CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212904Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204408

COMPLETE RESPONSE

AVEO Pharmaceuticals, Inc.
Attention: Margaret M. Taleff
Vice President, Regulatory Affairs
75 Sidney Street, 4th Floor
Cambridge, MA 02139

Dear Ms. Taleff:

Please refer to your New Drug Application (NDA) dated September 28, 2012, received September 28, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (tivozanib hydrochloride) capsules, 1.0 mg or 1.5 mg.

We acknowledge receipt of your amendments dated October 15, 2012; November 07, 2012; November 08, 2012; November 09, 2012; November 14, 2012; November 16, 2012; December 05, 2012; December 17, 2012; January 07, 2013(3); January 08, 2013; January 15, 2013; January 16, 2013; January 18, 2013; January 22, 2013; January 23, 2013; January 24, 2013, January 25, 2013; January 28, 2013(2); January 30, 2013; January 31, 2013(2); February 04, 2013; February 20, 2013; February 21, 2013(2); February 27, 2013; March 01, 2013; March 06, 2013; March 14, 2013; March 15, 2013; March 19, 2013; March 22, 2013; March 28, 2013; April 04, 2013(2); April 12, 2013; April 17, 2013; April 22, 2013; April 24, 2013; May 10, 2013.

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

1. This new drug application is supported by a single Phase 3 trial in which patients with advanced renal cell carcinoma were randomized to either tivozanib or sorafenib. While the results of the primary endpoint of progression-free survival (PFS) statistically favored tivozanib [hazard ratio of 0.80; p value of 0.04], a potential 25% decrease in overall survival (OS) was also demonstrated [hazard ratio: 1.25; p value: 0.1]. This potential increase in the risk of death is not acceptable, particularly when multiple other therapies are available for this disease. The inconsistent PFS and OS results and imbalance in post study treatments make the trial's results uninterpretable and inconclusive when making a risk-benefit assessment necessary for drug approval.

We recommend that you perform an adequate and well-controlled randomized trial(s) of tivozanib using PFS as the primary endpoint and OS as a secondary endpoint. You should ensure the applicability of the results from this trial to the US population. The trial should be powered to detect a difference in PFS and adequately sized to reassure us that there is no adverse effect on OS. The design, conduct, and results of this trial will determine whether one additional trial will be sufficient for approval purposes.

PRODUCT QUALITY

2. Your proposed dissolution acceptance criterion (Q= (b) (4)% at (b) (4) minutes) is not supported by the provided dissolution data and is not acceptable. The data support a dissolution acceptance criterion of Q= (b) (4)% at (b) (4) minutes for your product. Implement this criterion at release and on stability. When your NDA is resubmitted, please include the revised specifications table for the drug product with the updated dissolution acceptance criterion.

LABELING

We reserve comment on the proposed labeling until the 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

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 Kim J. Robertson, Regulatory Health Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
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/

RICHARD PAZDUR
06/06/2013