CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-856

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-856 Supplement # Efficacy Supplement Type SE-

Trade Name: Uloric
Established Name: febuxostat
Strengths: 80 mg and 120 mg tablets

Applicant: TAP Pharmaceuticals
Agent for Applicant: n/a

Date of Application: December 14, 2004
Date of Receipt: December 15, 2004
Date clock started after UN: n/a
Date of Filing Meeting: January 27, 2005
Filing Date: February 15, 2005
Action Goal Date (optional): August 1, 2005 User Fee Goal Date: October 15, 2005

Indication(s) requested: For the management of hyperuricemia in patients with gout

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) n/a

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.*

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☒ YES ☐ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☒ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, Five Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 58,229

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) June 30, 2005 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES ☒ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 27, 2005

BACKGROUND: Uloric (febuxostat), a new molecular entity, is being submitted for the management of hyperuricemia in patients with gout.

ATTENDEES: Sharon Hertz, MD, Joel Schiffenbauer, MD, Tatiana Oussova, MD, Stan Lin, PhD, Atiar Rahman, PhD, Asoke Mukherjee, PhD, Lei K. Zhang, PhD, Dennis Bashaw, PharmD, John Smith, PhD, Sue Ching Lin, MS, Brian E. Harvey, ME, PhD, Nancy Clark, PharmD, Jane Dean, RN, MSN

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	Reviewer
Medical:	Schiffenbauer (summary and efficacy)
Secondary Medical:	Oussova (safety)
Statistical:	Rahman
Pharmacology:	Mukherjee
Statistical Pharmacology:	
Chemistry:	Lin
Environmental Assessment (if needed):	
Biopharmaceutical:	Zhang
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Tesch
Regulatory Project Management:	Dean
Other Consults:	DDMETS (trade name review) DDMAC (labeling and package inserts) DSI (testing of samples used) ODS/DSCRS (label review - patient package insert)

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS		FILE ☒		REFUSE TO FILE ☐	
• Biopharm. inspection needed?				YES ☐	NO ☒
PHARMACOLOGY	N/A ☐	FILE ☒		REFUSE TO FILE ☐	
• GLP inspection needed?				YES ☐	NO ☒
CHEMISTRY		FILE ☒		REFUSE TO FILE ☐	
• Establishment(s) ready for inspection?				YES ☒	NO ☐
• Microbiology				YES ☐	NO ☐

ELECTRONIC SUBMISSION:
Any comments: eCTD submission

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional): Sponsor did not include mock ups of the container and carton. The proposed drug product specification does not include testing for degradation products.

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Jane A. Dean, RN, MSN
Regulatory Project Manager, HFD-550

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

/s/

Jane Dean
4/5/05 02:01:54 PM
CSO

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA; AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-856

NAME OF APPLICANT / NDA HOLDER
TAP Pharmaceutical Products Inc

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Uloric

ACTIVE INGREDIENT(S)	STRENGTH(S)
Febuxostat	80 mg, 120 mg

DOSAGE FORM
Tablet, Immediate Release; Oral

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314 53 at the address provided in 21 CFR 314 53(d)(4)
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314 53(c)(2)(ii) with all of the required information based on the approved NDA or supplement The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i e , one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the formation described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a United States Patent Number	b Issue Date of Patent	c Expiration Date of Patent
5,614,520	3/25/1997	3/25/2014

d Name of Patent Owner
Teijin Pharma Limited

Address *(of Patent Owner)*
Iino Building 1-1
Uchisaiwaicho 2-chome

City/State
Chiyoda-ku, Tokyo, Japan

ZIP Code	FAX Number *(if available)*
100-8585	
Telephone Number	**E-Mail Address *(if available)***
81-3-3506-4077	

e Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314 52 and 314 95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1 e)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	**E-Mail Address *(if available)***

is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b)	☐ Yes	☒ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3

The patent claims the form of the drug substance in the drug product that is the subject of the NDA and is submitted for listing on that basis. Accordingly, no additional testing is required.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)*: 15 — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

Claim 15: Treatment of gout or hyperuricemia as identified in the proposed labeling at page 12 (Indications and Usage) and page 18 (Dosage and Administration)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Kenneth D. Greisman	11-23-04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Kenneth D Greisman	
Address 675 North Field Drive	City/State Lake Forest, IL
ZIP Code 60045	Telephone Number 847-582-2704
FAX Number *(if available)* 847-582-5007	E-Mail Address *(if available)*

EXCLUSIVITY SUMMARY

NDA # 21856 SUPPL # HFD # 170

Trade Name Uloric

Generic Name febuxostat

Applicant Name Takeda Pharmaceuticals North America, Inc

Approval Date, If Known February 13, 2009

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

five

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ NO ☐
Explain:

Investigation #2

IND # YES ☐ NO ☐
Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Matthew Sullivan
Title: RPM, Division of Anesthesia, Analgesia and Rheumatology Products
Date: 13 February 2009

Name of Office/Division Director signing form: Bob A. Rappaport
Title: Director, Division of Anesthesia, Analgesia and Rheumatology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Bob Rappaport
2/13/2009 04:08:51 PM

12/15/08

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 21 856 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DAARP PDUFA Goal Date: Jan 18, 2009 Stamp Date: 7/18/2008

Proprietary Name: Uloric

Established/Generic Name: febuxostat

Dosage Form: oral tablets

Applicant/Sponsor: Takeda

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of hyperuricemia in patients with gout

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

* ***Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☒ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☒ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☒ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∆ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† *Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)*

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attached justification for full waiver, as necessitated by Q4, Section A.

Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I.

The Division concurs with the Sponsors rationale as provided in their pediatric waiver request and excerpted below:

> Hyperuricemia and gout are rare in the pediatric population, and when they do occur in childhood, it is most often the result of secondary cancer, diuretic therapy, dehydration, starvation, keto or lactic acidosis, renal shutdown, and hereditary disorders. The prevalence of secondary gout associated with the inherited disorder Lesch-Nyhan Syndrome, is reported to be as low as 1 in 380,000 in the United States. The other inherited disorders are even rarer. The claimed indication for febuxostat is the management of hyperuricemia in patients with gout, which is extremely rare in individuals below 18 years of age.

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

/s/

Matthew Sullivan
12/15/2008 06:37:21 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 21-856 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Uloric Established/Proper Name: febuxostat Dosage Form: oral tablets		Applicant: Takeda Agent for Applicant (if applicable):
RPM: Matt Sullivan		Division: Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	Jan 18, 2009 Jan 16, 2009
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None Oct 14, 2005 AE Aug 2, 2006 AE
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application[2] Characteristics	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	Dec 10, 2008
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Information Advisory

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	☐ Yes ☐ No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.* *If "**No**," continue with question (3).*	☐ Yes ☐ No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	☐ Yes ☐ No
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (5).*	☐ Yes ☐ No

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Feb 17, 2009
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AE Oct 14, 2005 AE Aug 2, 2006 AP Feb 13, 2009
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	Feb 9, 2009
• Original applicant-proposed labeling	Jul 2, 2008
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Feb 9, 2009
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	Jul 2, 2008
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	Jan 22 and 28, 2009
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEDP Feb 25, 2005 Mar 22, 2005 May 23, 2005 Jun 6, 2006 Dec 19, 2008 ☒ DRISK Apr 7, 2005 Jan 29, 2009 ☒ DDMAC Apr 14, 2005 Aug 31, 2005 Sep 2, 2005 Jan 2, 2009 Jan 5, 2009 ☐ CSS ☒ Other reviews SEALD Jan 14, 2009
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	Dec 5, 2008
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	July 20, 2006
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included Feb 13, 2009
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☐ None
• Outgoing communications *(if located elsewhere in package, state where located)*	Jan 9, 2009, Clinical DR Letter Aug 2, 2006, AE Letter
• Incoming submissions/communications	Jan 22, 2009
❖ Postmarketing Commitment (PMC) Studies	☐ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	Pre-Approval Safety Conference Dec 15, 2008
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable Dec 10, 2008
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☐ Not applicable Dec 5, 2008
• Regulatory Briefing *(indicate date)*	☐ No mtg August 12, 2005
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg Jun 30, 2004
• EOP2 meeting *(indicate date)*	☐ No mtg Sep 13, 2002
• Other (e.g., EOP2a, CMC pilot programs)	Type A post-action Dec 5, 2005
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	November 24, 2008
• 48-hour alert or minutes, if available	Full transcript included
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None Feb 13, 2009
Division Director Summary Review *(indicate date for each review)*	☐ None Feb 13, 2009 Aug 1, 2006 Oct 14, 2005
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None Feb 11, 2009 Jan 2, 2009
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Jul 17, 2006 Sep 12, 2005
• Clinical review(s) *(indicate date for each review)*	Jan 19, 2009 Dec 19, 2008 Jul 17, 2006

[5] Filing reviews should be filed with the discipline reviews.

