



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

**DISCIPLINE REVIEW LETTER**

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

6/14/06

Attention: Binita Kwankin  
Assistant Director, Regulatory Affairs

Dear Ms. Kwankin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uloric (febuxostat).

The Division of Medication Errors and Technical Support (DMETS) review of your submission is complete and the proprietary name, Uloric, has been found acceptable. In addition we have identified the following deficiencies with your packaging:

[Redacted content]

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2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Matt Sullivan, Regulatory Project Manager, at (301) 796-1245.

Sincerely,

*{See appended electronic signature page}*

Sara Stradley  
Chief, Project Management Staff  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Sara Stradley  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

2/8/06

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

Attention: Binita Kwankin  
Assistant Director, Regulatory Affairs

Dear Ms. Kwankin:

We acknowledge receipt on February 21, 2006 of your February 17, 2006 resubmission to your new drug application for Uloric (febuxostat) tablets, 80 mg and 120 mg.

We consider this a complete, class 2 response to our October 14, 2005 action letter. Therefore, the user fee goal date is August 21, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

If you have any question, call me at (301) 796-1202.

Sincerely,

*{See appended electronic signature page}*

Jane A. Dean, RN, MSN  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Jane Dean  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

TAP Pharmaceuticals, Inc.  
675 North Field Drive  
Lake Forest, IL 60045

Attention: Binita Kwankin  
Assistant Director, Regulatory Affairs

Dear Ms. Kwankin:

Please refer to your New Drug Application (NDA) for Uloric (febuxostat).

We also refer to the meeting between representatives of your firm and the FDA on December 5, 2005. The purpose of the meeting was to obtain the Division's clarification of deficiencies identified in the October 14, 2005, approvable letter for Uloric.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

*{See appended electronic signature page}*

Jane A. Dean, RN, MSN  
Project Manager  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure



**MEMORANDUM OF MEETING MINUTES**

MEETING DATE: December 5, 2005

TIME: 1:00 pm – 2:00 pm

LOCATION: Room 1309, 10903 New Hampshire Avenue, Silver Spring, MD

APPLICATION (DRUG): NDA 21-856 (Uloric)

SPONSOR: TAP Pharmaceuticals, Inc

INDICATION: Management of hyperuricemia in patients with gout

TYPE OF MEETING: Type A Post Action Guidance Meeting

MEETING CHAIR: Bob Rappaport, MD

MEETING RECORDER: Ms. Jane A. Dean, RN, MSN

**FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:**

| Name of FDA Attendee      | Title                                    | Division Name & HFD# |
|---------------------------|------------------------------------------|----------------------|
| 1. Robert Meyer, MD       | Director                                 | ODE II               |
| 2. Curtis Rosebraugh, MD  | Deputy Director                          | ODE II               |
| 3. Rigoberto Roca, MD     | Deputy Director                          | DAARP                |
| 4. Sharon Hertz, MD       | Deputy Director                          | DAARP                |
| 5. Joel Schiffenbauer, MD | Medical Team Leader                      | DAARP                |
| 6. Tatiana Oussova, MD    | Clinical Reviewer                        | DAARP                |
| 7. John Smith, PhD        | Chemist                                  | ONDQA                |
| 8. Lei K. Zhang, PhD      | Clinical Pharmacology Reviewer           | DAARP                |
| 9. Bob Rappaport, MD      | Director                                 | DAARP                |
| 10. Ali Al Hakim, PhD     | Chemistry Pharmaceutical Assessment Lead | ONDQA                |
| 11. Jane A. Dean, RN, MSN | Project Manager                          | DAARP                |

**EXTERNAL CONSTITUENT ATTENDEES AND TITLES:**

| External Attendee        | Title                                              | Sponsor/Firm Name         |
|--------------------------|----------------------------------------------------|---------------------------|
| 1. Michael Becker, MD    | Professor of Medicine                              | University of Chicago, IL |
| /                        | /                                                  | /                         |
| 3. Margaret Fletcher, MD | Director, Pharmacovigilance & Pharmacoepidemiology | TAP Pharmaceuticals       |
| 4. Xavier Frapaise, MD   | VP, Research & Development                         | TAP Pharmaceuticals       |

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| External Attendee         | Title                                                   | Sponsor/Firm Name   |
|---------------------------|---------------------------------------------------------|---------------------|
| 5. Nancy Joseph-Ridge, MD | Therapeutic Area Head, Internal Medicine & Rheumatology | TAP Pharmaceuticals |
| 6. Binita Kwankin         | Assistant Director, Regulatory Affairs                  | TAP Pharmaceuticals |

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|                                     |                                                        |                                         |
|-------------------------------------|--------------------------------------------------------|-----------------------------------------|
| 8. Nancy Siepman, PhD               | Director, Statistics & Study Programming               | TAP Pharmaceuticals                     |
| 9. Ullrich Schwertschlag, MD        | Sr. Dir., Translational Medicine/Clinical Pharmacology | TAP Pharmaceuticals                     |
| 10. Dean Sundberg                   | VP, Regulatory Affairs                                 | TAP Pharmaceuticals                     |
| 11. William B. White, MD            | Professor of Medicine                                  | University of Connecticut Health Center |
| 12. Harriet Glassman                | Director, Project Management                           | TAP Pharmaceuticals                     |
| 13. Christopher Lademacher, MD, PhD | Medical Director                                       | TAP Pharmaceuticals                     |

b(4)

**PURPOSE OF THE MEETING:** Clarify deficiencies identified in the October 14, 2005, approvable letter for NDA 21-856 and reach agreement on the acceptability of TAP Pharmaceutical's (hereafter referred to as TAP) proposals for resolution of the deficiencies, and approval of the NDA.

**MEETING OBJECTIVES:** FDA and TAP reach agreement on the following:

1. Clarification of the deficiencies identified in the Agency's October 14, 2005, approvable letter for NDA 21-856;
2. Reach agreement on the acceptability of TAP's proposals for resolution of the deficiencies, and approval of the NDA.

**BACKGROUND:**

Uloric (febuxostat) is a xanthine oxidase inhibitor used to lower serum uric acid in patients with gout. Clinical trials were conducted under IND 58.229, which was submitted to the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550 on April 28, 1999. Subsequently, the NDA was submitted on December 14, 2004 and filed on February 14, 2005. An approvable letter was sent to TAP on October 14, 2005 with a list of deficiencies and concerns about the drug's safety. TAP requested a Type A meeting with the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) to obtain clarification of the concerns and deficiencies and to propose resolutions to the Division.

**QUESTIONS:** The meeting began with introductions of the attendees and a proposal by TAP to address the two major areas of concern rather than reviewing each question and response. The

Division was amenable to the suggestion. Responses faxed to the Sponsor on December 2, 2005 are identified as "FDA Preliminary Responses" and formed the basis for the discussion which began after the Sponsor gave a brief presentation with slides (appended to these meeting minutes).

### List of Specific Questions

**Question 1:** The Approvable letter indicates that the Agency's review of the safety database submitted in the febuxostat NDA raises concerns regarding the potential for Uloric to cause clinically significant cardiovascular/thrombotic adverse events in excess to that seen with the other treatment arms, even when exposure-over-time is factored into the analysis.

**We request an understanding of the methodology that led the Agency to the perception of an apparent cardiovascular safety signal. In particular, which set of patients was selected? Which medical terms were included in the analysis?**

**FDA Preliminary Response:** We analyzed data from the original ISS and 120-day safety update.

We focused first on the primary APTC endpoints, including death from a vascular cause, non-fatal myocardial infarction, and non-fatal stroke. In addition to that, we looked at the incidence of other CV events (acute coronary syndrome, unstable angina, angina, PE/DVT, TIA, CHF) combined, and by individual event.

**Meeting Comments:** No further discussion was necessary.

**Question 2:** TAP has proposed a response strategy in Section 9.2 of this briefing document, to address the Agency's concerns regarding an apparent cardiovascular signal. This response strategy relies on the most current safety database, which includes data from the ongoing long-term extension trials.

**Is there agreement that this strategy is acceptable?**

**FDA Preliminary Response:** The approach you propose presents some concerns. The ongoing studies are open-label and cannot provide as robust safety data as the controlled trials. In addition, due to the study design (patients are allowed to change treatment), the assessment of causality would present an even greater challenge than in the pivotal phase 3 studies. Nonetheless, these data could potentially provide additional useful information on safety.

We would agree that the data from the open-label study and pivotal studies should be analyzed separately. However, your grouping of cardiovascular events does not appear to be consistent with groupings utilizing the acceptable APTC groupings. The analysis should be performed utilizing the primary APTC endpoint (combined incidence of vascular deaths or sudden deaths, non-fatal MIs and strokes). This is a composite endpoint commonly used in cardiovascular

trials. In addition to this analysis, incidence rates of other events should be calculated as well, both combined and for each individual event. Those events may be secondary APTC events combined, individual events (angina, revascularization, TIA, PE etc), all-cause mortality, and CHF. You may provide other analyses. We agree that risk estimates need to be adjusted for duration of exposure to the drug.

**Meeting Comments:** The Division emphasized the utility of including a blinded adjudication analysis of cardiovascular signals when TAP resubmits their application. The analysis should be clearly laid out and any additional adjudication of cases different from the NDA should be included in the resubmission, along with an explanation for any re-adjudication. The Sponsor also needs to provide evidence that these are not dose-related phenomena. If there is a dose-response in regard to safety, then lower doses need to be explored to reassure the Division of the product's cardiovascular safety. The Division also asked that the Sponsor present multiple approaches in analyzing CV events, i.e., the timing of events, analysis from raw data (not adjudicated data), and analysis corrected for exposure. Narratives of all adjudicated events should be submitted.

**Question 3:** TAP has proposed a response strategy in Section 9.3 of this briefing document to address the Agency's request concerning the potential for pharmacokinetic interactions with theophylline, azathioprine or mercaptopurine.

**Is there agreement that this strategy is acceptable?**

**FDA Preliminary Response:** The strategy seems acceptable. However, you need to provide the details of the risk minimization plans to prevent the concomitant use of these drugs with febuxostat in the actual use setting, to assure us that the proposed contraindications are adhered to.

**Meeting Comments:** The Sponsor accepted the response.

**Question 4:** TAP has proposed a response strategy in Section 9.4 of this briefing document to address the Agency's concern regarding the potential for hemorrhagic events when febuxostat is administered with or without warfarin, and the potential for an interaction between the two drugs.

**Is there agreement that this strategy is acceptable?**

**FDA Preliminary Response:** With regard to the warfarin interaction study (C03-057), because of large drop-out of patients (more than 1/3) and inconsistency in withdrawing the patients from the trial due to high INR, we cannot accept the conclusion that there is no interaction between febuxostat and warfarin (e.g., Pts 109, 119 and 120 who had pre-dose INR > 1.8 were kept in the study for several days). In particular, one patient (Subject 119) had consistently high INR values

throughout both phases of the trial with INR peaking at 3.09, and yet the subject did not receive vitamin K until 11 days later following study closure.

