CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205598Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205598

COMPLETE RESPONSE

Aeterna Zentaris GmBH
c/o Biologics Consulting Group, Inc.
Attention: Kerin Ablashi, US Agent
400 N. Washington Street, Suite 100
Alexandria, VA 22314

Dear Ms. Ablashi:

Please refer to your New Drug Application (NDA) dated November 4, 2013, received November 5, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Macrilen (macimorelin acetate granules) for oral solution.

We acknowledge receipt of your amendments dated November 12 and 19, 2013, and January 6 and 22, February 14, March 7 and 12, April 11, 17, 22, and 29, May 23, June 26 and 30, July 3, 23, and 31, August 1, 12, 20, and 26, September 2, 8, and 30, and October 8, 2014.

We have completed our review of this application, as amended, 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. The planned analysis of pivotal trial AEZS-130-047 did not meet its stated primary objective of demonstrating that the lower bound of the one-sided 99% confidence interval for the area under the Receiver Operator Characteristic (i.e., ROC) curve was above the pre-specified threshold of 0.85. We remind you that this analysis and the patient population for this analysis (i.e., the modified intent to treat population) were prospectively defined and pre-specified in your statistical analysis plan and agreed to in the special protocol assessment (SPA) agreement letter dated December 17, 2010.

   As discussed in detail at the late cycle meeting held on July 23, 2014, our review of trial AEZS-130-047 identified issues related to the lack of complete and verifiable source data for determining whether patients were accurately diagnosed with adult growth hormone deficiency (AGHD). These findings further undermine our confidence in the robustness of analyses (including the secondary per-protocol analysis) and in the reliability of the proposed diagnostic cut-offs. In light of the failed primary analysis and data deficiencies noted, clinical trial AEZS-130-047 does not by itself support the indication.

   To address the deficiencies identified above you will need to demonstrate the efficacy of macimorelin acetate as a diagnostic test for GH deficiency in a new, confirmatory clinical

study. The study should be a controlled clinical trial and should prospectively confirm the diagnostic performance of currently proposed cut-points in the spectrum of patients for whom the macimorelin test will be applied [e.g., not only in those patients with very high or very low pretest probability (i.e., as in trial AEZS-130-047) but also in those patients with intermediate pretest probability for AGHD]. We encourage you to request an End of Review meeting to discuss the path forward for this application and to begin discussion of the design of the newly requested study.

2. In your small clinical program, a serious event of QT prolongation occurred for which attribution to drug could not be excluded. Conduct a dedicated thorough QT study to evaluate the effect of macimorelin on the QT interval and submit a report of this evaluation with your resubmission. We recommend that you submit the thorough QT study protocol for Agency review and comments prior to initiating the study.

PRESCRIBING INFORMATION/CARTON AND CONTAINER LABELING

3. 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

4. Please refer to correspondence dated, January 27, 2014, which addresses the proposed proprietary name, Macrilen. 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.

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.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
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/

MARY H PARKS
11/05/2014