	Sep 12, 2005
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	Jul 17, 2006 Sep 23, 2005
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Feb 11, 2009 CDTL Review
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None DCRP Consult Oct 14, 2008
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☐ None Dec 23, 2008
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested Feb 2, 2009
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None Dec 19, 2008 Oct 12, 2005
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Dec 18, 2008 July 18, 2006 August 29, 2005
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None Jan 7, 2009
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None Dec 29, 2008 Sep 6, 2005
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None

❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Mar 19, 2004 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☐ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None Oct 12, 2005
• CMC/product quality review(s) *(indicate date for each review)*	☐ None Jan 16, 2009 Jan 6, 2009 Oct 31, 2008 July 18, 2006 Sept 22, 2005
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Oct 31, 2008
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per Oct 31, 2008 CMC review)
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: Jan 16, 2009 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Febuxostat Tablets
NDA 21-856

DEBARMENT CERTIFICATION
For
NDA Amendment 0046

Takeda Pharmaceuticals North America, Inc. (Takeda) hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act, in connection with this Application.

(see appended electronic signature)

Jenipher Dalton
Director, Clinical Quality Assurance
Takeda Global Research & Development Center, Inc.

Approval Signature Page

Document Title: Debarment Certification	TAP-DCN: TAP-08-001726-1.0
Document Approved Date (GMT): 7/1/2008 09:22:03 PM	

Description	User Name	User OS Name	Signature Date (GMT)	Meaning of Signature
Approver	Jenipher E. Dalton	daltonj	7/1/2008 09:22:03 PM	Approve

Febuxostat Tablets
NDA 21-856

DEBARMENT CERTIFICATION

TAP Pharmaceutical Products Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act, in connection with this Application.

_____

Harold Cohen
Director, Quality Assurance
TAP Pharmaceutical Products Inc.

2/2/09

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: February 2, 2009

TO: Matthew Sullivan, Regulatory Project Manager
Jane Gilbert, M.D., Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Products

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: #21-856

APPLICANT: Takeda Global Research & Development Center

DRUG: Uloric (febuxostat)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of hyperuricemia in patients with gout

CONSULTATION REQUEST DATE: 12/19/08

DIVISION ACTION GOAL DATE: 1/9/09
PDUFA DATE: 1/18/09

I. BACKGROUND:

NDA 21-856 was submitted by Takeda for approval of febuxostat, a new molecular entity and non-purine selective inhibitor of xanthine oxidase, for the indication of treatment of hyperuricemia in patients with gout. The Division of Anesthesia, Analgesia and Rheumatology Products requested clinical inspections to assess data integrity and human subject protection for a clinical trial conducted for approval febuxostat. The CDER reveiw division specifically requested that the reporting of serious adverse events, especially cardiac events, be verified. Sites were selected because of high enrollment. The sites were blinded to the primary efficacy endpoint, serum urate, so an inspection of _____, the contract laboratory was also conducted. b(4)

Product-related adverse events occurring in at least 1% of febuxostat treated subjects included liver function abnormalities, nausea, arthralgia, dizziness and rash.

The drug is supplied as 40mg and 80mg tablets and the recommended dose is 40mg or 80mg daily.

The protocol inspected was Protocol F-GT06-153 entitled "A Phase 3, Randomized, Multicenter, Double-Blind Allopurinol-Controlled Study Assessing the Efficacy and Safety of Oral Febuxostat in Subjects with Gout."

II. RESULTS (by Site):

Name of Clinical Investigator (CI) or Laboratory and Location	Protocol # and # of Subjects	Inspection Dates	Final Classification
CI #1 J. Edwin Dodd, Jr. MD CRC of Jackson 501 Marshall St. Suite 205 Jackson, MS 39202	Protocol F-GT06-153/ 44 subjects	January 12 to 23, 2009	Pending
CI #2 David Fitz-Patrick, MD 1585 Kapiolani Blvd Number 1500 Honolulu, HI 96814	Protocol F-GT06-153/ 69 subjects	January 13 to 19, 2009	Pending
CI#3 Howard R. Knapp, MD Billing Clinic Research Center 1045 N. 30th St. Billings, MT 59101	Protocol F-GT06-153/ 36 subjects	January 14 to 21, 2009	Pending
CI#4 Denny H. Lee, MD Irvine Center for Clinical Research, Inc. 16263 Laguna Canyon Rd, Suite 150 Irvine, CA 92618	Protocol F-GT06-153/ 32 subjects	January 13 to 27, 2009	Pending
Laboratory	Protocol F-GT06-153	January 26 and 27, 2009	Pending

b(5)

b(4)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. J. Edwin Dodd, Jr. MD
CRC of Jackson
501 Marshall St.
Suite 205
Jackson, MS 39202

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

a. **What was inspected**: For Protocol F-GT06-153, 53 subjects were screened at the site, 44 were enrolled and 41 completed the study. A total of 28 subject records were reviewed, including informed consent documents, medical history and laboratory data. There were no limitations to the inspection.

b. **General observations/commentary:** There was no underreporting of adverse events (AEs). No significant regulatory violations were noted.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. David Fitz-Patrick, MD
1585 Kapiolani Blvd, Number 1500
Honolulu, HI 96814

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. **What was inspected**: For Protocol F-GT06-153, 87 subjects were screened at the site, 69 were enrolled and 56 completed the study. Records were reviewed for 29 subjects who completed the study, 5 subjects who terminated early and 4 subjects who were screen failures. There were no limitations to the inspection.

b. **General observations/commentary**: There was no underreporting of AEs. No significant regulatory violations were noted.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Howard R. Knapp, MD
Billing Clinic Research Center
1045 N. 30th St.
Billings, MT 59101

Note: Observations noted for this site are based on the FDA Form 483 and communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. **What was inspected**: For Protocol F-GT06-153, 60 subjects were screened at the site, 36 were randomized and 34 completed the study. Informed consent documents were reviewed for all subjects screened. Records and laboratory values for randomized subjects were reviewed for the 36 subjects who were randomized. There were no limitations to the inspection.

b. **General observations/commentary**: There was an adverse event which was not reported to the study sponsor. This adverse event was a high blood pressure reading of 190/104 mm Hg on the six-month/final visit of subject 03613015 on 12/4/07. The reading was repeated three times with the same result. During other study visits, the subject had not had blood pressure readings exceeding 156/84 mm Hg. This was recorded in the Adverse Events log as "worsening hypertension." This entry was struck out by drawing a line through the entry and was not reported as an adverse event to the sponsor.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. Denny H. Lee, MD
Irvine Center for Clinical Research, Inc.
16263 Laguna Canyon Rd, Suite 150
Irvine, CA 92618

Note: Observations noted for this site are based on the FDA Form 483 and communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. **What was inspected**: For Protocol F-GT06-153, 49 subjects were screened at the site, 326 were randomized and 31 completed the study. There were no limitations to the inspection.

b. **General observations/commentary**: Inspection revealed that there was no underreporting of AEs. The following regulatory violations were cited on the FDA Form 483:
   i) The investigation was not conducted according to the investigational plan.