Because of clinical findings of adverse events in patients who took both febuxostat and warfarin and inconclusive results of Study C03-057, a new warfarin interaction study with sufficient subjects to complete the trial is needed for a clearer determination on whether there is an interaction between warfarin and febuxostat. In the new study, PK and PD information needs to be collected for patients who are withdrawn from the study due to high INR.

**Meeting Comments:** The Sponsor gave a brief presentation which provided clarification to address the Division's comments about the patients with elevated INRs as follows:

1. Six subjects who were withdrawn following randomization were withdrawn due to high unstable pre-dose INR values.
2. Two additional subjects (#109 and #120) were withdrawn during the study for safety reasons due to persistently high INR values. Subject #119, who had an INR greater than or equal to three in each period was not withdrawn since the INR values were not verified on repeat testing.
3. All withdrawals were blinded and did not affect the power of the study.

The Division noted that there were two more patients with increased INR in the ISS safety database who were on both febuxostat and warfarin. Additional information on these patients will be provided by the Sponsor in the complete response to the October 14, 2005 approvable letter.

The Sponsor noted that patients with elevations in INR were managed according to the protocol. Based on the information presented, they believed a new study is not necessary. The Division stated that if they do resubmit without an additional PK and PD study, it would be important to provide a detailed, data-based rationale to support their position in the resubmission.

**Question 5:** TAP has proposed a response strategy in Section 9.5 of this briefing document to address the Agency's request for evaluation of the induction potential of febuxostat on human CYP P450 enzymes.

**Is there agreement that this response strategy is acceptable?**

**FDA Preliminary Response:** The strategy is acceptable.

**Meeting Comments:** The Sponsor accepted the response.

**Question 6:** TAP has proposed a response strategy to address the Agency's request for a change in the dissolution method and acceptance criteria as described in the Action letter, in Section 11.1 of this briefing document.

**Is TAP's proposal acceptable?**

**FDA Preliminary Response:** The proposal is acceptable.

**Meeting Comments:** The Sponsor accepted the response.

**Question 7:** This briefing document includes a summary of re-analyses of the total current safety database that demonstrates the absence of a signal that is predictive of clinically important differences. In addition, this briefing document includes a summary of efficacy data from the ongoing long-term studies, showing a reduction in gout flares and resolution of tophi. These data will be fully described in the complete response to the Action letter.

**Does the Agency agree that the benefit-risk profile of febuxostat 80 mg and 120 mg doses is acceptable if the Agency's review of the complete response to the action letter confirms the information provided in this document.**

**FDA Preliminary Response:** If we agree with your analyses following our review, then your proposal may be acceptable. However, this will ultimately be a review issue.

**Meeting Comments:** The Sponsor accepted the response.

**Question 8:** In accordance with 21 CFR 314.50(d)(5)(vi)(b) and as requested in the October 14, 2005, Approvable letter, TAP will include a safety update with the complete response to the Approvable letter. The Safety Update will include the following information:

- **Phase 3 double-blind, randomized, controlled trials (C02-009 and C02-010):** Since data from these studies was fully reported in the original NDA and ISS, there is no updated information for these studies. However, TAP will include any new analyses agreed upon with the Agency (e.g., analyses using APIC criteria) for these studies.

- **Long-term, open-label, extension studies (TMX-01-005 and C02-021):** The safety update will include more than 12 months of new exposure data since the 4-month safety update. TAP will provide the type of analyses included in the 4-month safety update for these studies, as well as any new analyses agreed upon with the Agency.

We are not planning to update the analyses of combined Phase 2/3 studies as data will now be presented separately for the Phase 3, double-blind, randomized controlled studies and the open-label, long-term extension studies, due to the amount of long term data now available (See Section 9.2.1). TAP will provide CRFs for all deaths, other SAEs and premature terminations due to AEs. Narratives for deaths and other SAEs will be provided in CIOMS format. In addition, we will provide text narratives for premature

terminations due to AEs. TAP will also submit the SAS XPT datasets for the safety update. Is this proposal for the safety update acceptable?

**FDA Preliminary Response:** The proposal appears acceptable as presented.

**Meeting Comments:** The Sponsor accepted the response.

**Additional Meeting Comments:** The Sponsor assured the Division that they intend to propose a Phase 4 commitment to provide data on the effects of febuxostat on gout flares. They will provide a schematic of the protocol before resubmitting their complete response. They intend to

/ / / /

**Post Meeting Comment:** For clarification purposes, the Sponsor is reminded that in addition to what they proposed in their November 16, 2005, submission (separate analysis of open-label data and Phase 3 controlled data), to include a re-analysis of Phase 2 plus Phase 3 **controlled studies combined** for their resubmission.

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Jane Dean  
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

TAP Pharmaceuticals, Inc.  
675 North Field Drive  
Lake Forest, IL 60045

10/27/05

Attention: Binita Kwankin  
Assistant Director, Regulatory Affairs

Dear Ms. Kwnakin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uloric (febuxostat tablets) oral, 80 mg and 120 mg.

We also refer to your October 19, 2005, correspondence, received October 20, 2005, requesting a meeting to discuss deficiencies identified in the Agency's Approvable letter issued October 14, 2005 and to reach agreement on the resolution of these deficiencies.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: December 5, 2005

Time: 1:00 PM

Location: 10903 New Hampshire Ave., Silver Spring, MD 20993

CDER participants: Robert Meyer, MD, Curt Rosebraugh, MD, Bob Rappaport, MD, Rigoberto Roca, MD, Sharon Hertz, MD, Joel Schiffenbauer, MD, Tatiana Oussova, MD, Dennis Bashaw, PharmD, Suresh Doddapaneni, PhD, Lei K. Zhang, PhD and Jane A. Dean, RN, MSN

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at deanj@cder.fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Jane Dean, 301-796-1202 or Betty Clark, 301-796-1186.

Provide the background information for this meeting (three copies to the NDA and 15 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by November 21, 2005, we may cancel or reschedule the meeting.

NDA 21-856  
Page 2

If you have any questions, call me at (301) 796-1202.

Sincerely,

*(See appended electronic signature page)*

Jane A. Dean, RN, MSN  
Project Manager  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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9/2/05

MEMORANDUM  
SERVICES

DEPARTMENT OF HEALTH AND HUMAN  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 6/24/05

TO: Jane Dean, Regulatory Project Manager  
Joel Schiffenbauer, M.D., Clinical Reviewer  
Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550

THROUGH: Leslie K. Ball, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

FROM: Dianne Tesch, CSO

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-856

APPLICANT: TAP Pharmaceuticals

DRUG: febuxostat

CHEMICAL CLASSIFICATION: Type 1

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment \_\_\_\_\_ of hyperuricemia and gout

**b(4)**

CONSULTATION REQUEST DATE: January 6, 2005

ACTION GOAL DATE: August 15, 2005

PDUFA DATE: October 15, 2005

## I. BACKGROUND:

The primary objective of these studies was to assess the safety and efficacy of febuxostat in the treatment of gout. Gout refers to a mixed group of diseases characterized by deposition of urate crystals or uric acid in extracellular fluid. It is distinguished by recurrent, acute attacks of articular and periarticular joint inflammation, usually involving only one joint per episode. Other features are accumulation of tophi, uric acid kidney stones, and interstitial kidney disease leading to impaired kidney function. The natural course of classic gout consists of three stages: asymptomatic hyperuricemia, acute, intermittent gout, and chronic, tophaceous gout. The metabolic disorder underlying gout is hyperuricemia, caused either by overproduction or underexcretion of uric acid. Asymptomatic hyperuricemia in the absence of gout is not a disease. b(4)

Treatment of gout consists of reducing or eliminating the pain of an acute attack, and preventing the occurrence of acute gout. Allopurinol is a treatment for the prevention of gout. Allopurinol reduces the production of uric acid in the body. It is the comparator drug in this trial. Febuxostat, the test article, works in a similar manner, with fewer potential adverse metabolic side effects.

Protocol C02-009 was a 28 week study comparing febuxostat 80 mg, 120 mg or 240 mg, to allopurinol 300 mg, or placebo. The primary efficacy variable was the proportion of subjects whose last three serum urate levels were <6.0 mg/dL. The secondary efficacy variables were percent reduction in tophus size in subjects with a primary palpable tophus at the Screening Visit, reduction in total number of tophi, and the proportion of subjects requiring treatment for gout flare between weeks 8 and 28 of the treatment period.

Protocol C02-010 was a 52 week study comparing febuxostat 80 mg or 120 mg, with allopurinol 300 mg. There was no placebo arm. The primary and secondary efficacy variables were the same as in protocol C02-009.

Dr. Becker and Dr. Rosenblatt had subjects enrolled in both C02-009 and C02-010. \_\_\_\_\_

\_\_\_\_\_ Dr. Becker has five studies listed in the Clinical Investigator System (CIS) data base. He has no prior inspections. b(6)

Dr. Rosenblatt's site was chosen for high enrollment, and because he is a high volume researcher. Dr. Rosenblatt has 73 studies listed in CIS. He has one prior inspection done in March, 2001. The inspection was classified VAI-RR for the use of prostate volume and bladder capacity measuring equipment which had not been properly calibrated or maintained. This might have affected data integrity. Following the March 2001 inspection Dr. Rosenblatt responded in writing that the maintenance problems were corrected. For the current inspection, the field investigator was asked to verify that calibration and maintenance of office equipment was adequate and ongoing.

## II. RESULTS (by protocol/site):

| NAME              | CITY      | STATE | ASSIGNED DATE    | RECEIVED DATE  | CLASSIFICATION |
|-------------------|-----------|-------|------------------|----------------|----------------|
| Sidney Rosenblatt | Irvine    | CA    | January 14, 2005 | March 30, 2005 | VAI            |
| Michel A. Becker  | Chicago   | IL    | January 14, 2005 | March 28, 2005 | NAI            |
| TAP, Inc.         | Deerfield | IL    | January 14, 2005 | March 21, 2005 | NAI            |

A. Protocol #C0-02-009 titled "A Phase III Randomized, Multicenter, Allopurinol and Placebo-Controlled Study to Assess the Safety and Efficacy of Oral Febuxostat in Subjects with Gout"; and Protocol #C0-02-010 titled "A Phase III Randomized, Multicenter Study of Oral Febuxostat Comparing the Safety and Efficacy of Oral Febuxostat Versus Allopurinol in Subjects with Gout".

1. Site #1 Sidney Rosenblatt, M.D., Irvine, CA: The data were acceptable.

- a. For Protocol C02-009, three subjects were randomized and all three records were reviewed for the audit. One of the required physical exams for one of the subjects was omitted because the principal investigator was not on site at the time of the visit.

