CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21945Orig1s000

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

COMPLETE RESPONSE

Cytyc Corporation
Attention: Robb Hesley
Vice President, Business Development
1240 Elko Drive
Sunnyvale, CA 94089-2212

Dear Mr. Hesley:

Please refer to your new drug application (NDA) dated April 14, 2006, and received April 20, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gestiva (hydroxyprogesterone caproate injection), 250 mg/mL.

We acknowledge receipt of your presubmissions dated August 30, 2005, January 10, March 28, and April 7, 2006.

We further acknowledge receipt of your amendments dated April 20, June 23, July 14, 21, 28 and 30, August 14 (2), 22 (2) and 23, September 7, 12, 19 (2) and 25, October 10, 15 and 30, November 3, 2006, January 7 and 19, March 14, April 27, June 15, 2007, January 30, April 24 (2), May 16, June 12, August 28, September 3 and 25, October 1 (2), 16 and 31, December 12, 2008, and January 15, 2009.

Your April 24, 2008 amendment, received on April 25, 2008, constituted a complete response to our October 20, 2006 action letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

We acknowledge your commitment to complete a confirmatory study as a condition of approval under Subpart H 21 CFR 314.510. Your draft clinical protocol entitled "A Multi-Center, Randomized, Double-Blind Study of 17-α-Hydroxyprogesterone Caproate (17-P) versus Placebo for the Prevention of Preterm Birth in Women with a Previous Singleton Spontaneous Preterm Delivery," submitted on January 15, 2009, has adequately addressed our recommendations regarding such a confirmatory study. We are in agreement with the design of the trial, planned

sample size, primary and secondary objectives, and proposed analysis plan. The purpose of this trial (hereafter referred to as the "Confirmatory Study") is:

1. To confirm at least one of the previous findings of efficacy in Study 17P-CT-002 (i.e., a reduction in preterm birth at $< 35^0$ weeks of gestation),
2. To obtain further information regarding the effect of treatment with hydroxyprogesterone caproate on neonatal morbidity and mortality, and
3. To address the concern regarding early pregnancy loss identified in our action letter of October 20, 2006.

Clinical Deficiencies

1. You have not provided adequate documentation that it will be feasible for you to conduct and successfully complete the Confirmatory Study. The American College of Obstetrics and Gynecology (ACOG) Committee Opinion[1], issued in October 2008, on use of progesterone in women with a history of spontaneous preterm birth has raised our concern that successful completion of the placebo-controlled study that you have proposed is not likely to be feasible if the trial is conducted primarily in the U.S. We believe that the ACOG opinion has virtually established offering treatment with progesterone to such high-risk patients as a *de facto* standard of care. Institutional Review Boards (IRBs) and patients may interpret the ACOG committee opinion as indicating that any remaining questions regarding the efficacy and safety of hydroxyprogesterone caproate are not sufficient to justify conducting a placebo-controlled study. While you have provided some reassurance that there remain U.S. physicians who appear to be willing to participate in the trial, the information provided in the current application does not provide assurance of IRB approval of, or patient enrollment into, the Confirmatory Study. We believe that adequate assurance of feasibility can only be addressed by actual initiation of the trial.
2. Additional developmental assessment at ages 18-24 months is needed for children whose mothers participate in the Confirmatory Study. This information is needed to provide additional reassuring data that treatment of mothers with hydroxyprogesterone caproate does not have a detrimental effect on early infant/child development.

Resolution of Clinical Deficiencies

1. The Confirmatory Study will need to enlist investigators at a sufficient number of U.S. and non-U.S. sites to support target enrollment of 1,700 subjects; no site should enroll more than 15% of the total number of subjects. You will need to provide sufficient documentation that the Confirmatory Study can be initiated and is likely to be conducted successfully. Acceptable documentation of feasibility would include the following elements:
   - Documentation of IRB approval for at least 15 investigational sites (including U.S. and non-U.S. sites).
   - Enrollment of at least 5% of the total anticipated sample size.
   - Enrollment of at least 15 subjects at U.S. study sites.

[1] ACOG Committee on Obstetric Practice. Use of progesterone to reduce preterm birth. No. 419, October 2008.

- Agreement (with supporting evidence) to enroll at least 10% of the total sample of 1,700 subjects from U.S. and Canadian sites.

2. Submit a final clinical protocol for a study that will provide additional data to address whether treatment of mothers with hydroxyprogesterone caproate has a detrimental effect on early infant/child development. For those children whose initial screening examination suggests a developmental delay, the protocol should include formal psychometric and developmental assessments as well as an assessment by a pediatric neurologist.

LABELING

We reserve further comment on your proposed labeling until your application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

ADDITIONAL ISSUES THAT WOULD NEED TO BE ADDRESSED POSTMARKETING, IF THE PRODUCT WERE TO BE APPROVED:

Clinical

Initiate and complete a study that will provide additional information supporting your earlier data that treatment of mothers with hydroxyprogesterone caproate does not have a detrimental effect on early infant/child development (see Resolution of Clinical Deficiencies: Item No. 2).

Clinical Pharmacology

1. Provide data characterizing the pharmacokinetics of hydroxyprogesterone caproate and its metabolites in plasma and urine in pregnant women throughout different gestational stages.
2. Conduct an *in vitro* study using human hepatocytes to determine whether hydroxyprogesterone caproate induces or alters the metabolic activities of CYP1A2, CYP2A6 and CYP2B6.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.

- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings with Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Scott Monroe

1/23/2009 06:46:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-945

Adeza Biomedical
Attention: Durlin E. Hickok, M.D., M.P.H.
Vice President, Medical Affairs
1240 Elko Drive
Sunnyvale, CA 94089

Dear Dr. Hickok:

Please refer to your April 14, 2006, new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Gestiva™ (hydroxyprogesterone caproate injection), 250mg/mL.

