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APPLICATION NUMBER:

204441Orig1s000

OTHER ACTION LETTERS



NDA 204441

COMPLETE RESPONSE

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: Craig Ostroff, Pharm.D., RPh.
Senior Director, Regulatory Affairs
1 University Square Drive, Suite 500, Room 5125
Princeton NJ 08540

Dear Dr. Ostroff:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tolvaptan tablets, 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg. We acknowledge receipt of your amendments dated March 6, 11, 14, 18, 19, 21, 26, 27, 29, April 1, 4, 9, 12, 15, May 15, 16, 30, June 11, 17, 18, 21, 27, July 3, 9, 11, 12, 15, 17, 18, 24, and 25, 2013.

We have completed our review of your application, as amended, to market tolvaptan to slow kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD) and cannot approve it at this time.

You and we agreed that as the sole study providing evidence of effectiveness to support approval of an NDA, study 156-04-251 would need to achieve a p-value < 0.01 for the first secondary efficacy endpoint, a composite of

- Worsening renal function events (about a 33% increase in serum creatinine),
- Renal pain events requiring medical intervention,
- Worsening in category of hypertension, and
- Worsening in category of albuminuria.

We conclude that the analysis specified in the final statistical analysis plan indicates the study was statistically successful, or nearly so. This outcome was driven principally by decreases in events of worsening renal function and events of renal pain; there was no effect on the other two components. Your analysis of the second secondary endpoint assessing the effect of tolvaptan on the decline of glomerular filtration rate (GFR) suggests that tolvaptan slows the decline in renal function. However, the following elements of study 156-04-251 lessen confidence in these results serving as the sole basis for approval:

1. The protocol for 156-04-251 stipulated that subjects who discontinued study drug no longer were followed at investigative sites and so the information necessary to determine their outcomes was not collected. This affected 23% of tolvaptan subjects and almost 14% of placebo subjects, so confidence in the observed results is lessened by the potential bias introduced by the loss of data from subjects who may have had different outcomes had they

remained in the study. Sensitivity analyses meant to explore how robust the results are to the data missing from subjects who discontinued study drug are not reassuring. An analysis of the secondary composite endpoint that imputes the outcomes of the placebo subjects to the tolvaptan subjects after they discontinued study drug (which we believe is not conservative) results in a p-value of 0.04.

2. Loss to follow-up was already a significant problem by the time of your post-randomization “baseline” assessment of renal function. Beyond that, the effect of tolvaptan in slowing the decline in GFR amounted to only about 1 mL/min/1.73 m², which is only about a 30% reduction. The clinical significance of this small reduction hinges upon the assumption that it will continue unabated for much of a patient’s life, a theory that runs counter to assumptions you held in designing this development program.
3. Reduction of pain is an important clinical benefit. The reduction in pain events observed in 156-04-251 was ~35%, but the absolute reduction in the number of moderate to severe pain events (those requiring a procedure or a narcotic or a tricyclic drug) is only about 1 event per 100 patient years. Again, we have concerns that even this modest effect may be an overestimation.
 - a. Pain is subjective. Its perception and reporting are known to be affected if subjects and/or investigators are aware of treatment assignment (investigators in study 251 decided if events were “medically significant” enough to require intervention). The aquaretic effects of tolvaptan are likely to have unblinded many subjects and investigators.
 - b. Differential loss of information between the treatment groups may have biased the observed results. The occurrence of these renal pain events was not collected systematically from subjects who stopped taking study drug. The subjects who stopped taking study drug generally did so because they were unable to tolerate the aquaretic side effects. We suspect that these subjects would have been more likely to seek medical attention for pain had they remained in the trial, likely biasing the observed results in favor of tolvaptan.

While we did not accept change in total kidney volume (TKV) as a valid surrogate, the mechanism by which you expected tolvaptan to improve outcome in ADPKD was based on affecting TKV, so we considered TKV potentially supportive. The data demonstrate an acute decrease in TKV of about 100 mL during the first year (you suggested during the advisory committee meeting that most of that may occur in the first few weeks of tolvaptan administration) with an about 50 mL smaller increase in TKV compared to placebo over the next two years. Hence, the effect of tolvaptan on the increase in TKV is not only small (no more than a 10% decrease in kidneys that are many times the normal size), but it is not sustained.

We agree with the conclusion of your hepatic adjudication panel that in the absence of measures to mitigate the risk of hepatotoxicity tolvaptan can “cause liver injury capable of progression to liver failure.... with a rough incidence of liver failure ...estimated as 3/860 x 10, or about 1:3000 patients (who) receive long term treatment with tolvaptan.” The proposed risk evaluation and mitigation strategy that resulted from your discussions with us is likely to decrease significantly

the incidence of tolvaptan-induced liver injury progressing to death or transplantation (at least in the USA). We have some residual concern that marketing tolvaptan for ADPKD may result in the unfortunate but very rare patient developing severe irreversible liver injury, but that concern could have been outweighed by an unambiguous demonstration that tolvaptan provided an important clinical benefit in a serious illness without useful therapy.

For this application to be approved, you need to conduct an additional efficacy trial that tests the hypothesis that tolvaptan slows the loss of renal function and is successful at a p-value < 0.05. Because the effect of tolvaptan appears to be small and long-term studies are clearly infeasible, we think that the confirmatory study should be conducted in patients at a later stage of their disease. This study should also provide additional information about tolvaptan-induced hepatotoxicity and determine the effectiveness of a risk mitigation plan for identifying liver injury before it results in permanent morbidity. Because of the unmet medical need in this serious condition, we are anxious to work with you on the design of this trial.

**DIVISION OF BIOEQUIVALENCE AND GOOD LABORATORY PRACTICE (GLP)
COMPLIANCE OFFICE OF SCIENTIFIC INVESTIGATIONS**

The Division of Bioequivalence and GLP Compliance (DBGLPC) notes that for Study 156-11-295, (b) (4)

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>.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

We acknowledge receipt of your proposed REMS, included in your submission dated March 1, 2013, and amended July 18, 2013, which contains elements to assure safe use, an implementation system and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for tolvaptan (NDA 204441), if it is approved for ADPKD, to ensure that the benefits of the drug outweigh the risks of hepatotoxicity associated with tolvaptan treatment.

The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

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>.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
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/

NORMAN L STOCKBRIDGE
08/28/2013