For Protocol C0-010, 37 subjects were randomized, and 12 records were reviewed in depth for the audit. The most persistent and pervasive deficiency was Dr. Rosenblatt's failure to perform both brief and complete physical examinations at protocol specified intervals. Since physical exams were done at each visit, it is unlikely that the absence of one or two exams, mostly brief ones, had an effect on the data. It is troublesome that the principal investigator was so frequently unavailable for routine data collection.

- b. The inspector was granted access to all study records.
- c. There was no evidence of under-reporting of adverse events or other violations affecting data validity.

2. Site #2 Michael Becker, M.D., Chicago, IL: The data were acceptable.

- a. For protocol #C02-009 five subjects were enrolled. There was one dropout. All records were reviewed for the data audit. There were no deficiencies.

For protocol #C02-010 seven subjects were entered into the study. All records were reviewed for the data audit. There were no deficiencies.

- b. There were no limitations to the inspection. The inspector was granted access to all study records.
- c. There was no evidence of under-reporting of adverse events or other violations affecting data validity.

3. Site #3 TAP Pharmaceuticals, Deerfield, IL

The inspection of the Sponsor, TAP Pharmaceuticals, Ltd., covered study Protocol #C02-009, and #C020-010. The inspection included review of monitoring reports, adverse experience/reaction reporting, data collection and handling, record retention, and test article accountability. Records from the inspected clinical sites were compared to the sponsor records and monitoring logs. There were no apparent discrepancies. Company standard operating procedures (SOPs) for data collection and retention, as well as correction of case report forms (CRFs) were reviewed and appeared to be in order.

There were no limitations to the inspection. The inspector was granted access to all records pertaining to the protocols. No deficiencies were found. The inspection was classified NAI.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Dr. Rosenblatt was cited for failure to follow the investigational plan. He had several instances of not performing protocol specified physical examinations. Dr. Becker did not have any deficiencies. No deficiencies were noted on the sponsor inspection. The deficiencies found were relatively minor in nature and did not affect the integrity or reliability of the data.

Signature  
GCPB Reviewer Name  
Title

CONCURRENCE:



Supervisory comments

Leslie K. Ball, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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Leslie Ball  
9/2/2005 09:19:30 AM  
MEDICAL OFFICER

**To:** 'binita.kwankin@TAP.com'  
**Subject:** 7-10-05 Information Request for NDA 21-856

Binita, the following request comes from Clinical Pharmacology:

In the Warfarin Drug Interaction study C03-057, nine patients were given vitamin K due to increased INR - Pts: 102, 103, 108, 109, 110, 112, 115, 117, and 120. We are unable to locate in the NDA the INR values that prompted the vitamin K administration and the followup INR values once the INR resolved.

Please provide this information.

Thanks.

Jane

-----  
Jane A. Dean  
Regulatory Health Project Manager  
FDA/CDER/ODEII/DAARP

Office: 301-827-2090  
Fax: 301-827-2531  
Email: [deanj@cder.fda.gov](mailto:deanj@cder.fda.gov)

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/s/

-----  
Jane Dean

7/10/05 02:27:22 PM

CSO

**From:** Dean, Jane  
**Sent:** Tuesday, August 02, 2005 9:50 AM  
**To:** 'binita.kwankin@tap.com'  
**Subject:** 8-2-05 Chemistry Information Request for NDA 21-856

**Importance:** High

Binita, this information request comes from the Chemists on the review team. Can you please respond as quickly as possible? Thank you. Jane

1. Please include testing for degradation products in the drug product specification, with (at a minimum) acceptance criteria for any unspecified degradation product and for total degradation products. Based on the data presented, it is not justified to exclude this test. Testing for degradation products is one of the critical parameters used to demonstrate equivalence for post-approval changes. It is more important to include this test, in light of the proposed comparability protocols. The exclusion of this test may be proposed after NDA approval when more stability data has been collected.
2. Please remove the sunset provision from your proposed stability protocol for annual stability batches. The proposed reduced testing protocol for  esting at release is acceptable but the submitted stability data on the  test are too limited to justify the proposed sunset testing proposal. **b(4)**
3. Please revise the matrix design for the annual stability studies so that all selected factor combinations will be tested at the final time point (48 months). Refer to ICH Q1D, section II.D.2.

-----  
Jane A. Dean  
Regulatory Health Project Manager  
FDA/CDER/ODEII/DAARP

Office: 301-827-2090  
Fax: 301-827-2531  
Email: deanj@cder.fda.gov

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/s/

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Jane Dean  
8/2/05 09:51:13 AM  
CSO



NDA 21-856

INFORMATION REQUEST LETTER

TAP Pharmaceutical Products Inc.  
Attention: Binita Kwankin  
Assistant Director, Regulatory Affairs  
675 N. Field Drive  
Lake Forest, IL 60045

6/7/05

Dear Ms. Kwankin:

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

We are reviewing the pharmacokinetic and chemistry sections of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please provide patient-years of exposure for febuxostat and the comparators across the NDA. This should include trials included in the analyses of such safety endpoints as deaths and serious adverse events. It should not include any short term trials of less than 6 weeks duration.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Parinda Jani  
Chief, Project Management Staff  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Parinda Jani  
6/7/05 12:48:30 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

INFORMATION REQUEST LETTER

TAP Pharmaceutical Products, Inc.  
Attention: Binita Kwankin  
Assistant Director, Regulatory Affairs  
675 N. Field Drive  
Lake Forest, IL 60045

5/25/05

Dear Ms. Kwankin:

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

We are reviewing the pharmacokinetic and chemistry sections of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. The proposed dissolution method and acceptance criterion for febuxostat tablets are not acceptable. As proposed, we do not think the dissolution method is sufficiently discriminating

*[Redacted content]*

b(4)

2. Please develop a new dissolution method that is discriminating

*[Redacted content]*

b(4)

a.

*[Redacted content]*

b(4)

3. Once a new dissolution method is established, a comparative evaluation of the revised method vs. the current proposed method should be done with the 120 mg tablet with sufficient sampling timepoints incorporated into the test.

NDA 21-856

Page 2

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, RPh  
Chief, Project Management Staff  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Jane Dean  
5/25/05 06:07:02 PM  
For Carmen DeBellas

NDA 21-856  
5/10/05

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 6, 2005

TO: ✓ Brian Harvey, M.D., Ph.D.  
Acting Director  
Division of Anti-Inflammatory Analgesic and  
Ophthalmologic Drug Products (HFD-550)

FROM: John A. Kadavil, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV 5/9/05  
Associate Director - Bioequivalence  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs covering NDA 21-856, Uloric  
(febuxostat) Tablets, 80 and 120 mg, Sponsored by TAP  
Pharmaceutical Products Inc.

At the request of HFD-550, the Division of Scientific Investigations conducted sample collections and inspections of drug accountability records for the following Phase 3 clinical trials:

**Study C02-009**: A Phase III Randomized, Multicenter, Allopurinol and Placebo-Controlled Study to Assess the Safety and Efficacy of Oral Febuxostat in Subjects with Gout.

**Study C02-010**: A Phase III Randomized, Multicenter Study Comparing the Safety and Efficacy of Oral Febuxostat Versus Allopurinol in Subjects with Gout.

The review division expressed concern regarding the integrity of the allopurinol tablets used in studies C02-009 and C02-010. Upon HFD-550's request, DSI initiated inspections for the following clinical sites:

1. Michael A. Becker, M.D., Chicago, IL
2. Sidney Rosenblatt, M.D., FACP, Irvine, CA
3. H. Malin Prupas, M.D., FACP, Reno, NV

A separate inspection assignment was also issued for drug accountability records and collection of drug samples from the sponsor at the following sites:

1. Abbott Laboratories, North Chicago, IL (contract testing laboratory)
2. \_\_\_\_\_ (clinical packaging) **b(4)**

Following the inspections of Dr. Michael A. Becker (2/23/05 - 3/09/05), Dr. Sidney Rosenblatt (2/7-16/05), Dr. H. Malin Prupas (2/24-28/05) and \_\_\_\_\_ (4/04-06/05), no issues were found regarding drug accountability, and no Forms FDA-483 were issued. An inspection of Abbott Laboratories was not conducted by the FDA office in Chicago (see below). **b(4)**

Dr. Michael A. Becker, Chicago, IL; Dr. Sidney Rosenblatt, Irvine, CA; Dr. H. Malin Prupas, Reno, NV

Per protocol, all of the used and unused study drugs were shipped to a third party storage facility \_\_\_\_\_ from the clinical sites at the completion of the trial. Therefore, no samples were available for collection at the clinical sites. **b(4)**

For Study C02-010, correspondence from the CRO, \_\_\_\_\_ to the clinical sites indicated that study drugs with an expiration date of March 2003 would be re-labeled with an expiration date of September 2003 or March 2004. Inspectional documents and the randomization code reveal that the re-labeling involved both allopurinol and febuxostat lots. **b(4)**

Abbott Laboratories, North Chicago, IL

Prior to visiting the facility, the FDA investigator was informed through telephone contact with TAP Pharmaceuticals and Abbott Laboratories that there were no allopurinol samples at the Abbott site. The FDA office in Chicago, therefore, did not inspect the Abbott site.

TAP informed the FDA investigator that over-encapsulation of commercially-available allopurinol tablets \_\_\_\_\_ ) was done by \_\_\_\_\_

The blinded allopurinol tablets were shipped directly from \_\_\_\_\_ to Abbott Labs for release and stability testing, and to \_\_\_\_\_ where the samples were repackaged and shipped to the clinical sites (see attachment). **b(4)**

The sponsor indicated that allopurinol reserve samples could be collected at \_\_\_\_\_ DSI subsequently initiated an inspection of that site.

b(4)

The FDA investigators collected samples of 100 mg and 300 mg blinded allopurinol tablets that were representative of the drug products used in studies C02-009 and C02-010 (see attachment). As requested by Dr. Bashaw, the samples were sent to the Division of Pharmaceutical Analysis on April 7, 2005 for testing. The inspectional findings also indicated that \_\_\_\_\_ was responsible for the over-encapsulation of two lots of febuxostat tablets for study C02-010 (see attachment).

b(4)

**Conclusion:**

Following our evaluation of the inspectional findings, DSI concludes that:

1. No deficiencies were found in the clinical investigator records for drug accountability and drug storage conditions for Studies C02-009 and C02-010. Similarly, no deficiencies were noted at \_\_\_\_\_ (the clinical supplies packager) in this regard.
2. The re-labeling of study drugs with new expiration dates should be considered by the review division for possible impact on study outcome.
3. While there is no evidence to suggest that the integrity of the allopurinol samples was compromised at the inspected sites, determination of sample integrity should be made by the review division once analyses of the allopurinol samples collected from \_\_\_\_\_ are completed by the Division of Pharmaceutical Analysis.

b(4)

b(4)

After you have reviewed this transmittal memo, please append it to the original NDA submissions.