Specifically, subject 32657-034 was enrolled into the study even though he had taken Indocin 10 days prior to enrollment. The protocol stated that this medication was not allowed within 30 days prior to or during the study.

ii) The investigator did not maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically, there is a discrepancy between the case report form (CRF) and the source document for subject 32857-005 for the screening visit dated 2/22/07. The CRF states that there are palpable tophi on the left toe, but the source document has a late entry dated 5/15/07 stating, "Tophi assessment was done and not present."

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

5. / / /

b(4)

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. **What was inspected**: The inspection verified the primary efficacy endpoint data for the final serum urate level (uric acid) for approximately one-half of the subjects from each of the four sites inspected (Dodd, Fitz-Patrick, Knapp and Lee).

b. **General observations/commentary:** All of the results matched the results provided in the line listings of the NDA by the sponsor.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections of Drs. Knapp and Lee found regulatory violations as noted above. All other inspections did not find violations. The data from all sites and from [redacted] s appear acceptable in support of the proposed indication. b(4)

The final classifications for all inspections are pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIRs.

{See appended electronic signature page}

Susan Leibenhaut, MD
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, MD, MPH
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Susan Leibenhaut
2/2/2009 03:33:09 PM
MEDICAL OFFICER

Constance Lewin
2/2/2009 05:10:25 PM
MEDICAL OFFICER

Sullivan, Matthew

From: Fava, Walter
Sent: Monday, January 26, 2009 5:26 PM
To: Sullivan, Matthew
Cc: Taylor, Kellie
Subject: RE: Febuxostat NDA 21-856: 3 Count Blister Back

Hi Matt,

The revisions to the 3 tablets blister package are acceptable. DMEPA has no other recommendations for the carton labeling and container labels at this time.

Thanks,
Walter

From: Sullivan, Matthew
Sent: Monday, January 26, 2009 11:43 AM
To: Fava, Walter
Cc: Taylor, Kellie
Subject: FW: Febuxostat NDA 21-856: 3 Count Blister Back

Walter –

Here is the back of the 3 count blister pack for febuxostat. You had asked that the prominence be increased here as well for the "contains 3 tabs" statement.

Matt

From: Villinski, Allison (TGRD) [mailto:allison.villinski@tgrd.com]
Sent: Monday, January 26, 2009 11:43 AM
To: Sullivan, Matthew
Subject: Febuxostat NDA 21-856: 3 Count Blister Back

Hello Matt-

I just thought that I would touch base with you regarding the following:

1. Carton and Container Labeling: I received your comment over the weekend and am attaching a revised blister label with the 80 mg text increased in size on the back. Can you please let me know if the updated documents that have been submitted to you informally (i.e. front of blister on Friday and back of blister attached to this e-mail) are acceptable? If so, I will formally submit to the NDA. Can you confirm that all of the other carton and container labels provided last week are acceptable?

2. Package Insert: Do you have any questions on the e-mail that I provided Friday with Takeda's comments/questions regarding the 2nd version of the package insert? Do you have any more of an idea of when Takeda will receive feedback on the handling of Table 3 and the patient package insert?

Thanks for your willingness to keep the lines of communication open. I am trying to ensure that Takeda continues to be responsive to the Division's requests in an attempt to complete all outstanding items as soon as possible. If you have any questions, please feel free to give me a call. Thanks!

Kindest Regards,

Allison

Allison M. Villinski
Manager, Regulatory Affairs Strategy
Takeda Global Research and Development, Inc.
W: (847) 582-2708
C: (847) 894-2051
allison.villinski@tgrd.com

###
This message is for the designated recipient only and may contain privileged or conf

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/s/

Matthew Sullivan
1/27/2009 09:38:35 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

DISCIPLINE REVIEW LETTER

NDA 21-856

1/9/09

Takeda Pharmaceuticals North America, Inc
675 N. Field Drive
Lake Forest, IL 60045

Attention: Allison Villinski
Senior Regulatory Product Manager

Dear Ms. Villinski:

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

Our review of the clinical and non-clinical sections of your submission is complete, and we have the following comments:

1. Although the most recent Phase 3 trial (Study F-GT06-153) did not show a higher rate of cardiovascular adverse events in the febuxostat groups, in the first two clinical trials a higher rate of cardiovascular thromboembolic events was observed among patients receiving febuxostat than those receiving allopurinol. The new trial did not exclude the possibility of a moderate increase in risk of cardiovascular events with febuxostat. To fully characterize the cardiac safety of febuxostat a cardiovascular outcome study will be necessary. If your application is approved, a cardiovascular outcome study will be required as a postmarketing study.
2. In the clinical development program, relatively few women and elderly patients were enrolled, making it difficult to fully characterize the safety in these patient groups. In designing any additional postmarketing studies and clinical trials, it would be important to endeavor to enroll women and the elderly in proportions similar to their representation in the patient population. In addition, renal impairment is a common co-morbidity in patients with gout and patients with renal impairment experience a higher exposure to febuxostat. Postmarketing studies should also include adequate numbers of patients with renal impairment so that firm conclusions can be drawn about the safety of febuxostat in this subgroup as well.
3. We are recommending that febuxostat be designated a Pregnancy Category C drug based on the findings of increased incidence of post-natal deaths in the segment 3 study. It is possible that this finding may be due to adverse effects on the fetus that occurred in utero which would also be consistent with a Pregnancy Category C as per the CFR.

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, MS
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/

Sara Stradley
1/9/2009 10:41:49 AM

From: Sullivan, Matthew
To: "Villinski, Allison (TGRD)";
Subject: RE: carton labeling
Date: Friday, January 16, 2009 11:06:00 AM

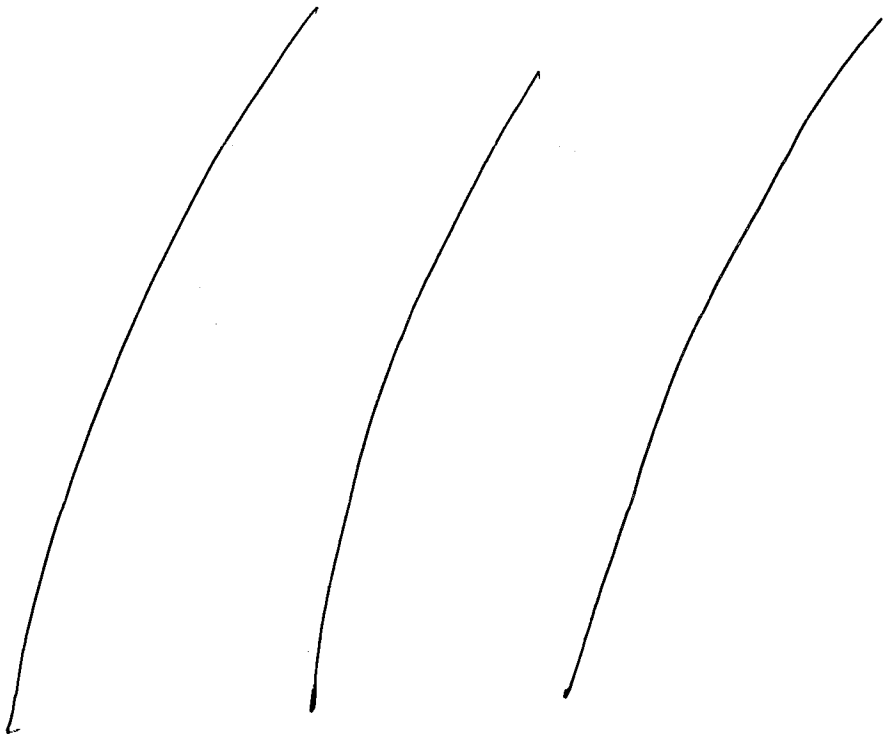
Sorry, forgot one:

