

**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 #	22432 (000)
Supplement#	
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. 2003¹, 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. 1986³; Hrachovy et al. 1994⁴; Hrachovy et al. 1983⁵); 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 than 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 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. 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.

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 Sponsor has provided additional new information on the PK of Acthar Gel in patients with IS. This information 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 referred to as study 01), Hrachovy et al. and (1983; also referred to as study 04) Hrachovy et al. (1994; also referred 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) administered 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 be slightly older than 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 disproportionately 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 adequate 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 assessed 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 than 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 adequate 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 adequate 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 adequate 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. Prednisone	150 U/m ² /d (75U/m ² BID)	15	87%	15%	15.1±13.66 (2-48)
		2mg/kg (1 mg BID)	14	27%	NR	16.9±14.39 (2-46)
Snead 83	Retrospective: Acthar vs. Prednisone	150 U/m ² /d (75U/m ² BID)	30	97%	20%	24.6
		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 vs. Acthar High Dose	20 U QD (≈50U/m ² QD)	26	58%	21%	1.9±0.47 (0.5-2.6)
		150 U/m ² QD	24	50%	15%	3.1±1.55 (1.4-9.5)
Hrachovy 83#	RCT: Acthar vs. Prednisone	20 U QD (≈50U/m ² QD)	12	42%	33%	12-33
		2 mg/kg QD	12	33%	28%	12-33
Acthar Patients			122	89/122 (73%)	18/89 (20%)	
<small>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</small>						

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 adequate 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 2007⁶) 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 than pivotal trial doses (≥ 80 U/m²/day, n=133) and doses lower <80 U/m²/day, n=52) than 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 occurring in greater than 3 patients or greater ($\geq 0.9\%$ 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 were some recommendations, however, that the FDA should not make it too 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 than 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 immaturity⁷, 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 difficult². 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 filing, 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 adequate risk-benefit. While the treatment with Acthar Gel is not without serious consequences, these may be dealt with by adequate 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