John A. Kadavil, Ph.D.

**Final Classification:**

NAI - Michael A. Becker, M.D., Chicago, IL  
NAI - Sidney Rosenblatt, M.D., FACP, Irvine, CA  
NAI - H. Malin Prupas, M.D., FACP, Reno, NV  
NAI - \_\_\_\_\_

b(4)

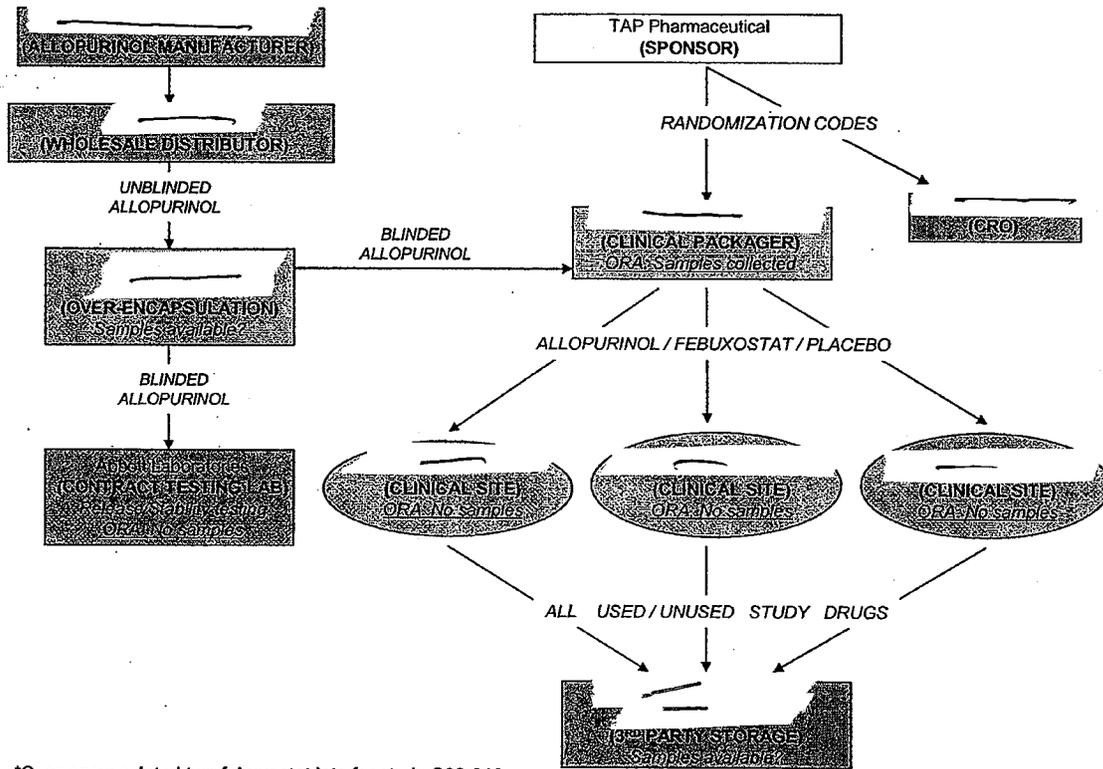
cc:

HFD-45/RF  
HFD-48/Kadavil (2) /Himaya/CF  
HFD-550/Schiffenbauer/Dean/NDA 21-856  
HFD-880/Bashaw ✓  
HFD-47/Tesch ✓  
HFR-CE650/Love ✓  
HFR-CE6521/Nicholson ✓  
HFR-CE150/Laska ✓  
HFR-CE1500/McEvoy ✓  
HFR-PA250/Van Leeuwen ✓  
HFR-PA1510/Harris ✓  
Draft: JAK 5/4/05  
Edit: JAO 5/5/05  
DSI: 5596; O:\BE\EIRCOVER\21856tap.ulo.doc  
FACTS: 611755  
622133

Attachments:

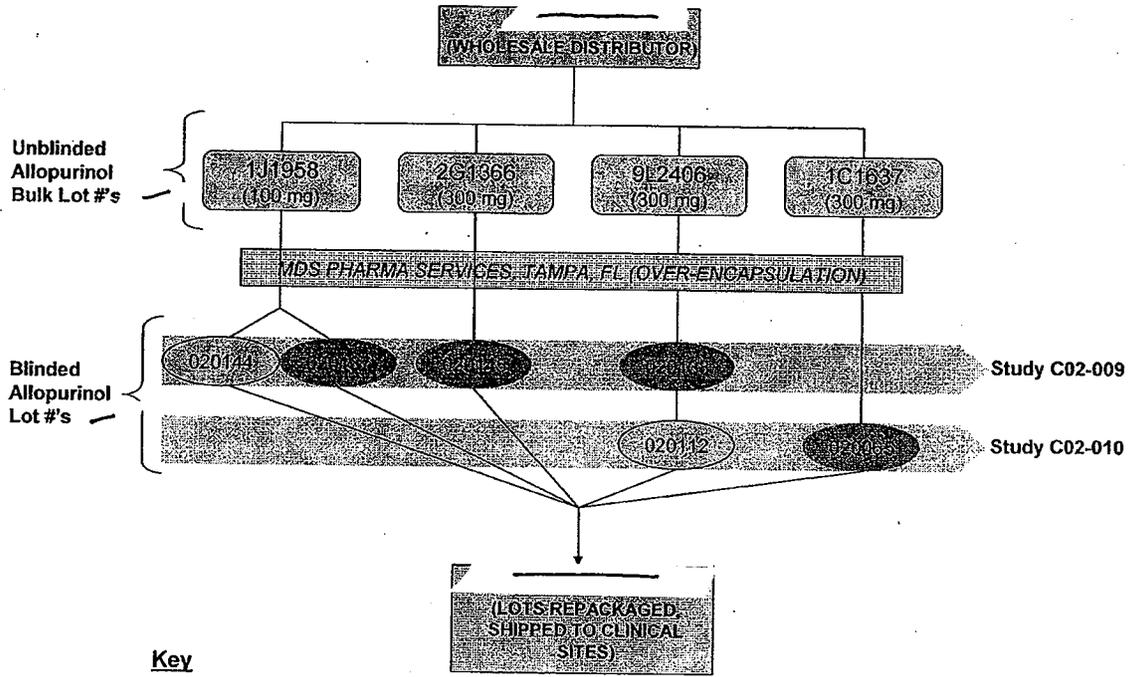
Flow charts - Allopurinol Sample Collection

Findings: Allopurinol Samples Inspection (Studies C02-009 & C02-010; NDA 21,856)



\*Over-encapsulated two febuxostat lots for study C02-010

### Allopurinol Sample Collection - Tracing the Lot Numbers



b(4)

**Key**

- = ORA Collected at
- = Not Collected at (supply exhausted)

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/s/

-----  
Amalia Himaya

5/10/05 02:28:26 PM

CSO

Hard copy signed by Dr. Viswanathan on 5/9/05 and  
available upon request.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

INFORMATION REQUEST LETTER

TAP Pharmaceutical Products Inc.  
Attention: Binita Kwankin  
Senior Regulatory Products Manager  
675 N. Field Drive  
Lakefield Drive, IL 60045

4/29/05

Dear Ms. Kwankin:

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

We are reviewing the pharmacokinetic section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. For Study TMX-01-008, because there was no measured creatinine clearance data for Subjects 1110 and 1111 at baseline, and Subject 1114 may have had some degree of hepatic impairment, please re-analyze the PK data for TMX-67 and the effect of renal impairment on TMX-67 excluding patients 1110, 1111 and 1114.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, RPh  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Jane Dean  
4/29/05 04:08:40 PM  
For Carmen DeBellas



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

INFORMATION REQUEST LETTER

TAP Pharmaceutical Products Inc.  
Attention: Binita Kwankin  
Senior Regulatory Products Manager  
675 N. Field Drive  
Lakefield Drive, IL 60045

4/4/05

Dear Ms. Kwankin:

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

We are reviewing the clinical section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please explain the discrepancy between the table in trial 009 that demonstrates "Subjects Requiring Treatment for a Gout Flare by Time Interval - ITT Subjects" (Phase 3 Pivotal Studies) and the table that pools information for trials 009 and 010 in the integrated summary of efficacy. In trial 009 the table shows weeks 24-28 as the last set of data for the placebo group while in the ISE the table shows the last set of results for weeks 28-32. Also, the numbers of flares in the 2 tables do not match.
2. For trial 010 and tables entitled "Median and Mean Percent Change from Baseline in Primary Tophus Size at the Week 28, Week 52, and Final Visits - ITT Subjects with a Primary Palpable Tophus at Baseline", please confirm the values for mean percent change from baseline for the 80 mg group. The values provided do not appear reasonable (588 and 936).
3. For trial 010 and tables entitled "Median and Mean Percent Change from Baseline in Primary Tophus Size by Average Post-Baseline Serum Urate Level at the Week 28, Week 52, and Final Visits - ITT Subjects with a Primary Palpable Tophus at Baseline", please confirm the values for mean percent change from baseline for the 80 mg group. Again, the values provided do not appear reasonable.

NDA 21-856

Page 2

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, RPh  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD 550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Jane Dean  
4/4/05 03:39:57 PM  
For Carmen DeBellas



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

INFORMATION REQUEST LETTER

TAP Pharmaceutical Products Inc.  
Attention: Binita Kwankin  
Senior Regulatory Products Manager  
675 N. Field Drive  
Lakefield Drive, IL 60045

3/30/05

Dear Ms. Kwankin:

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

We are reviewing the clinical section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. For studies 009 and 010, please provide a Kaplan-Meier analysis of time to event for gout flares.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, RPh  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Jane Dean  
3/30/05 01:53:36 PM  
For Carmen DeBellas



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

INFORMATION REQUEST LETTER

3/25/05

TAP Pharmaceutical Products Inc.  
Attention: Binita Kwankin  
Senior Regulatory Products Manager  
675 N. Field Drive  
Lakefield Drive, IL 60045

Dear Ms. Kwankin:

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

We are reviewing the clinical section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide any safety information in regards to the co-use of febuxostat with theophylline or azathioprine from any ongoing clinical trials. In the safety update, provide a specific section discussing the potential interactions between these drugs and include a presentation of any clinical data available.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, RPh  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Jane Dean  
3/25/05 12:35:41 PM  
For Carmen DeBellas



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

INFORMATION REQUEST LETTER

3/8/05

TAP Pharmaceutical Products Inc.  
Attention: Binita Kwankin  
Senior Regulatory Products Manager  
675 N. Field Drive  
Lakefield Drive, IL 60045

Dear Ms. Kwankin:

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

We are reviewing the nonclinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

In regards to NDA 21-856, in order to complete the review of study #T-883 titled "*Study for effects on embryo-fetal development in rabbits treated orally with TEI-6720.*", please provide the historical control data for knobby ribs in rabbits.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, RPh  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Jane Dean  
3/8/05 05:51:02 PM  
For Carmen DeBellis



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

2/24/05

TAP Pharmaceutical Products, Inc.  
Attention: Binita Kwankin  
Assistant Director, Regulatory Affairs  
675 N. Field Drive  
Lake Forest, IL 60045

Dear Ms. Kwankin:

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

We also refer to your February 3, 2005, correspondence, received February 9, 2005, requesting the Division reconsider review priority classification of your NDA submission.