6. **Professional sample blister carton label (3-count, 7-count)**
   Delete the statement

From: Sullivan, Matthew
Sent: Friday, January 16, 2009 11:03 AM
To: 'Villinski, Allison (TGRD)'
Subject: RE: carton labeling

Allison –

In addition to the carton and container comments sent to you previously (below), please see the following comments. I would not anticipate additional comments on the carton/container.



b(4)

(A)

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

From: Sullivan, Matthew
To: "Villinski, Allison (TGRD)";
Subject: CMC information request
Date: Wednesday, January 07, 2009 5:16:00 PM

Please request from the API product manufacturer (Abbott) the following tabulated info:

All manufactured Lot Number	Expn Date	Quantity Available	OOS? If so, copy of investigation	Stability? If so, copy of data chart

In addition, we need some questions answered for the API:

1. How much quantity of API is used per lot and how long it expected to last?
2. What is the timeline for a new API source?

Could you get from the finished product manufacturer (Abbott) the following tabulated info:

FP Lot Number	API Lot Number used	Expn Date	OOS? If so, copy of investigation	Stability? If so, copy of data chart

---

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

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

/s/

Matthew Sullivan
1/8/2009 06:42:48 PM
CSO

MEMORANDUM

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

DATE: December 15, 2008

TO: File

FROM: Matthew Sullivan, MS, Regulatory Project Manager

SUBJECT: **Pre-Approval Safety Conference**
NDA 21-856, Febuxostat 40 mg and 80 mg Tablets

In lieu of a separately scheduled preapproval safety conference with OSE staff, the Division chose to include OSE staff in the planned review division Wrap-Up meeting. OSE staff members were invited, and attended, the Wrap-Up meeting for NDA 21-856, on December 5, 2008. Members of OSE staff present at the meeting were Chris Wheeler, Regulatory Project Manager, Joann Lee, Acting Team Leader, Division of Pharmacovigiliance II, Walter Fava, Safety Evaluator, and Suzanne Berkman, Acting Team Leader, DRISK. Also present were the following: Curt Rosebraugh (phone), Bob Rappaport, Dionne Price, Joan Buenconsejo, Tom Permutt, Jeff Siegel, Leah Ripper, Asoke Mukherjee, Dan Mellon, Olen Stephens, Ali Al Hakim, Danae Christodoulou (phone), Larissa Lapteva, Lei Zhang, Jane Gilbert, and Sarah Okada (phone).

Prior to the meeting, Dr Gilbert (Primary Medical Officer) provided OSE with slides that had been recently presented at an Advisory Committee, and contained a comprehensive overview of the safety of febuxostat.

During the meeting, the Dr Gilbert gave a review of the clinical studies, adverse events, safety concerns, and potential post-marketing requirements. Specifically, she noted that while there appeared to be a safety signal for CV events in trials submitted during the first and second cycles, there were small numbers of subjects, and the 95% CI of the risk estimates largely overlapped one another. The trial submitted for the third cycle did not confirm that a CV signal existed.

Dr Gilbert reminded those at the meeting that the recent Advisory Committee had recommended one or more post-marketing studies to assess the CV signal that had been previously observed. The specifics of a post-marketing study would be discussed in more detail at a later time.

Dr Berkman of OSE noted that they will briefly review the risk management proposal that has been submitted.

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/s/

Matthew Sullivan
12/15/2008 05:49:32 PM
CSO

From: Sullivan, Matthew
To: "Villinski, Allison (TGRD)";
Subject: RE: Febuxostat NDA 21-856: API Manufacturing Site
Date: Thursday, December 04, 2008 1:39:00 PM

Allison –

I passed this on to the CMC group. Here's what they'd like:

An official submission of the information below, including as much detail (with dates) as you can.

We would also like to see a commitment that you'll be submitting a CMC supplement post-approval for the [redacted] site. b(4)

I think that will be enough for now. Once we look it over, we'll let you know if we still have concerns. (Of course, we still have to review the full District Office report. I'm guessing no 483 was issued since you didn't mention it. Is that accurate?)

Matt

From: Villinski, Allison (TGRD) [mailto:allison.villinski@tgrd.com]
Sent: Thursday, December 04, 2008 12:47 PM
To: Sullivan, Matthew
Subject: Febuxostat NDA 21-856: API Manufacturing Site

Dear Matt-

Per our discussion earlier today, the following describes the use of febuxostat drug substance manufactured at the Abbott Laboratories North Chicago facility. API material from Abbott Laboratories North Chicago was provided for all clinical studies and will be used for the launching of commercial product. The NDA is accurate listing Abbott as the supplier of API material for commercial launch. Two PAI inspections (July 2005 and September 2008) have been conducted at Abbott Laboratories, the first of which was conducted while the manufacturing facility (North Chicago) was in existence. Since the first PAI was conducted, Abbott has demolished the manufacturing facility as reflected in the FDA inspector's notes. Takeda has [redacted] of API inventory from the Abbott Laboratories North Chicago facility and will remove Abbott Laboratories as the API manufacturer when the API from the facility has been consumed. There are no open issues as a result of either of these API inspections. As a post-approval supplement, Takeda will be submitting [redacted] as their supplier of future drug substance. b(4)

Please let me know if the chemistry reviewers have any additional questions or further clarification is required. Thanks!

Kindest Regards,
Allison

Allison M. Villinski
Manager, Regulatory Affairs Strategy
Takeda Global Research and Development, Inc.
W: (847) 582-2708
C: (847) 894-2051
allison.villinski@tgrd.com

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From: Sullivan, Matthew
To: "Villinski, Allison (TGRD)";
Subject: Febuxostat Information Request 8/25/08
Date: Monday, August 25, 2008 5:06:00 PM

Allison –

Please find below an information request for febuxostat. Thanks
matt

> Provide a table with rates of APTC events (in events per 100 pt-yrs) for patients in the clinical development program exposed to febuxostat for varying periods of time. The table should include rates for all febuxostat as well as broken down by dose (40, 80, 120 mg), in addition to rates for patients exposed to placebo and allopurinol. The rates should be calculated for patients exposed for 0-6, 6-12, 12-18 months, etc. Provide separate analyses of event rates for adjudicated APTC events as well as for APTC events as designated by the investigator.

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

From: Sullivan, Matthew
To: "Villinski, Allison (TGRD)";
Subject: 9/16/08 Information request N21856 febuxostat
Date: Tuesday, September 16, 2008 10:52:00 AM

Allison –

Another request:

1. Prior cardiovascular history may influence the risk of subsequent cardiovascular events. In the study report on F-GT06-153 (p. 299), Table 14.1.9.2 breaks down treatment by prior cardiovascular history. Provide a subgroup analysis of cardiovascular events (i.e., adjudicated and investigator reported APTC events) broken down by treatment and cardiovascular history such as given in this table.

2. In your current application your analysis of Investigator Reported and Adjudicated APTC (and non-APTC) events includes estimates of Relative Risk (Tables 41, 42 and 44, pages 167, 168 and 172, respectively) in addition to Confidence Intervals around the point estimates. We have been unable to locate similar relative risk estimates in your previous submission (Complete Response to October 14, 2005 Approvable Letter, February 2006). Since we plan to evaluate the relative risk in both submissions, provide information about where comparable relative risk estimates can be found in your previous (February 2006) submission. Moreover, if these estimates were not completed for the previous submission, then provide them to us.

Thanks
Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov

From: Sullivan, Matthew
To: "Villinski, Allison (TGRD)";
Subject: info request
Date: Tuesday, October 21, 2008 2:44:00 PM

Allison –

This doesn't necessarily have to trigger an official response from you. I think we may be able to do it just via email.

