CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-856

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 21-856

TAP Pharmaceutical Products Inc.
675 N. Field Drive
Lake Forest, IL 60045

Attention: Binita Kwankin
Assistant Director, Regulatory Affairs

Dear Ms. Kwankin:

Please refer to your new drug application (NDA) dated December 14, 2004, received December 15, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uloric (febuxostat tablets), 80 mg and 120 mg.

We acknowledge receipt of your submissions dated February 17, April 18, June 1 and 14, and July 12, 19, and 21, 2006. The February 17, 2006, submission constituted a complete response to our October 14, 2005, action letter.

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

> Provide further data to clarify the cardiovascular risks of the proposed doses and/or provide data on the safety and efficacy of lower doses of febuxostat in order to assure us that a dose level(s) with favorable risk-benefit characteristics has been defined.

We are withholding labeling comments pending resolution of the above deficiency.

While not a deficiency impacting the approvability of Uloric, we request that you conduct a new warfarin-febuxostat interaction study. In the new study, the lead-in period for identifying a stable warfarin dose may need to be more than nine days and/or you should enroll more subjects such that a sufficient number of subjects are able to complete the trial. We would like data from this study to be submitted as a part of a resubmission. However, we would entertain a later submission of such data (including post-approval) if appropriate labeling were proposed —

c [redacted] b(4)

In addition, we remind you of your February 17, 2006, commitment to perform the following studies. While we agreed to allow these studies to be performed in the post-approval period, in light of this approvable action, please consider beginning any of these studies that you have not already undertaken at the earliest possible time.

1. A Randomized, Multicenter Study Comparing the Efficacy and Safety of Febuxostat to Allopurinol in Reducing the Incidence of Gout Flares in Subjects with Gout.

2. A Double-Blind, Randomized, Two-Period Crossover Study to Evaluate the Effect of Multiple Oral Doses of Febuxostat on the Pharmacokinetics of a Single Oral Dose of Theophylline. b(4)

3. *In Vitro* Assessment of Induction Potential of Febuxostat in Primary Human Hepatocytes.

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:

   a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   b. Present tabulations of the new safety data combined with the original NDA data.

   c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   d. 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.

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

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 an informal 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 Matt Sullivan, Regulatory Project Manager, at 301-796-1245.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Robert Meyer
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We acknowledge receipt of your submissions dated January 20, 25, 27, and 28, February 15, March 22, 30, and 31, April 1, 6, and 14, May 5, June 2, 14, 27, and 30, July 8, 13, 18, and 19, August 12, 22, and 31, and September 12 and 16, 2005.

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

1. Further evaluate the safety profile of Uloric, especially in regard to its potential to result in cardiovascular adverse events. Our review of the safety database submitted in your application raises concerns regarding the potential for Uloric to cause clinically significant cardiovascular/thrombotic adverse events in excess to that seen with allopurinol or placebo, even when exposure-over-time is factored into the analysis. This safety signal may be addressed by providing further comparative controlled clinical safety data or, possibly, through reanalyses of the current database (augmented by any recently completed or on-going studies) that demonstrate the apparent signal of increased risk is not predictive of clinically important differences. Should a differential signal of thromboembolic CV events remain upon the analysis of any new data and/or reanalyses of existing data, we would strongly encourage you to consider proposing the use of lower doses of Uloric, rather than those proposed.

2. Evaluate the potential for pharmacokinetic interactions with Uloric when coadministered with theophylline, azathioprine or mercaptopurine. Uloric should be studied at its maximum proposed clinical dose, and theophylline, azathioprine and mercaptopurine may be studied at sub-therapeutic doses in order to decrease the incidence of adverse effects, if indeed Uloric does increase the exposure to these compounds in which xanthine oxidase plays a role in their metabolism. The results of these studies will provide information on dose selection when these drugs are co-administered. Without these studies, co-administration of Uloric with theophylline, mecaptopurine or azathioprine will need to be contraindicated and risk minimization strategies may be needed to assure that no such concomitant use will occur in the actual use setting.

3. Evaluate the potential for concomitant administration of warfarin and Uloric to result in hemorrhagic adverse events, and further address the potential for Uloric to cause hemorrhagic events without co-administration of an anticoagulant . A significant concern exists due to the finding that two subjects died as a result of retroperitoneal hemorrhages while being treated with Uloric, both of whom were receiving warfarin as well. Additional hemorrhagic events were also noted in the safety database. We do not agree with your conclusion that there were no drug-drug interaction with warfarin in the clinical pharmacology study, due to our conclusion that the drug-drug interaction study with warfarin was inadequate to allow for definitive conclusions. The removal of subjects with an increased INR from the final analysis in the warfarin drug-drug interaction trial was problematic. In addition, there were reports of increased INR values in the clinical database in subjects receiving concomitant treatment with Uloric and warfarin.

4. Evaluate the induction potential of Uloric on human CYP P450 enzymes. This study may be conducted in vitro or in vivo.

5. Test the dissolution of febuxostat 80-mg and 120-mg tablets using a USP Apparatus 2 (paddle) at 75 rpm with 900 mL of 0.05 *M* potassium phosphate buffer, at pH 6.8, and maintained at 37°C with the following acceptance criteria: Q= — at T=15 min. The current dissolution method and acceptance criterion will be revisited if lower dose-strength tablets will be developed for future clinical studies. Solubility permitting, a different pH medium (such as phosphate buffer pH 6.2) may be appropriate to slow down the drug release at early time points and provide a discriminating condition. b(4)

We are withholding labeling comments pending resolution of the above deficiencies.

While not a deficiency impacting on approvability of Uloric, we request that data be provided to show that Uloric impacts some important outcome for gout patients, beyond the surrogate of uric acid levels, since the design and results of the submitted studies do not allow for us to conclude that the efficacy of Uloric in lowering serum uric acid levels leads to a reduction in gouty flairs, tophus size or other important manifestations of gout with chronic use. While such data would be helpful in making an assessment of risk-benefit considerations for approval, these data would be acceptable as a phase 4 commitment should the above deficiencies be adequately addressed prior to the availability of outcomes data.

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.

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- 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.

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If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
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/

Robert Meyer
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