We also acknowledge receipt of your presubmissions dated August 30, 2005, January 10, March 28, and April 7, 2006.

We further acknowledge receipt of your submissions dated April 20, June 23, July 14, 21, 28 and 30, August 14 (2), 22 (2) and 23, September 7, 12, 19 (2) and 25, October 10 and 15, 2006.

This application proposes the use of Gestiva™ for prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, it will be necessary for you to address the following deficiencies:

Clinical

1. Further study is needed to provide confirmatory evidence of the drug's efficacy in terms of a benefit on neonatal morbidity and mortality either directly, or through a well-established surrogate, such as the rate of preterm birth prior to 35 and 32 weeks of gestation.
2. There are insufficient data to evaluate a potential association of hydroxyprogesterone caproate (HPC) with increased risk of early fetal loss (second trimester miscarriage and stillbirth).

Information needed to address the clinical deficiencies

1. Submit a draft protocol and evidence of the feasibility of conducting an additional multicenter, well-controlled trial to verify and describe further the observed clinical benefit of HPC for the prevention of recurrent preterm birth, as stated in Subpart H 21 CFR 314.510. If a placebo-controlled trial is determined not to be feasible, provide alternative study design proposals.
2. Provide a draft protocol to evaluate the potential association of HPC with increased risk of second trimester miscarriage and stillbirth. This could be assessed as a part of the confirmatory efficacy study referred to in Item No. 1 above.

Pharmacology and Toxicology

There is a lack of nonclinical data from a multi-generational reproductive toxicology study for this product.

Information needed to address the toxicology deficiency

A GLP-compliant, multigenerational reproductive toxicology study needs to be performed, evaluating all stages of pregnancy during which dosing will be administered in humans. The study should be designed and conducted to assess potential effects on developmental and reproductive parameters, including learning, behavior and reproductive function, in offspring exposed *in utero*. At the time of a Complete Response submission to this approvable letter, provide, at a minimum, an unaudited interim final report of the requested study.

Chemistry, Manufacturing and Controls (CMC)

1. Significant degradation was observed for the light-stressed drug product sample with respect to content (assay) during the HPLC method validation studies. Thus, the drug product appears to be photosensitive; however, the resulting photodegradation products are not detectable by your HPLC method.
2. Given the results from your photostability study in which both the Stage 1 (fully exposed to light) and Stage 2 (enclosed in a chipboard box) samples showed decreases in content (assay) from that of the control (wrapped in foil) without corresponding increases in impurities by your HPLC method, you have not demonstrated that the secondary packaging provides adequate light protection for the drug product.
3. Your proposed expiration date of 24 months for the drug product is not acceptable based on the stability data included in your application to date.

Information needed to address the CMC deficiencies

1. Since you cannot account for the degradation of the active ingredient under light-stress conditions by your HPLC method, you should develop a supporting method that can adequately detect and quantitate the potential photodegradation products. The drug product specifications should include limits for any potential impurities observed using the new method, and a detailed description of the new analytical procedure with appropriate validation should be provided.
2. Alternative primary and/or secondary packaging should be used to protect the drug product from light. A description and justification for the new packaging system should be submitted with appropriate letters of authorization. In addition, you should revise the drug product labeling to state that the vials should be protected from light.
3. Based on the limited stability data provided in the application and the out-of-specification (OOS) results for particulate matter observed at accelerated conditions, an expiration date of NMT (b) (4) would be appropriate for the drug product when stored at controlled room temperature, protected from light. You are encouraged to determine the cause of the OOS results for particulates under accelerated conditions, and if necessary, you should consider a different container closure for storage of your drug product.

Additional issues that would need to be addressed postmarketing, if the product were to be approved:

Clinical

1. Completion of the additional efficacy and safety study(ies) requested above under the description of clinical deficiencies will be required as a condition of an approval under Subpart H 21 CFR 314.510 (Item No. 1 above under clinical deficiencies) or as a formal phase 4 commitment (Item No. 2 above under clinical deficiencies).
2. Long-term post treatment safety data (at least through puberty) from children whose mothers had been treated with HPC is lacking in the NDA. This information is requested and could be obtained through the establishment of a surveillance program (e.g., registry) to evaluate the effects of prenatal exposure in adolescents and young adults. Submit your proposal as to how these data would be obtained.
3. Additional developmental assessment is needed of children at ages 18-24 months whose mothers had been treated with HPC. This assessment could be obtained from the offspring of women enrolled in the confirmatory efficacy study or the safety study addressing early fetal loss. Children who screen positive for developmental delay should have a formal psychometric assessment and an additional assessment by a neurologist.

Clinical Pharmacology

In planning your subsequent clinical trial(s), the following pharmacokinetic elements should be considered as part of the design to allow for better understanding of HPC pharmacokinetics and optimal dosing:

- Characterize the pharmacokinetics of HPC and its metabolites in pregnant women (including both plasma and urine concentrations) at several periods throughout the pregnancy.
- Assess the HPC exposure-response relationship and the effect of body weight on the pharmacokinetics of HPC via sparse sampling of all subjects.
- Collect the dose and duration of all concomitant medications that are known strong inducers or inhibitors of drug metabolizing enzymes and analyze their effect on HPC pharmacokinetics.

Further comments on labeling are deferred until the above deficiencies are addressed.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration, regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Reproductive and Urologic Products and two copies of both the promotional materials and the package insert directly 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

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this Division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Eufrecina DeGuia, Regulatory Project Manager, at (301) 796-2130.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Acting Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Scott Monroe

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