Your request for reconsideration to change the review from a standard review to a priority review is denied for the following reasons:

1. Your assertion of the superiority of febuxostat to existing therapy is not entirely clear from a cursory review of the efficacy data and will require a thorough review.
2. There is existing reasonably effective uric acid lowering treatment currently on the market.

If you have any questions, please call Ms. Jane A. Dean, RN, MSN, Regulatory Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Sharon Hertz, MD  
Deputy Director  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Sharon Hertz  
2/24/05 02:19:38 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

INFORMATION REQUEST LETTER

TAP Pharmaceutical Products Inc.  
Attention: Binita Kwankin  
Senior Regulatory Products Manager  
675 N. Field Drive  
Lakefield Drive, IL 60045

2/2/05

Dear Ms. Kwankin:

Please refer to your December 14, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for febusostat tablets.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- Please provide electronic datasets and control files (basic and final models) used for population PK/PD analyses for Studies TMX-01-005 and C-02-009. If they are in the NDA submission, direct the reviewer to the location.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, RPh  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Jane Dean  
2/2/05 04:20:30 PM  
For Carmen DeBellas



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-856

2/1/05

TAP Pharmaceutical Products, Inc.  
Attention: Binita Kwankin  
Assistant Director, Regulatory Affairs  
675 N. Field Drive  
Lake Forest, IL 60045

Dear Ms. Kwankin:

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

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 13, 2005 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. No mock-ups of the carton and container labels were included in the submission.
2. The proposed drug product specification does not include testing for degradation products.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We request that you submit the following information:

1. Mock-ups of the carton and container labels.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NDA 21-856

Page 2

If you have any questions, call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Sharon Hertz, MD  
Deputy Director  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Sharon Hertz  
2/1/05 03:06:51 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

TAP Pharmaceutical Products, Inc.  
Attention: Binita Kwankin  
Assistant Director, Regulatory Affairs  
675 N. Field Drive  
Lake Forest, IL 60045

2/1/05

Dear Ms. Kwankin:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Uloric (febuxostat) 80 mg and 120 mg tablets  
Review Priority Classification: Standard (S)  
Date of Application: December 14, 2004  
Date of Receipt: December 15, 2005  
Our Reference Number: NDA 21-856

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 13, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 15, 2005.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submission to the Central Document Room at the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room (CDR)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

NDA 21-856

Page 2

If your submission only contains paper, send it to the following address:

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
9201 Corporate Boulevard  
Rockville, Maryland 20850

If you have any questions, call me at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Jane Dean  
2/1/05 02:56:29 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

INFORMATION REQUEST LETTER

TAP Pharmaceutical Products Inc.  
Attention: Binita Kwankin  
Senior Regulatory Products Manager  
675 N. Field Drive  
Lakefield Drive, IL 60045

1/24/05

Dear Ms. Kwankin:

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

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

In regards to NDA 21-856 and study 009, please provide responses to the following requests:

- 1) Provide an analysis of the number of subjects with  $UA < 6$  for every visit after the first month of treatment initiation for each treatment group (at your discretion, you may choose another time that is more appropriate, such as 6 weeks, etc).
- 2) If any of these analyses have already been performed and are in the NDA submission, please direct us to the location.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, RPh  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Jane Dean  
1/24/05 12:53:26 PM  
For Carmen DeBellas



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-856

INFORMATION REQUEST LETTER

TAP Pharmaceutical Products Inc.  
Attention: Binita Kwankin  
Senior Regulatory Products Manager  
675 N. Field Drive  
Lakefield Drive, IL 60045

1/18/05

Dear Ms. Kwankin:

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

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

In regards to NDA 21-856 and study 009, please provide responses to the following requests:

- 1) Provide a responder analysis of those who completed the study and had the last 3 uric acid values less than 6 mg/dl.
- 2) Provide an analysis of average uric acid for each group. Also, please provide an analysis of average uric acid for those who completed the study.
- 3) Provide an analysis of only those subjects on allopurinol 300 mg.
- 4) Provide an analysis of last 3 uric acid values <6 mg/dl for those with prior allopurinol therapy versus those without prior allopurinol therapy.
- 5) Provide an analysis of the number of subjects with average uric acid <6 mg/dl versus >6 mg/dl for each group.
- 6) Was there an analysis of subjects who previously failed allopurinol therapy and received febuxostat?
- 7) If any of these analyses have already been performed and are in the NDA submission, please direct the reviewer to the location.

NDA 21-856

Page 2

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, RPh  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Jane Dean

1/18/05 02:08:35 PM

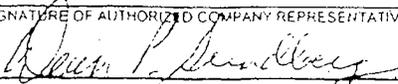
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

# PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297  
Expiration Date: December 31, 2006.

## See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdofa/default.htm>

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1. APPLICANT'S NAME AND ADDRESS<br>Dean P. Sundberg<br>Vice President, Regulatory Affairs<br>TAP Pharmaceutical Products Inc.<br>675 North Field Drive<br>Lake Forest, Illinois 60045                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  | 4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER<br>21-856                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 2. TELEPHONE NUMBER (Include Area Code)<br><br>( 847 ) 582-5780                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  | 5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?<br><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO<br><br>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.<br><br>IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:<br><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.<br><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:<br><br>_____<br>(APPLICATION NO. CONTAINING THE DATA). |
| 3. PRODUCT NAME<br>Febuxostat                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  | 6. USER FEE I.D. NUMBER<br>4878                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?<br><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO<br>(See item 8, reverse side if answered YES)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:<br><br>Department of Health and Human Services      Food and Drug Administration      An agency may not conduct or sponsor, and a person is not<br>Food and Drug Administration      CDER, HFD-94      required to respond to, a collection of information unless it<br>CDER, HFM-95      and 12420 Parklawn Drive, Room 3046      displays a currently valid OMB control number.<br>1401 Rockville Pike      Rockville, MD 20852 |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE<br>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  | TITLE<br>Vice President, Regulatory Affairs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  | DATE<br>11/19/2004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |



TAP PHARMACEUTICAL PRODUCTS INC.

675 North Field Drive  
Lake Forest, IL 60046

November 19, 2004

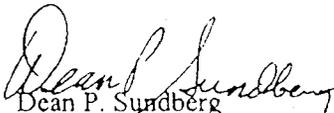
Food and Drug Administration (360909)  
Mellon Client Service Center – Room 670  
500 Ross Street  
Pittsburgh, PA 15262-0001

Dear Sir or Madam:

Enclosed please find TAP Pharmaceutical Products Inc.'s check number 66-763/0531 in the amount of \$672,000.00. This check represents payment for FDA User Fee ID 4878, for NDA Number 21-856, Febuxostat. We are also enclosing a copy of your User Fee Bill issued on November 4, 2004.

Should there be any questions, please direct them to my attention.

Thank you,

  
Dean P. Sundberg  
Vice President, Regulatory Affairs

DPS/ul

Enclosures: Check 66-763/0531  
User Fee Bill #4878  
FDA Form 3397 (12/03)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 58,229

TAP Pharmaceuticals, Inc.  
Attention: Benita Kwankin  
Assistant Director, Regulatory Affairs  
675 N. Field Drive  
Lake Forest, IL 60045

Dear Ms. Kwankin:

Please refer to your Investigational New Drug Application (IND) file for Febuxostat (TMX-67).

We also refer to the meeting between representatives of your firm and the FDA on June 30, 2004. The purpose of the meeting was to have a PreNDA (New Drug Application) meeting before submitting your NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

*{See appended electronic signature page}*

Sharon Hertz, MD  
Deputy Director  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

Enclosure



**MEMORANDUM OF MEETING MINUTES**

MEETING DATE: June 30, 2004

TIME: 11:35 am – 12:10 pm

LOCATION: 9201 Corporate Boulevard, Rockville, MD

APPLICATION (DRUG): IND 58,229 (TMX-67)

SPONSOR: TAP Pharmaceuticals, Inc.

TYPE OF MEETING: PreNDA Meeting

MEETING CHAIR: Sharon Hertz, MD

MEETING RECORDER: Ms. Jane A. Dean, RN, MSN

**FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:**

| Name of FDA Attendee      | Title                                            | Division Name & HFD# |
|---------------------------|--------------------------------------------------|----------------------|
| 1. Sharon Hertz, MD       | Deputy Director                                  | ODEV/DAAODP, HFD-550 |
| 2. James Witter, MD, PhD  | Medical Team Leader                              | ODEV/DAAODP, HFD-550 |
| 3. Terri Rumble           | ADRA                                             | ODEV, HFD-105        |
| 4. Dennis Bashaw, PharmD  | Clinical Pharmacology Team Lead                  | OCPB/DPEIII, HFD-880 |
| 5. Joel Schiffenbauer, MD | Primary Medical Team Leader and Medical Reviewer | ODEV/DAAODP, HFD-550 |
| 6. Asoke Mukherjee, PhD   | Pharmacology Reviewer                            | DPS/DPEIII, HFD-880  |
| 7. Lei Zhang, PhD         | Clinical Pharmacology Reviewer                   | OCPB/DPEIII, HFD-880 |
| 8. Atiar Rahman, PhD      | Statistics Reviewer                              | OB/DBIII/HFD-725     |
| 9. Jane A. Dean, RN, MSN  | Project Manager                                  | ODEV/DAAODP, HFD-550 |

**EXTERNAL CONSTITUENT ATTENDEES AND TITLES:**

| External Attendee             | Title                                  | Sponsor/Firm Name   |
|-------------------------------|----------------------------------------|---------------------|
| 1. Barbara Hunt               | Assistant Director, Statistics         | TAP Pharmaceuticals |
| 2. Nancy Joseph-Ridge         | Therapeutic Area Head IM/Rheum         | TAP Pharmaceuticals |
| 3. Binita Kwankin             | Assistant Director, Regulatory Affairs | TAP Pharmaceuticals |
| 4. Lhando Gunawardhana        | Sr. Toxicology Investigator            | TAP Pharmaceuticals |
| 6. Michael A. Becker, MD      | Rheumatologist, Univ. of Chicago       | Consultant          |
| 7. Margaret (Dordal) Fletcher | Director, Pharm/Vig & Pharm/Epi        | TAP Pharmaceuticals |
| 8. Laurent Vernillet          | Asst. Dir., Drug Metab. & Pharm/Epi    | TAP Pharmaceuticals |
| 9. Dean Sundberg              | VP, Regulatory Affairs                 | TAP Pharmaceuticals |
| 10. Denise Moyer              | Assoc. Director, Project Management    | TAP Pharmaceuticals |

b(4)

**PURPOSE OF THE MEETING:** PreNDA meeting to discuss Clinical and Nonclinical issues relating to TAP's New Drug Application (NDA) for febuxostat for the management of hyperuricemia in patients with gout.

