CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205054Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205054

COMPLETE RESPONSE

ELC Group
Attention: Julia Valentine
US Agent for GP Pharm, S.A.
1500 Market Street, 12th Floor East Tower
Philadelphia, PA 19102

Dear Ms. Valentine:

Please refer to your New Drug Application (NDA) dated July 31, 2014, received July 31, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lutrate® Depot (leuprolide acetate for injection), (b) (4) 22.5 mg/vial.

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

CLINICAL/STATISTICAL

1. In the approval of gonadotropin releasing hormone agonists for the palliative treatment of advanced prostate cancer, testosterone levels serve as a surrogate marker of efficacy. When all available testosterone levels are used in the analysis, (b) (4) Lutrate Depot 22.5 mg failed to achieve and maintain castrate testosterone levels in an acceptable percentage of patients. (b) (4) In study GP/C/05/PRO, Lutrate Depot 22.5 mg achieved and maintained castrate testosterone levels between Days 28-168 in 83.9% of patients. Further, the results of these studies are difficult to interpret since there may have been marked variations in dose due to the extent of overfill in each Lutrate vial.

   To address this deficiency, you should optimize your formulations of (b) (4) Lutrate Depot 22.5 mg and conduct additional clinical trials to demonstrate the safety and efficacy of your products.

PRODUCT QUALITY

2. The batch formula cannot accurately reflect drug product composition because batches were manufactured with different amounts of excipients. Provide a batch formula that reflects the proposed composition of the drug product registration batches.

(b) (4)

4. You did not provide new information about overfill; however, you referenced Section 3.2.P.2.3.2.4 regarding the justifications provided in the original NDA. Provide justifications but NOT calculations to estimate the amount of product (b) (4)

5. The chemical physical properties of the drug substance have to be generated from the actual drug substance batches produced from manufacture. Provide chemical and physical properties of the drug substance from your manufactured batches.

6. The stability of the three primary batches of drug substance and drug product is not acceptable because no stability data for the drug substance were provided in the NDA. We consider the provided drug product stability data to only be supportive since they were obtained from annual reports. In addition, these data were collected from drug product batches obtained from marketed product available in foreign countries and packaged in a different packaging configuration. Based on the above information, expiry dating for the drug substance and drug product cannot be established. Provide a stability study and related test data of the three primary batches of the drug substance and drug product.

(b) (4)

(b) (4)

REGULATORY:

(b) (4)

9. As stated in our PreNDA meeting minutes dated October 24, 2012, if you rely for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate. (b) (4)

(b) (4)

PRESCRIBING INFORMATION

10. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

    If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

PROPRIETARY NAME

11. Please refer to correspondence dated December 19, 2014, which addresses the proposed proprietary name, Lutrate® Depot. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

FACILITY INSPECTIONS

12. During a recent inspection of the GP Pharma manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

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/trials 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/clinical trials 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 trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial 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 studies/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 other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. 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 Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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 Wheeler, Senior Regulatory Project Manager, at (301) 796-1141.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, M.D.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
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/

GEOFFREY S KIM
05/29/2015