> Regarding the allopurinol doses used in Study C02-009, we note that it is written "Allopurinol 300/100 mg", does that mean 300 mg and 100 mg were the *only* doses administered?

Thanks

Matt

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

7/29/08

NDA 21-856

Takeda Pharmaceuticals North America, Inc
675 N. Field Drive
Lake Forest, IL 60045

Attention: Allison Villinski
Senior Regulatory Product Manager

Dear Ms. Villinski:

We acknowledge your July 17, 2008, resubmission, received July 18, 2008, to your new drug application for Uloric (febuxostat tablets), 80 mg and 120 mg.

We consider this a complete, class 2 response to our August 2, 2006, action letter. Therefore, the user fee goal date is January 18, 2009.

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

Sincerely,

[See appended electronic signature page]

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

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/s/

Sara Stradley
7/29/2008 09:25:06 AM

SPONSOR MEETING AGENDA

MEETING DATE: January 18, 2007

TIME: 12:00 to 1:00 pm

LOCATION: FDA White Oak Campus
Silver Spring, MD

APPLICATION: NDA 21-856

STATUS OF APPLICATION: Approvable

PRODUCT: ULORIC (febuxostat)

INDICATION: Management of hyperuricemia in patients with gout

SPONSOR: TAP Pharmaceutical Products Inc.

TYPE OF MEETING: Type B

MEETING CHAIR: Jeff Siegel, M.D., Deputy Director, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

MEETING RECORDER: Matthew Sullivan, M.S., Regulatory Project Manager

FDA Attendees	Title
Robert Meyer, M.D.	Director, Office of Drug Evaluation II (ODE II)
Curtis Rosebraugh, M.D.	Deputy Director, ODE II
Bob Rappaport, M.D.	Director, DAARP
Rigoberto Roca, M.D.	Deputy Director, DAARP
Jeff Siegel, M.D.	Medical Team Leader, DAARP
Keith Burkhart, M.D.	Medical Officer, DAARP
Ravi Harapanhalli, Ph.D.	Chief, CMC Branch V, Office of New Drug Quality Assessment (ONDQA)
Sue Ching Lin, Ph.D.	CMC Reviewer, ONDQA
Suresh Doddapaneni, Ph.D.	Team Leader, Clinical Pharmacology, DAARP
Lei Zhang, Ph.D.	Clinical Pharmacology Reviewer, DAARP
Dionne Price, Ph.D.	Team Leader (acting), Statistics, DAARP
Joan Buenconsejo, Ph.D.	Statistics Reviewer, DAARP
Matthew Sullivan, M.S.	Regulatory Project Manager
TAP Attendees	**Title**
Nancy Joseph-Ridge, MD	Vice President, Research and Development
Dean Sundberg	Vice President, Regulatory Affairs
Christopher Lademacher, MD	Medical Director, Internal Medicine & Rheumatology
Maria Paris, MD	Senior Director, Clinical Safety, Pharmacovigilance

Uwa Kalu, MD	Medical Director, Pharmacovigilance
Nancy Siepman, PhD	Director, Statistics and Study Programming
Harriet Glassman	Senior Director, Project Management
Robert Jackson, MD	Head of Clinical Development
Jean-Marie Geoffroy, PhD	Director, Pharmaceutical Development
Beth-Anne Knapp	Regulatory Products Manager
Binita Kwankin, MS	Associate Director, Regulatory Affairs

Question 1. Efficacy requirements for approval of Uloric 40 mg:

1.1. Will the proposed Phase 3 study be sufficient for approval of Uloric 40 mg for the management of hyperuricemia in patients with gout, if it demonstrates that Uloric 40 mg is non-inferior or superior to allopurinol based on the primary efficacy analysis described in Section 9.1.3 of the protocol (Appendix 1)?

FDA RESPONSE:
Yes. Your Phase 2 study has already demonstrated that febuxostat 40 mg statistically significantly lowered the serum uric acid level when compared to placebo. Your previous studies showed greater lowering of serum uric acid levels with the febuxostat 80-mg and 120-mg doses than with allopurinol. Your proposed Phase 3 study uses a primary efficacy analysis of non-inferiority based upon the lower bound of the 95% confidence interval (CI) for the proportion of febuxostat 40-mg subjects with serum urate levels less than 6.0 mg/dL using a 10% non-inferiority margin. The previous data plus a positive result in the proposed Phase 3 trial will be adequate to establish efficacy of the febuxostat 40-mg dose.

1.2. Will the proposed Phase 3 study [redacted] b(4)

FDA RESPONSE:

[redacted] b(4)

Question 2. Evaluation of cardiovascular safety: Is the plan for evaluation of cardiovascular safety (including definition of APTC events, adjudication process, and the proposed cardiovascular analyses) described in Sections 6.6 and 9.1.3.3 of the proposed protocol (Appendix 1) and in the Charter for the Cardiovascular Endpoints Committee (Appendix 2), acceptable?

FDA RESPONSE:
The definition of APTC events, non-fatal MI, non-fatal stroke and cardiovascular deaths, is acceptable. However, sub-analyses of the additional events including unstable angina, transient ischemic attacks, congestive heart failure and arrhythmias should also be carried out. The adjudication process is acceptable. The power analysis that provides 90% probability that the relative risk of febuxostat 40 mg is not greater than 2.34 compared to allopurinol is acceptable.

Question 3. *TAP understands the Agency's expectation regarding safety data for approval of Uloric 80 mg as described in the September 8, 2006 FDA Correspondence. However, with regards to safety requirements for approval of Uloric 40 mg: Will the proposed study be sufficient for approval of Uloric 40 mg for the management of hyperuricemia in patients with gout, if it demonstrates that the rates of APTC events for Uloric 40 mg are comparable to or lower than for allopurinol, and the study also demonstrates adequate assay sensitivity?*

FDA RESPONSE:
On its face, a study that demonstrates rates of APTC events for febuxostat 40 mg that are comparable to or lower than for allopurinol would be reassuring. However, if the study does not reproduce the possible cardiovascular safety signal seen in prior studies of febuxostat 80 and 120 mg then it would raise issues of assay sensitivity. However, provided that an adequate number of cardiovascular events are observed in the allopurinol control arm, if the rates of cardiovascular events in the febuxostat 40- and 80-mg arms are similar or lower than the rates in the allopurinol arm, then these results would still be both informative and potentially reassuring. A conclusion of safety for the febuxostat 40-mg dose will depend on a review of the totality of the data, including the risk of other cardiovascular events, including those outlined in the response to question #2 above.

Question 4. *Is the design of the proposed Phase 3 study, including subject eligibility criteria, treatment regimens, gout flare prophylaxis regimens, efficacy and safety endpoints, sample size assumptions, and proposed analyses, acceptable to achieve the objectives specified in Questions 1-3 above?*

FDA RESPONSE:
The subject inclusion and exclusion eligibility criteria are acceptable. The treatment regimens are also acceptable. The gout flare prophylaxis regimens of colchicine 0.6 mg BID or, if colchicine is not tolerated, naproxen 250 mg BID with lansoprazole 15 mg qd are within the current standard of care and are acceptable. The primary efficacy endpoint of reduction of serum urate levels to less than 6.0 mg/dL is acceptable. Management of hyperuricemia would become the label indication. A decrease in the total number of actual gout flares would provide important confirmation that the surrogate marker of lowering uric acid levels is also associated with a clinical benefit. The meeting package confirms your post-marketing commitment to obtain evidence regarding reduction in gout flares.