**MEETING OBJECTIVES:**

1. To reach agreement on the Fileability of the proposed NDA with regards to Clinical and Nonclinical issues.
2. To identify and discuss review issues.
3. To reach agreement on the format and organization of the proposed Clinical and Nonclinical information in the NDA.
4. To obtain responses to TAP's proposals relating to Clinical and Nonclinical content of the NDA.
5. To obtain feedback on TAP's proposals relating to electronic submission.

**BACKGROUND:** Febuxostat (TMX-67), a new molecular entity, is a non-purine selective inhibitor of xanthine oxidase (XO) being developed by TAP Pharmaceuticals (hereafter referred to as TAP) for the management of hyperuricemia in patients with gout. It has been shown to be a potent selective XO inhibitor in vitro and to have a strong effect on lowering serum urate levels in animals. Phase 1 and Phase 2 studies have also confirmed the ability of febuxostat to reduce serum urate levels in humans.

TAP had an End of Phase 2 meeting with the Division on September 13, 2002 and has periodically received guidance from the Division throughout its clinical development program. TAP plans to submit the NDA in the format of an electronic Common Technical Document (CTD) either at the end of 2004 or the beginning of 2005.

**QUESTIONS:**

The meeting opened with general comments and introductions. Because draft responses to the questions had been provided the day before (labeled "Original FDA Response"), discussion began immediately with the questions (bolded) as follows:

1) **Overall Questions:**

- 1a. **Has the Agency identified any issues that could impact the filing of the NDA under 21 CFR 314.101?**

*Original FDA Response:*

*Nonclinical: The presented nonclinical studies are adequate for the NDA filing. However, the acceptability of these studies is a review issue.*

*Clinical: There are no filing issues identified at this time. However, we remind you that the safety database should consist of a sufficient number of patients to address ICH guidances and to support the proposed labeling at the time of the NDA filing.*

*Meeting Comments: This was acceptable to TAP.*

**1b. Has the Agency identified any review issues?**

*Original FDA Response: For the tabulated summary of all Clinical Studies, please specify how many male and female subjects were enrolled in each study. There are no other review issues that can be identified at this time until the whole NDA submission is available for review.*

*Meeting Comments: TAP agreed to the Division's request.*

- 1c.** PDUFA provides for priority review of a drug which, if approved, would be a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease. Allopurinol is currently the only xanthine oxidase inhibitor available for management of hyperuricemia in patients with gout. As discussed in Section 9.3.2 of this briefing document, the two double-blind, placebo and/or allopurinol-controlled trials (C02-010 and C02-009) indicate increased effectiveness of febuxostat in comparison to allopurinol for the proposed indication. The NDA will also demonstrate safety and effectiveness of febuxostat in a subset of subjects with renal impairment.

**Does the Agency believe that the febuxostat NDA would meet the requirements for priority review if the Agency's review of the NDA confirms TAP's understanding of the data?**

*Original FDA Response: The data is encouraging but based on available information in the package, including study design, it is not sufficiently persuasive to support a priority review. The final determination will be made at the time of filing the NDA.*

*Meeting Comments.: TAP asked what type of data was needed for the NDA submission to qualify for priority review. The Division explained that the type of review was a filing issue that was determined at the time of submission. The main question was if uric acid could serve as a surrogate for the basis of making it a priority review. TAP was told to make their justification for a priority review clear in their request when they send in the NDA.*

**2) Questions Relating to Clinical Data:**

**2a. Allopurinol Response Rate in Pivotal Trials:**

It was important to define the clinically important effect size of allopurinol for the Phase 3 studies since they were designed to show that febuxostat was non-inferior to allopurinol. An expected response rate of 60% for allopurinol was based on a single urate level of <6.0 mg/dL from previous literature data and chart reviews.

In addition, historical mean baseline serum urate levels have been <9.0 mg/dL. In the febuxostat Phase 3 studies C02-010 and C02-009, baseline serum urate levels were higher than those reported in the literature (baseline serum urate levels >10.0 mg/dL for 40% and 42% subjects respectively). In these studies, allopurinol had a response rate of 57% and 56% respectively for the last single serum urate measurement <6.0 mg/dL in subjects with baseline serum urate levels 8 - <9.0 mg/dL. The allopurinol response rate was lower in subjects with higher baseline serum rate. When the endpoint requested by the Agency, last *three* serum urate measurements <6.0 mg/dL, was considered for all subjects enrolled in studies C02-010 and C02-009 regardless of baseline serum urate, the response rate for allopurinol was 21% and 22% respectively. Preliminary study results are discussed in section 9.3.2 of this document.

Considering that the baseline serum urate levels in these studies were higher than those reported in the literature, the primary endpoint was objective and was based on the last *three* serum urate measurements, the results were reproducible across two large, double-blind, randomized, controlled studies, and considering that febuxostat response rate was superior to allopurinol regardless of baseline serum urate or the serum urate endpoint used (last three measurements versus last measurement), **does the Agency find the allopurinol response rate acceptable for demonstration of non-inferiority and superiority of febuxostat to allopurinol?**

*Original FDA Response: The allopurinol response rate appears acceptable to demonstrate non-inferiority and superiority. Final determination of the success of the trials will be a review issue.*

*Meeting Comments: This was acceptable to TAP.*

- 2b. *Clinical Study C02-021: Study C02-021, a Phase 3, open-label, randomized, allopurinol-controlled, 2-year extension study will be ongoing at the time of the NDA. Subjects enrolled in this study after completing the Phase 3 pivotal studies (C02-009 or C02-010). We plan to include a synopsis of interim data in the NDA because of the limited exposure at the time of the interim analysis. The focus of the interim analysis will be safety. The synopsis will follow the format recommended in the Agency's 1999 guidance: **Submission of Abbreviated Reports and Synopses in Support of Marketing Applications**. Please note that all safety data from the interim analysis will be included in the synopsis as well as in the Integrated Summary of Safety (ISS).*

**Is this proposal acceptable?**

*Original FDA Response: This proposal is not acceptable because the safety results from this study are necessary to support language in the label. All available safety data from this study must be submitted to the NDA at the time of initial NDA submission with all additional information submitted at the time of the 120-day safety update.*

*Meeting Comments:* TAP asked if the open label study would be a pivotal study and the Division replied that while not a pivotal study to support efficacy, the results from the study contribute important information about safety. The studies that will provide information on the safety and efficacy of the product and contribute to labeling should be submitted in complete reports.

The Division asked for clarification of which parts of the submission would be in synopsis form, especially since we were interested in having all of the safety data. TAP reassured the Division that they would send in all of the data.

2c. **Population Pharmacokinetics:** Population pharmacokinetic (PK) data were collected in the following studies:

- Study C02-009. A Phase 3, Randomized, Multicenter, Allopurinol and Placebo-Controlled Study Assessing the Safety and Efficacy of Oral Febuxostat in Subjects with Gout. Population PK data were collected in approximately 300 subjects.
- Study TMX-01-005. Phase 2, Open-Label Study to Assess the Long-Term Safety of Oral TMX-67 in Subjects with Gout. Population PK data were collected in approximately 85 subjects.

Population PK analyses from Study TMX-01-005 will be submitted in the NDA. However, population PK analyses from Study C02-009 will not be available in time for the NDA submission. We propose submitting the clinical study report for Study C02-009 in the NDA without population PK results, with the population PK analyses to follow as an amendment to the NDA within 60 days of the NDA submission.

**Is this proposal acceptable?**

*Original FDA Response:* No. Please submit a complete study report at the time of NDA submission.

*Meeting Comments:* TAP agreed to submit a complete study report.

2d. **Foreign Clinical Studies Conducted by Teijin Limited, Japan (Teijin):** TAP's licensing partner, Teijin, has conducted clinical studies with febuxostat for a Japanese development program. Teijin studies utilize a formulation of febuxostat that is different from TAP's formulation and evaluate doses of febuxostat that are lower (up to 40 mg QD) than those being developed in the United States. (80 and 120 mg QD). TAP does not have English translations of complete study reports for Teijin studies. We have received English translations of Sections 1-13 of Teijin clinical study reports (report sections per ICH E3 guideline: Structure and Content of Clinical Study Reports). Therefore, we plan to include only Sections 1-13 of available Teijin clinical study reports in the NDA.

Integrated documents such as the ISS will include a summary of only serious adverse events (including deaths) from Teijin's studies.

**Are these proposals acceptable?**

*Original FDA Response: The submission of foreign clinical study reports appears to be acceptable. Please confirm the content of sections 1-13. We acknowledge that these studies will be considered supportive and are not intended to provide pivotal efficacy data. Please include information from all patients who discontinue study participation due to adverse events.*

*Meeting Comments: TAP agreed to include the information requested by the Division. They also confirmed that sections 1-13 followed the Guidance.*

2e. **Financial Disclosure:** The NDA will contain financial disclosure for four studies, which we believe meet the definition of "covered study" stated in 21 CFR 54. These studies are:

- Phase 2 and 3 double-blind, controlled safety and efficacy studies (TMX-00-004, C02-009, C02-010), and
- Phase 3 open-label, long-term, extension study, which includes an allopurinol comparator arm (C02-021).

We request a waiver from financial disclosure for the following studies listed below. Please note that the briefing document will contain the proposed Table of Contents for the NDA listing all studies:

- All Phase 1 pharmacokinetic or pharmacology studies. Phase 1 tolerance, PK and clinical pharmacology studies that are not critical to an efficacy determination are generally excluded from the definition of "covered study" under 21 CFR 54.2 (e).
- The Phase 2 open-label, long-term, multi-center, safety study TMX-01-005. Large, open, safety studies conducted at multiple sites, are generally excluded from the definition of "covered study" under 21 CFR 54.2 (e). Please note that we are proposing to submit financial disclosure for the Phase 3, open-label, long-term, multi-center study C02-021, since this study includes an allopurinol comparator arm.
- All foreign studies conducted by Teijin. These studies utilized a different formulation as well as lower doses than those that will be proposed in our application, and are only intended to provide supportive safety information.

