

**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) [redacted]. The original clinical pharmacology review of NDA 08-372 s039 dated 4/20/2007 concluded that the proposal to include labeling language (b) (4) [redacted] 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 [REDACTED] (b) (4) and [REDACTED] (b) (4) in [REDACTED] (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.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Reviewer's comments:

To be consistent with previous review, using [REDACTED] (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/m² 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. _____

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

/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)



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 [REDACTED] (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. _____

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

/s/

Ju-Ping Lai
2/12/2009 12:36:10 PM
BIOPHARMACEUTICS

Veneeta Tandon
2/12/2009 12:47:04 PM
BIOPHARMACEUTICS