents reported not receiving a Medication Guide. Most (70%) reported that they received their MG as a package insert (the MG is distributed as part of the packaging). Almost 80% said they read all or most of the MG with less than 6% not reading any of it. Of the readers, almost all reported understanding all or most of the content, but almost a fourth reported that no one offered to explain it to them. Nearly all responders (90%) reported having no questions regarding the MG.

3.3 Sponsor's overall assessment of whether the REMS is meeting the goals

"Overall, the processes in place for providing the Medication Guide appear to be functioning as intended with nearly all patients having reported receiving these materials. The information provided in the Medication Guide appears to be easy to comprehend as most responders reported understanding most of the Medication Guide… No adjustments are planned to the survey instrument or methodology based on these results."

4 STATUS OF POST APPROVAL STUDIES AND CLINICAL TRIALS

There are no ongoing safety-related studies.

5 DISCUSSION

The aim of a DRISK REMS assessment review is to determine (1) whether the report is complete, and (2) whether the REMS is meeting the goals.

This assessment report is complete in addressing all issues outlined in the approved REMS assessment plan.

Is the REMS meeting its goals? The results of the patient survey suggest that the participating parents/caregivers have a good understanding of the product's risks.

As noted earlier, the survey's foil questions would need revision *if* the MG was to remain in the REMS (necessitating future surveys). However, DRISK and DNP met June 14, 2012 and determined that the REMS for H.P. Acthar Gel is no longer necessary and that the sponsor can be released from their REMS requirements. The Medication Guide will continue to be a component of the Professional Labeling in accordance with 21 CFR 208.

The regulatory background for this decision is as follows: In November 2011, FDA published the Guidance *Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)* that addresses when a Medication Guide will be required as part of a REMS. Based on the risks of a drug and public health concerns, FDA has the authority to determine whether a Medication Guide should be required as part of a REMS or should be required as labeling but not part of a REMS.

Prior to the finalization of the Medication Guide Guidance, DNP and DRISK met jointly and determined that the H.P. Acthar Gel Medication Guide could be removed from the REMS.

Questcor Pharma submitted the H.P. Acthar Gel 8 month REMS Assessment Report and DRISK review concluded that the Assessment was complete. Questcor Pharma also submitted a request to eliminate the REMS on March 12, 2012.

6 RECOMMENDATION

On June 14, 2012 DRISK, DNP, Patient Labeling, and Office of Compliance met to discuss this REMS assessment report. It was agreed that the assessment report is complete and that the REMS for H.P. Acthar Gel is no longer necessary. The sponsor can be released from their REMS requirements. The Medication Guide will continue to be a component of the Professional Labeling in accordance with 21 CFR 208.

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/s/

KATHRYN A O CONNELL
06/19/2012

MARY E WILLY
06/19/2012
I concur

DORIS A AUTH
06/19/2012