Question 5. *Exposure requirements for approval of Uloric 40 mg: Based on all US and Japanese studies, the exposure on Uloric 40 mg will be as follows after completion of the proposed study (See Section 9.4 for additional details):*

- *Total of approximately 1200 subjects exposed to Uloric 40 mg*
- *Approximately 600 subjects exposed to Uloric 40 mg for ≥6 months*
- *Approximately 8 subjects exposed to Uloric 40 mg for ≥1 year (66 subjects total, including those who received febuxostat for 52 weeks who titrated step-wise from 10 mg to 20 mg to 40 mg in Japanese Study TMX-67-11) In light of the extensive data available for Uloric through*

doses up to 300 mg, will this exposure for 40 mg be sufficient for approval of this dose?

FDA RESPONSE:
The total number of proposed subjects that will be exposed to Uloric 40 mg, as described above, is acceptable.

Question 6. *Will the Agency require any other clinical data in addition to the proposed Phase 3 study in order to approve Uloric 40 mg — for the management of hyperuricemia in patients with gout?* **b(4)**

FDA RESPONSE:
As stated above, the previously acquired data along with data from the proposed Phase 3 trial should be adequate to assess efficacy and safety of febuxostat 40 mg. If the data 1) demonstrate efficacy, 2) demonstrate that the 40-mg febuxostat dose is not associated with a cardiovascular risk and 3) show no new safety signals that outweigh the potential benefits, these data would be adequate to support approval of febuxostat 40 mg.

Question 7. *Section 9.5 provides a proposal for the Safety Update required under 21 CFR 314.50(d)(5)(vi)(b) and requested in the August 2, 2006 Approvable Letter. Is this proposal acceptable?*

FDA RESPONSE:
This proposal is acceptable. Make sure to include translations of any reports that are in foreign languages. The integrated safety data should also be presented for the 80-mg dose whether approval for this dose is sought or not.

Question 8. *The ongoing long-term extension studies C02-021 and TMX-01-005 will be completed and clinical study reports for these studies will be submitted to IND 58,229 prior to submission of the Complete Response to the Approvable Letter. The Complete Response will cross-reference the IND for these study reports (as opposed to resubmission of these reports to the NDA). Note that safety information from these studies will be included as part of the Safety Update submitted with the Complete Response, as described in Section 9.5. Is this proposal acceptable?*

FDA RESPONSE:
This proposal is acceptable.

Question 9. *In the event TAP's licensing partner, Teijin, or their partners, complete new studies with Uloric prior to submission of our Complete Response to the Approvable letter, we will submit the study reports to the IND as they become available. Our Complete Response will cross-reference the IND for this*

information (as opposed to resubmission of these reports to the NDA). Note that safety information from these studies will be included as part of the Safety Update submitted with the Complete Response, as described in Section 9.5. Is this proposal acceptable?

FDA RESPONSE:
This proposal is acceptable.

Question 10. Section 11.0 of this document includes a proposal for submission of CMC information for Uloric 40 mg as part of the Complete Response. Is this proposal acceptable for approval of Uloric 40 mg?

FDA RESPONSE:
The proposal appears acceptable, with the exception of section 3.2.P.5. regarding the dissolution method and acceptance criteria (see Response to Question #11 below).

Question 11. Based on the FDA's October 14, 2005 approvable letter and the dissolution profiles presented in Section 11 (Figure 11.0.a); does the Agency have any comments regarding the use of this method with the 40 mg dosage strength?

FDA RESPONSE:
The current dissolution method appears to be inadequate for the 40-mg strength because it does not provide discriminating conditions. Provide dissolution profiles at lower pH media (e.g., between pH 6.0 to 6.5) for both 40-mg and 80-mg strengths using the current dissolution apparatus and speed. Establish dissolution acceptance criteria based on the dissolution profiles. Solubility permitting, a lower pH medium may be appropriate to slow down the drug release at early timepoints and provide a discriminating condition.

Question 12. Would the Agency be willing to receive and review the CMC data for 40 mg if TAP is able to submit it prior to the completion of the proposed Phase 3 study?

FDA RESPONSE:
No, this application does not meet the usual criteria for performing a rolling review.

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/s/

Matthew Sullivan
1/17/2007 03:26:43 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

1/17/07

NDA 21-856

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

Attention: Binita Kwankin
Assistant Director, Regulatory Affairs

Dear Ms. Kwankin:

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

We also refer to your January 17, 2007, email acknowledging receipt of the enclosed responses, initially provided to you on January 11, 2007, and noting that a meeting will not be necessary.

Attached are the Division's responses to the questions from your November 20, and December 11, 2006, meeting packages for our upcoming meeting, scheduled for January 18, 2007, to discuss development of febuxostat for the treatment of hyperuricemia in patients with gout. Your questions are in italics and the Division's responses are in bold.

The previously agreed upon time is still set aside to meet with you, but, if you would like to either cancel the meeting, because you feel all your questions have been answered to your satisfaction, or re-focus the meeting (i.e., only focus on items which you feel require additional clarification), that would be acceptable to the Division as well. Alternatively, you can change the format of the meeting from face-to-face to teleconference. If you decide to change the format of the meeting, please contact us promptly by phone or e-mail.

We will be happy to provide clarification on any of the Division's responses, but **WILL NOT entertain any NEW questions, topics or review additional data** (there is simply not enough time prior to the meeting for the team to review such materials). Please let me know if you would like to change anything about our forthcoming meeting.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-856

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

10/13/06

Attention: Binita Kwankin
Assistant Director, Regulatory Affairs

Dear Ms. Kwankin:

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

We also refer to your September 18, 2006, correspondence, received September 19, 2006, requesting a Type A meeting to discuss the design of your proposed Phase 3 study.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B 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:	January 18, 2007
Time:	12:00 pm – 1:00 pm
Location:	FDA/CDER White Oak Building 22, Conference Room 1313 10903 New Hampshire Ave Silver Spring, MD 20903
CDER participants:	Bob Rappaport, MD; Division Director, Rigoberto Roca, MD; Deputy Division Director Ravi Harapanhalli, PhD; Chief, CMC Branch V Ali Al Hakim, PhD; Pharmaceutical Assessment Lead Sue Ching Lin, PhD; CMC Reviewer Adam Wasserman, PhD; Supervisory Pharmacologist Dan Mellon, PhD; Supervisory Pharmacologist Asoke Mukherjee, PhD; Pharm/Tox Reviewer Suresh Doddapaneni, PhD; Clinical Pharmacology Team Leader Lei K Zhang, PhD; Clinical Pharmacology Reviewer Jeff Siegel, MD; Clinical Team Leader Keith Burkhart, MD; Medical Officer

Dionne Price, PhD; Statistics Team Leader (Acting)
Joan Buenconsejo, PhD; Statistics Reviewer
Matthew Sullivan, MS; Regulatory Project Manager
Bob Meyer, MD; Director, ODE II
Curtis Rosebraugh, MD; Deputy Director, ODE II

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 matthew.sullivan@fda.hhs.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: Matthew Sullivan, 796-1245; the division secretary, 796-2280.

Provide the background information for this meeting (three copies to NDA 21-856 and 20 desk copies to me) at least one month prior to the meeting. If possible, submit the meeting package by December 5, 2006. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by December 19, 2006, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Matthew Sullivan
10/13/2006 12:54:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-856

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

Attention: Binita Kwankin
Assistant Director, Regulatory Affairs

Dear Ms. Kwankin:

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

We also refer to the meetings between representatives of your firm and the FDA on August 21 and September 11, 2006. The purpose of the meeting was to discuss your August 2, 2006, action letter and your development plans for febuxostat.

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, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE #1

DATE: August 21, 2006

APPLICATION NUMBER: NDA 21-856 (Uloric)

BETWEEN:

Name:	Dean Sundberg, Vice President, Regulatory Affairs Nancy Joseph-Ridge, MD, Vice President, Research and Development Polly Meade, Director, Corporate Project Management Office Binita Kwankin, MS, Assistant Director, Regulatory Affairs
Phone:	1-847-582-6585
Representing:	Tap Pharmaceutical Products, Inc.