**Is the waiver granted?**

*Original FDA Response: The proposal is acceptable as long as the preponderance of data does not come from one study site. Submit your justification and rationale with your submission.*

*Meeting Comments: This was acceptable to TAP.*

- 2f. **Individual Subject Data Listings (Patient Profiles):** We propose that consolidated subject data listings (ICH E3 report guidance, Appendix 16.2) by CRF domain will be provided in lieu of individual subject data listings (ICH E3 report guidance, Appendix 16.4) for all clinical studies. Please note that SAS datasets will also be submitted for all studies in XPT format, in accordance with applicable guidances.

**Is this proposal acceptable?**

*Original FDA Response: Individual study listings should be provided.*

*Meeting Comments: TAP stated that they intend to submit data listings with each individual study report with adverse events listed for each study. They also stated the listings are those described in ICH 16.2 section and that they will send the datasets for each study. These data sets will be integrated into the ISS and ISF sections. They also stated that the Phase 1 data sets would remain separate from the others. SAS XPT datasets, with appropriate descriptions and variable definitions, corresponding to those used in the efficacy analyses presented in the study reports should be included in the submission.*

- 2g. **Proposal for 4-Month Safety Update:**

TAP plans to conduct new interim analyses for our ongoing long-term open-label studies C02-021 and TMX-01-005. A summary of the new safety and long-term exposure data, including information specified in 21 CFR 314.50 (d)(5)(vi), will be provided in the 4-month safety update to the NDA. The new data will represent approximately 1 additional year of data from Study TMX-01-005 and approximately 9 months additional data from Study C02-021; the number of subjects for whom new data will be reported is not expected to increase since enrollment in both studies was complete at the time of interim analysis for the NDA. The additional exposure and safety information for the 4-month safety update will be provided in the format of an update to the ISS.

If the new safety data warrant a revision of the Package Insert, Patient Package Insert or the Risk Management Plan, these documents will also be updated and included in the 4-month safety update.

**Is this proposal for the 4-month safety update acceptable?**

*Original FDA Response: The 120-day safety update should include tables that display a column with the original data, a column of the new data and a column integrating the original and new data.*

*Meeting Comments: This was acceptable to TAP.*

3) **Questions Relating to Preclinical Data:**

3a. **SAS Datasets in XPT Format for Preclinical Studies:** SAS datasets in XPT format were submitted to the IND for the following nonclinical studies:

- Study 4257 (011-25). Carcinogenicity Study of TEI-6720 in Mice, including histopathological examination [Study 6421 (011-034)]. SAS datasets in XPT format, submitted to the FDA on May 22, 2003 (Serial No. 0112).
- Study 4259 (011-027). Carcinogenicity Study of TMX-67 in Rats including histopathological examination [Study 6422 (011-035)]. SAS datasets in XPT format, submitted to the FDA on September 2, 2003 (Serial No. 0123).

**TAP is not planning to re-submit these SAS datasets to the NDA. Is this proposal acceptable?**

*Original FDA Response: Please follow the FDA carcinogenicity data submission guidance.*

*Meeting Comments: TAP asked during the meeting if they should resubmit the carcinogenicity data with the NDA. The Division told them that was not necessary. However, when TAP submits the NDA, they should reference the submission date and number where the data could be found.*

4) **Electronic Submission: General Question**

The NDA will be in the format of a Common Technical Document (CTD). It will also be a completely electronic application. We plan to follow all applicable CTD and electronic filing guidelines. Since the application will be completely electronic, prepared in compliance with applicable Agency guidelines, we are not planning to submit paper review copies of the NDA.

**Is this proposal acceptable?**

*Original FDA Response: Please clarify whether you are planning to file an eCTD or an NDA/CTD hybrid? We concur that paper copies will not be submitted.*

*Meeting Comments: TAP stated they had been in telephone contact with Ken Edmunds of the Office of Information Management (OIM) and he had provided guidance to them on submitting an electronic CTD. Furthermore, the Agency's test of TAP's sample eCTD was acceptable by the OIM.*

5) **Electronic Submission: Labeling format question**

FDA's February 2004 draft guidance entitled "Providing Regulatory Submissions in Electronic Format - Content of Labeling" states that after the automated system using SPL for processing and managing labeling and labeling changes is implemented, PDF would no longer be a format that the Agency can use to process, review, and archive the content of labeling. Since the guidance has not been finalized and since TAP is not currently able to submit labeling in SPL, we plan to submit labeling for febuxostat in PDF format.

**Is this proposal acceptable?**

*Original FDA Response: Please submit the labeling in Microsoft Word format. It must be submitted in PDF as well.*

*Meeting Comments: This was acceptable to TAP.*

6) **Electronic Submission: Clinical Questions**

The following eCTD recommendations were provided by the Agency's Office of Information Management. **Are these recommendations also acceptable to the Review Division:**

6a. **Clinical reports in legacy format in the eCTD (instead of granular format):** FDA's August 2003 eCTD draft guidance encourages sponsors to break clinical study reports up into the various study file tags. Since the eCTD guidance is relatively recent and TAP has not had experience with breaking clinical reports into various study file tags, we propose that all clinical reports submitted in the febuxostat eCTD will be in legacy format, as allowed by the guidance.

*Original FDA Response: This is acceptable but it is preferable that you follow the ICII recommendations. The legacy format is intended for those reports prepared in the past for which the source document is not longer available. It is very important that these be text-based PDF regardless of the format.*

*Meeting Comments: This was acceptable to TAP.*

6b. **List of Investigators:** FDA's 1988 Guideline for the Format and Content of the Clinical and Statistical Sections of an Application requested a complete alphabetical list of investigators for all studies. However the eCTD backbone does not contain a place for such a list. The FDA Office of Information Management has advised that such a large comprehensive list is no longer needed since Appendix 16.1.4 of each study report includes the list of investigators for the study.

*Original FDA Response: Yes*

*Meeting Comments: This was acceptable to TAP.*

- 6c. ***Drug Abuse and Overdosage:*** 21 CFR 314.50(d)(5)(vii) requires sponsors to provide information on the abuse potential of a drug and overdose. The information required under this part will be provided in the Clinical Summary (Module 2.7.4.5.6 and 2.7.4.5.7) as well as the Integrated Summary of Safety.

*Original FDA Response: That is acceptable.*

*Meeting Comments: This was acceptable to TAP.*

- 6d. ***Integrated Summary of Benefits and Risks:*** 21 CFR 314.50(d)(5)(viii) requires an integrated summary of the benefits and risks of the drug. The information required under this part will be included in Module 2.5.6 (Clinical Overview / Benefits and Risks Summary).

*Original FDA Response: Module 2.5 is intended for an overview. Module 2.7 is intended for summaries such as executive summaries. Module 5 is intended for analyses integrating data from several studies (ISS & ISE) and as such, can accommodate all information relevant to these analyses. In particular, Module 5.3.5.3 is intended for what is known as the ISS. The ISS should be structured according to 21 CFR 314.50(d)(5)(vi) and all sections of the ISS should be located in the same module.*

*If you and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).*

*If the NDA/BLA application includes RiskMAPs or pharmacovigilance plans and will be submitted in the Common Technical Document format, please submit as follows:*

***RiskMAPs***

*2.5.5 Overview of Safety with appropriate cross references to section 2.7.4 Summary of Clinical Safety and any other relevant sections of the Common Technical Document for the NDA/BLA application.*

***Pharmacovigilance plans***

*2.5.5 Overview of Safety, with any protocols for specific studies provided in 5.3.5.4 Other Clinical Study Reports or other sections as appropriate (e.g., module 4 if the study is a nonclinical study).*

*If the application is not being submitted as a Common Technical Document, include proposed RiskMAPs in the*

*NDA Clinical Data Section (21 CFR 314.50 (d)(5)) or  
BLA Clinical Data Section (21 CFR 601.25(b)(3))  
and clearly label and index them.*

*For the most recent publicly available information on CDER's views on  
RiskMAPs, please refer to the Draft Guidance for Industry Development and Use  
of Risk Minimization Action Plans and the Draft Guidance for Industry Good  
Pharmacovigilance Practices and Pharmacoepidemiologic Assessment which can  
be located electronically at <http://www.fda.gov/cder/guidance/5766dft.pdf> and  
<http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0189-gdl0001-5767dft.doc>.*

*If there is any information on product medication errors from the premarketing  
clinical experience, ODS requests that this information be submitted with the  
NDA/BLA application.*

*You are encouraged to submit the proprietary name and all associated labels and  
labeling for review as soon as available.*

*Meeting Comments: The above comments were acceptable to TAP. The Division  
clarified further that a large, complete Integrated Summary of Safety and  
Integrated Summary of Efficacy would not fit into the limited space of Module 2.  
Module 5 is intended to hold analyses across studies and does not have the size  
restriction of Module 2. TAP stated they planned to put the ISS and ISE in  
module 5. TAP also asked for confirmation that the summary benefit:risk  
document should go into the Clinical Overview section and the Division said that  
was acceptable.*

- 6e. *Compliance with IRB and Informed Consent: 21 CFR 314.50(d)(5)(ix) requires  
a statement with respect to each study involving human subjects that it was  
conducted in compliance with IRB and informed consent regulations. The  
information required under this part will be provided within each individual study  
report in the following locations: Title page stating compliance with GCP,  
Section 5.0 (Ethics) and Appendix 16.1.3 (List of IEC's or IRB's and  
representative written information for patient and sample consent forms).*

*Original FDA Response: That is acceptable.*

*Meeting Comments: This was acceptable to TAP.*

- 6f. *Delegation to a Contract Research Organization: 21 CFR 314.50(d)(5)(x)  
requires sponsors to provide information on the use of contract research  
organizations including a list of obligations transferred to a contract research  
organization. This information will be included in Module 1  
Administrative - Transfer of Obligation.*

*Original FDA Response: That is acceptable.*

*Meeting Comments: This was acceptable to TAP.*

- 6g. *Auditing of Subject Records:* 21 CFR 314.50(d)(5)(xi) requires sponsors to provide information on clinical studies audited or reviewed in the course of monitoring to verify the accuracy of the case reports submitted to the sponsor. The information required under this part will be provided within each individual study report in Section 9.6 (Data Quality Assurance) and Appendix 16.1.8 (Audit Certificates) of each report.

