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