AND

Name:	Sara Stradley, MS, Chief, Project Management Staff Bob Rappaport, MD, Director, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) Robert Meyer, MD, Director, Office of Drug Evaluation II

SUBJECT: Approvable letter dated August 2, 2006

The Sponsor noted that they believed that the cardiovascular (CV) safety issues were more an example of a random event than an actual signal. The Division replied that the imbalance could not be ignored, even if it was not statistically significant. The Division stated that there was enough of a signal with regard to CV events that the Sponsor needs to provide more reassurance in order for the Division to make a risk/benefit assessment. The Division stated that it may be possible to reanalyze the data, but the safety concern may not be mitigated since there still appears to be a trend.

The Division inquired if the Sponsor had [redacted] b(4)

The Sponsor questioned if additional data could be generated in a post-marketing study. The Division stated that the safety signal should be addressed prior to approval, and a randomized, controlled trial will be needed to investigate the current CV concern. Even if Uloric is beneficial compared to allopurinol, a relative increase in CV events and mortality as has been observed would not be acceptable. It was reiterated that labeling and post-approval studies would not adequately address this type of cardiovascular signal.

The Division clarified that a new study could potentially be of similar duration to the previous study. The Sponsor asked if a new study would be needed or if additional data from a long term study might provide enough information. The Division stated that it is unclear if the incidence of CV events would increase over time or if they only occurred early in a clinical trial. Thus a new

trial of similar design may need to be initiated. It was agreed that a Phase 3 trial might be sufficient and the Sponsor proposed sending an outline of the study to the Division for comment. It was also agreed that a teleconference could be arranged to discuss the trial outline.

MEMORANDUM OF TELECONFERENCE #2

DATE: September 11, 2006

APPLICATION NUMBER: NDA 21-856 (Uloric)

BETWEEN:

Name:	Dean Sundberg, Vice President, Regulatory Affairs Nancy Joseph-Ridge, MD, Vice President, Research and Development Christopher Lademacher, MD, Medical Director Nancy Siepman, PhD, Director, Statistics and Study Programming Binita Kwankin, MS, Assistant Director, Regulatory Affairs
Phone:	1-847-582-6585
Representing:	Tap Pharmaceutical Products, Inc.

AND

Name:	Matt Sullivan, MS, Regulatory Project Manager, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) Jeff Siegel, MD, Rheumatology Team Leader, DAARP Keith Burkhart, MD, Clinical Reviewer, DAARP Bob Rappaport, MD, Director, DAARP Curt Rosebraugh, MD, Deputy Director, Office of Drug Evaluation II Tom Permutt, PhD, Chief, Division of Biostatistics II Dionne Price, PhD, Acting Team Leader, Biostatistics, DAARP

SUBJECT: Follow-up to August 21, 2006 teleconference

The Sponsor submitted an overview of a new Phase 3 protocol on August 30, 2006 (Attachment A). The following comments, presented in bold text, are in response to that protocol overview, and were sent to the Sponsor on September 8, 2006.

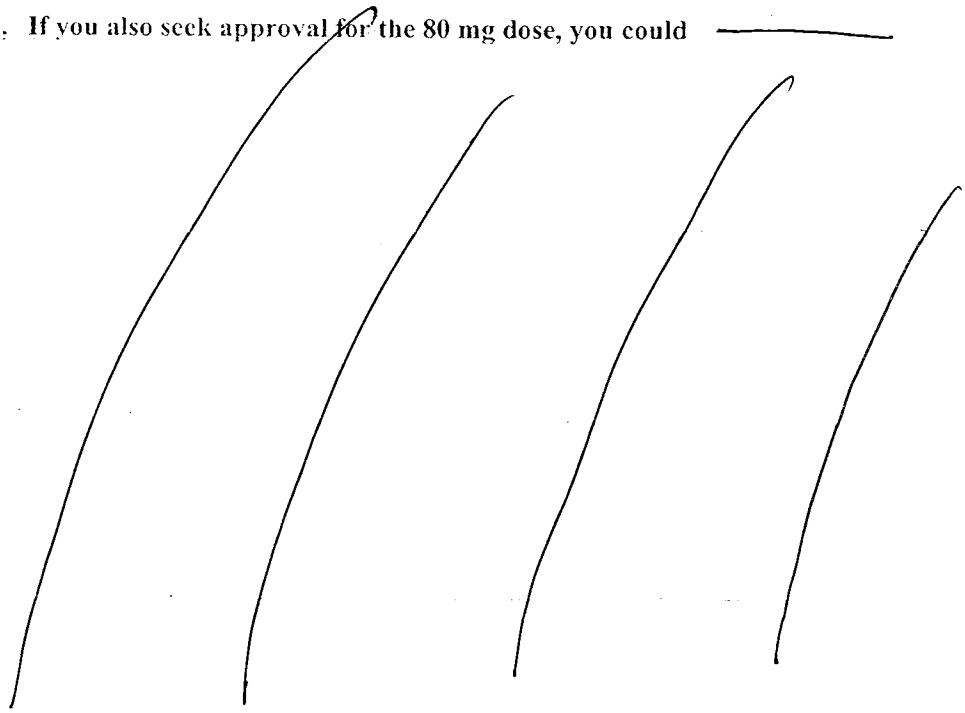
The discussion that occurred during the teleconference is captured in normal font.

We have reviewed the one page summary you submitted of a new proposed Phase 3 protocol (refer to Attachment A). This protocol is a randomized, multicenter, allopurinol-controlled study to assess the efficacy and safety of febuxostat at doses of 40 and 80 mg versus allopurinol 200 or 300 mg, depending upon renal function. We have also reviewed the submission of June 14, 2006 which contained a proposal for a Phase 4 study.

The design of the Phase 3 protocol could provide some very useful data in helping to address our concerns. The protocol proposes to study a lower dose, 40 mg, that may demonstrate efficacy and possibly demonstrate more favorable safety (comparable to or better than allopurinol), and the study would include a significant number of renally impaired patients. If the study demonstrates efficacy of the 40 mg dose and no relative safety concerns are identified with the 40 mg dose, the results could, in principle, support an approval for the 40 mg dose. However, unless this study were to show that the 80 mg trended better than allopurinol, it is not clear it would necessarily provide sufficient assurance to approve the 80 mg dose, since the study is not sized to prove cardiovascular safety relative to allopurinol (that is, it is not formally testing a non-inferiority on safety to allopurinol). Therefore, you can consider the following options:

a. You could conduct the proposed 6-month Phase 3 study of 40 and 80 mg. Depending on the study results it could provide data to support approval of the 40 mg dose and, somewhat less likely, the 80 mg dose.

b. If you also seek approval for the 80 mg dose, you could



b(4)

b(4)

Discussion

The Sponsor requested that the Division define the term "relative safety concern" that was used in the second paragraph of the September 8, 2006, response to the Sponsor. The Division replied

that APTC (Anti-Platelet Trialists Collaboration) events were the primary concern, but any other adverse events, including other cardiovascular events, would be reviewed as well.

The Division further commented that a new study, such as the one proposed, should have adequate assay sensitivity. That is, a new study would be expected to replicate the safety signal at the 80-mg dose. Without the expected signal at the 80-mg dose as a 'positive control', the possible lack of a signal at the 40-mg dose would be difficult to interpret.

The Sponsor questioned what the criteria would be for an approval action, given a trial with 40-mg and 80-mg arms. The Division replied that any results would be evaluated during the NDA review phase, but a finding of no CV safety signal at the 40-mg dose, coupled with a repeat finding of a signal at the 80-mg dose, would be the most reassuring that adequate assay sensitivity had been achieved.