*Original FDA Response: That is acceptable.*

*Original Additional comments:*

- *Human metabolism study reports contained in Sections 4.2.2.4.1, 4.2.2.4.2, 4.2.2.4.4, 4.2.2.4.5, 4.2.2.4.11, 4.2.2.4.12, 4.2.2.4.15, and 4.2.2.4.16 should be accessible through Section 5.3.2.2 with hyperlinks.*
- *Please be sure to include in the Adverse Event databases the following: include unique patient identifiers, verbatim terms, as well as preferred terms and body systems, date or study day that the adverse event began, either date or study day that the adverse event resolved or the duration of the event in days, dose at onset if different than assigned dose, treatment assignment, any interventions resulting from the AE.*
- *All databases should use unique patient identifiers that are consistent across databases.*
- *If a pediatric waiver is sought, this should be submitted with the NDA.*

*Meeting Comments: TAP found the comments from the Division to be acceptable. They added that the human metabolism study reports would be located in module 4 as well as module 5. The unique identifiers would be based on the following three criteria – study number, investigator and patient number.*

*TAP stated that they believed their protocols met the criteria established at the June 2004 Advisory Committee on Gout and asked if the Division thought another Advisory Committee would be necessary. The Division stated that we do not anticipate needing another Advisory Committee meeting unless outside input is needed to come to a decision on the NDA, but that this is an issue that will be determined based on the review.*

Minutes Preparer: Jane A. Dean, RN, MSN

Chair Concurrence:

Drafted by: JAD/7-1-04

Revised by: JS/7-2-04

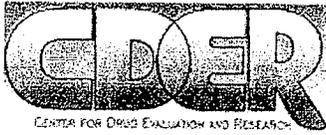
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| Initialed by: | MD/7-2-04  |
|               | GG/7-2-04  |
|               | JS/7-2-04  |
|               | AR/7-2-04  |
|               | SL/7-2-04  |
|               | JY/7-2-04  |
|               | DB/7-12-04 |
|               | SH/7-21-04 |
| Final:        | SH/7-21-04 |

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Sharon Hertz  
7/23/04 01:21:47 PM



**MEMORANDUM OF MEETING MINUTES**

MEETING DATE: September 13, 2002

TIME: 12:30pm – 1:45pm

LOCATION: Corp S300

APPLICATION (DRUG): IND 58,229

TYPE OF MEETING: End of Phase 2 Meeting

MEETING CHAIR: James Witter, M.D., Ph.D.

MEETING RECORDER: Ms. Jane A. Dean, RN, MSN

**FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:**

| <u>Name of FDA Attendee</u>  | <u>Title</u>                          | <u>Division Name &amp; HFD#</u> |
|------------------------------|---------------------------------------|---------------------------------|
| 1. Lee S. Simon, M.D.        | Division Director                     | ODEV/DAAODP, HFD-550            |
| 2. James Witter, M.D., Ph.D. | Medical Officer Team Leader           | ODEV/DAAODP, HFD-550            |
| 3. Asoke Mukherjee, Ph.D.    | Pharmacology Reviewer                 | ODEV/DAAODP, HFD-550            |
| 4. Larry Goldkind, M.D.      | Deputy Director                       | ODEV/DAAODP, HFD-550            |
| 5. Carmen DeBellis, R.Ph.    | Chief Project Manager                 | ODEV/DAAODP, HFD-550            |
| 6. Terri Rumble              | Associate Director Regulatory Affairs | ODE V                           |
| 7. John Smith, Ph.D.         | Chemistry Team Leader                 | ODEV/DAAODP, HFD-550            |
| 8. Lourdes Villalba, M.D.    | Medical Reviewer                      | ODEV/DAAODP, HFD-550            |
| 9. Rao Puttagunta, Ph.D.     | Chemistry Reviewer                    | ODEV/DAAODP, HFD-550            |
| 10. Michael Yao, M.D.        | Medical Reviewer                      | ODEV/DAAODP, HFD-550            |
| 11. Joel Schiftenbauer, M.D. | Medical Reviewer                      | ODEV/DAAODP, HFD-550            |
| 12. Ms. Jane A. Dean         | Project Manager                       | ODEV/DAAODP, HFD-550            |

**EXTERNAL CONSTITUENT ATTENDEES AND TITLES:**

| <u>External Attendee</u>                | <u>Title</u>                                                              | <u>Sponsor/Firm Name</u>    |
|-----------------------------------------|---------------------------------------------------------------------------|-----------------------------|
| 1. Nancy Joseph-Ridge, M.D.             | Medical Director, Clinical Development                                    | TAP Pharmaceutical Products |
| 2. Darcy J. Mulford, Ph.D.              | Director, Drug Metabolism and Pharmacokinetics                            | TAP Pharmaceutical Products |
| 3. Barbara Hunt, MS                     | Assistant Director, Statistics                                            | TAP Pharmaceutical Products |
| 4. Dean Sundberg                        | Vice President, Regulatory Affairs                                        | TAP Pharmaceutical Products |
| 5. Leslie D. Abelson                    | Assistant Director, Regulatory Affairs                                    | TAP Pharmaceutical Products |
| 6. Denise Moyse, MS, MBA                | Assistant Director, Project Management                                    | TAP Pharmaceutical Products |
| 7. Deborah Milkowski, Ph.D. (telephone) | Director, Pharmacology                                                    | TAP Pharmaceutical Products |
| 8. Lin Zhao, Ph.D. (telephone)          | Senior Research Scientist, Pharmacology                                   | TAP Pharmaceutical Products |
| <hr/>                                   |                                                                           |                             |
| 10. Michael A. Becker, M.D.             | Professor of Medicine, Medical Center, University of Chicago, Chicago, IL | Consultant                  |

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**PURPOSE OF THE MEETING:** End of Phase 2 meeting with FDA and TAP Pharmaceuticals for guidance and discussion before implementing Phase 3 studies.

## **MEETING OBJECTIVES:**

FDA and TAP Pharmaceuticals agreement on:

- 1) indication;
- 2) proposed Phase 3 program and safety database;
- 3) ECG/QT program;
- 4) pediatric waiver;
- 5) toxicology program (with the exception of the carcinogenicity program).

### **Sponsor Question 1:**

**Is the Phase III plan acceptable to support the proposed indication of management of hyperuricemia in patients with gout?**

### **FDA Response to Question 1:**

*The Sponsor needs to provide an in-depth justification for their clinical development program. In particular, the Sponsor needs to address why the 6.0 mg/dl endpoint was selected and how their program will adequately study this surrogate endpoint in a way that will inform labeling about the documented benefits and risks associated with TMX-67. For example, the Sponsor should define a clinically meaningful difference from placebo in any study containing a placebo control.*

*The Sponsor should also address how allopurinol will be included in their overall development plan. For example, the sponsor should consider at least one study with allopurinol and placebo along with the compound TMX-67.*

*At least one study should include a dose higher than what is anticipated to be the maximum recommended dose.*

*Sponsor should consider stratifying subjects' baseline uric acid levels (e.g. 8-10, 10-12, greater than 12) and presence of tophi.*

*Additional comments and questions:*

- a) *The Sponsor may wish to consider excluding subjects with secondary hyperuricemia.*
- b) *The Sponsor should obtain several (at least three) baseline uric acid determinations to exclude regression to the mean.*
- c) *The Sponsor should include some subjects not previously on allopurinol.*
- d) *The Sponsor should strongly consider studying individuals with abnormal renal functions as well as individuals with normal renal function, elderly and female subjects should also be in the studies.*
- e) *The Sponsor should clarify whether a subject with UA<6 who drops out before 52 weeks will be counted as a responder. An analysis of responders (primary endpoint) and completers (secondary endpoint) should be defined in the protocols.*
- f) *The Sponsor should clarify the treatment of acute gout attack, as the recommended treatment (see page 20, 27) may not be adequate; there may be difficulty determining which AEs are related to TMX-67 or to other drugs.*
- g) *The Sponsor should add urine cytology to labs in at least one trial because of reports of bladder tumors in nonclinical studies.*
- h) *The Sponsor should provide data on CNS toxicity because of CNS effects seen in phase II studies (page 13 and 16).*

i) The Sponsor should define vasodilatation as reported in EOP II package (page 41).

j) The Sponsor needs to document the outcome of the one patient who was pregnant.

k) The Sponsor should consider excluding subjects with a history of stones in the study with placebo but may include them in the study with allopurinol as the comparator.

**Sponsor Question 2:**

**Does the FDA agree that the non-inferiority criteria delta of 15% used in the allopurinol controlled serum urate study is acceptable?**

**FDA Response to Question 2:**

a) The Sponsor needs to clarify the statistical issues surrounding non-inferiority. Please provide a rationale for the 15% delta. (For example, if the percentage of subjects on allopurinol with uric acid <6.0 is only 30%, a delta of 15% would preserve only 50% of the effect size.)

b) Please explain why you chose a non-inferiority delta of 15%.

c) The trial including placebo patients may be 6 months in duration.

As part of the inclusion criteria, consider recruitment of individuals with significantly elevated uric acid (such as >10). Placebo controlled trials are preferred for establishment of efficacy although non-inferiority trials with well-supported non-inferiority margins may be considered.

d) Clinically relevant outcomes such as numbers of gouty attacks are strongly recommended as secondary endpoints.

Additional Comments:

Phase 4 studies should be proposed to further define efficacy and safety.

**Sponsor Question 3:**

**Is the number of subjects proposed for the safety package acceptable?**

**FDA Response to Question 3:**

ICH guidelines provide for a minimum of exposure to include at least 300-600 subjects exposed for 6 months and at least 100 for one year at the maximum proposed doses. This is only a recommended minimum number. Longer studies may need to be done in Phase 4 studies.

Sponsor Question 4:

Does the FDA agree with the ECG/QT program?

FDA Response to Question 4:

*The following comments are provided by the Cardio-renal Division:*

The available data raise no particular concerns with regard to the potential for TMX-67 to be arrhythmogenic.

The plan is to base decisions on QTcF, which is entirely reasonable and for which the study appears to be adequately powered. The Sponsor might consider using the rich baseline data to perform individualized QT corrections, to achieve greater discriminatory power.

If the dose of TMX-67 used in this study produces plasma levels well above those encountered with target dosing combined with common metabolic competitors, food, or hepatic or renal impairment, if the study successfully distinguishes moxifloxacin from placebo, and if the results exclude that TMX-67 has as much as a 10-ms effect on QTc, then this study would be very reassuring.

*It is suggested that the Sponsor perform EKGs as part of phase A and not just with phase B. If 300 mg is not tolerated in phase A and the sponsor does not proceed to phase B, there will be no EKG data.*

Sponsor Question 5:

Does the FDA agree that pediatric studies are not warranted for TMX-67?

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Sponsor Question 6:

Are the toxicology studies submitted to the FDA to this date adequate for initiating phase III clinical studies for the proposed indication?

Yes.

Sponsor Question 7:

Other than the carcinogenicity studies, is the toxicology development plan acceptable to support an NDA for TMX-67 with the proposed label claim?

*This will be a review issue.*

**FDA Post-Meeting Comments:**

1. *For safety and efficacy, studies in renal insufficiency will be necessary given the high anticipated use in this vulnerable population.*

**Minutes Preparer:** Jane A. Dean, RN, MSN

**Chair Concurrence:** Dr. James Witter

**Drafted by:** J. A. Dean

**Initialed by:** J. Witter, M.D, Ph.D.

**Final:** 10/10/02