The Sponsor requested confirmation that a CV outcome study would be needed for an approval action, to which the Division replied that, for the 80-mg dose, a CV study would be required. The Sponsor then asked if they could study the 40-mg dose in a six-month clinical trial, and the Division replied that they could do so, but that the study would need to include an 80-mg dose arm to assess the ability of the study to capture the signal found in the previous study.

There was no further discussion.

Attachment A [Phase 3 Study Outline Submitted by Email on August 30, 2006]

Title: A phase 3, randomized, multicenter, allopurinol-controlled study assessing the efficacy and safety of febuxostat in patients with gout.

Objective: To assess the efficacy and safety of febuxostat compared to allopurinol in patients with gout.

Inclusion and exclusion criteria: Similar to the Phase 3 pivotal studies; allopurinol doses stratified by renal function. Subjects who participated in one of the previous febuxostat studies can be enrolled, washout period is 30 days.

Treatments:
At baseline, 2000 subjects will be randomized to one of 3 fixed-dose treatment groups in a 1:1:2 ratio:

1. Febuxostat 40 mg QD
2. Febuxostat 80 mg QD
3. Allopurinol (200 mg QD for subjects with mild-moderate renal impairment and 300 mg QD for subjects with normal renal function)

Subjects will be stratified by renal impairement (mild to moderate or normal) such that a total of 50% of subjects will have mild to moderate renal impairement.

Total treatment duration is 6 months.

All subjects will receive prophylactic treatment with colchicine 0.6 mg BID[1]. Alternatively, in case colchicine is not tolerated by a subject, subjects will receive naproxen 250 mg BID / lansoprazole 15 mg QD.

Efficacy: Primary endpoint will be the proportion of subjects with serum urate level <6 mg/dL at the Final Visit.

Safety: Safety evaluations: adverse events including cardiovascular adverse events such as APTC events, physical exam, laboratory evaluation and vital signs. An adjudication committee consistent of 3 cardiologists will adjudicate each cardiovascular adverse event. The primary treatment comparison for the safety endpoint of primary APTC will be comparing the febuxostat total (40 mg QD and 80 mg QD groups combined) and the allopurinol group. Assuming the incidence rate for primary APTC events is 0.8% for both the febuxostat combined groups and allopurinol group, the sample size of 1000 subjects per group for this comparison will provide a 95% probability to expect that the observed relative risk in this study is within 0.377
and 2.654.

References
1. Borstad GC, et al. Colchicine for Prophylaxis of Acute Flares When Initiating Allopurinol for Chronic Gouty Arthritis. J Rheumatology. 31:2429-32, 2004.

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/s/

Matthew Sullivan
10/12/2006 01:20:35 PM

For Internal Use Only

Meeting Request Granted Form**

(Use this form to document the meeting granted via telephone.)

Complete the information below and check form into DFS.

Application Type	☐ P-IND ☐ IND X NDA
Application Number	21 856
DATE Meeting Granted	9/22/06
Sponsor was informed of: • date/time & meeting location • expected FDA attendees • meeting briefing package due date • number of copies	☐Yes X No XYes ☐ No ☐Yes (date:_____) X No ☐Yes X No ☐ Other: please indicate _____
Project Manager	Matt Sullivan

Any follow-up letter must be checked into DFS as an advice letter, **NOT as a meeting request granted letter.

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/s/

Matthew Sullivan
9/27/2006 09:35:46 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-856

9/8/06

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

Attention: Binita Kwankin
Assistant Director, Regulatory Affairs

Dear Ms. Kwankin:

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

Attached are the Division's comments on your Phase 3 clinical trial outline for our upcoming teleconference, scheduled for September 11, 2006. We have also reviewed your June 14, 2006 submission which contained a proposal for a Phase 4 study.

The previously agreed upon time is still set aside to meet with you, but, if you would like to either cancel the meeting, because you feel all your questions have been answered to your satisfaction, or re-focus the meeting (i.e., only focus on items which you feel require additional clarification), that would be acceptable to the Division as well. If you decide to change the format of the meeting, please contact us promptly by phone or e-mail.

We will be happy to provide clarification on any of the Division's responses, but **WILL NOT entertain any NEW questions, topics or review additional data** (there is simply not enough time prior to the meeting for the team to review such materials). Please let me know if you would like to change anything about our forthcoming meeting.

If you have any questions, please call me at 301-796-1298.

Sincerely,

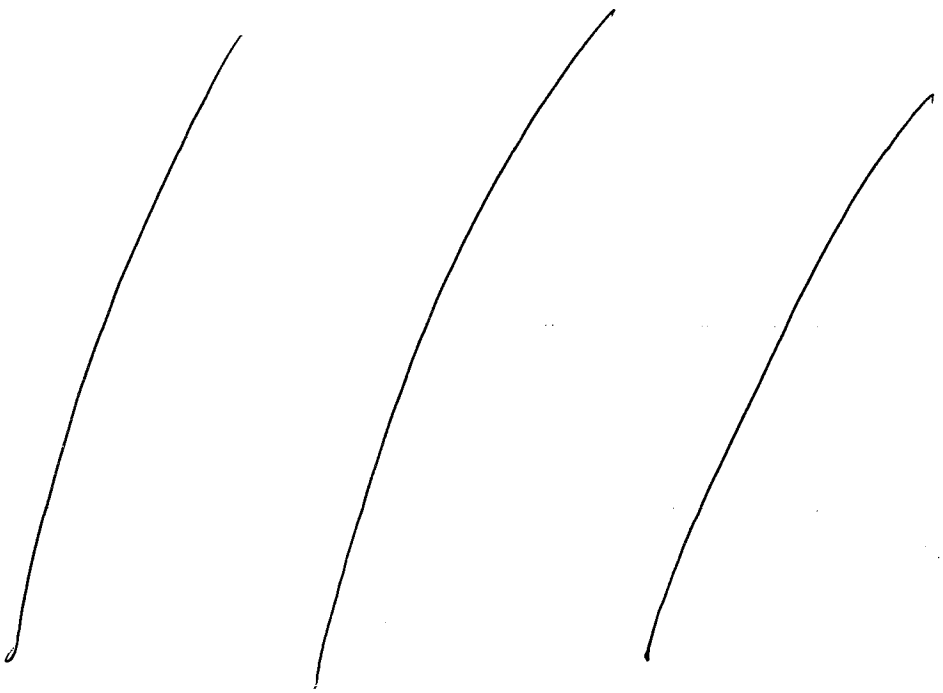
[See appended electronic signature page]

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

We have reviewed the one page summary you submitted of a new proposed Phase 3 protocol (refer to Attachment A). This protocol is a randomized, multicenter, allopurinol-controlled study to assess the efficacy and safety of febuxostat at doses of 40 and 80 mg versus allopurinol 200 or 300 mg, depending upon renal function. We have also reviewed the submission of June 14, 2006 which contained a proposal for a Phase 4 study.

The design of the Phase 3 protocol could provide some very useful data in helping to address our concerns. The protocol proposes to study a lower dose, 40 mg, that may demonstrate efficacy and possibly demonstrate more favorable safety (comparable to or better than allopurinol), and the study would include a significant number of renally impaired patients. If the study demonstrates efficacy of the 40 mg dose and no relative safety concerns are identified with the 40 mg dose, the results could, in principle, support an approval for the 40 mg dose. However, unless this study were to show that the 80 mg trended better than allopurinol, it is not clear it would necessarily provide sufficient assurance to approve the 80 mg dose, since the study is not sized to prove cardiovascular safety relative to allopurinol (that is, it is not formally testing a non-inferiority on safety to allopurinol). Therefore, you can consider the following options:

a. You could conduct the proposed 6-month Phase 3 study of 40 and 80 mg. Depending on the study results it could provide data to support approval of the 40 mg dose and, somewhat less likely, the 80 mg dose.



b(4)

Attachment A [Phase 3 Study Outline Submitted by Email on August 30, 2006]

Title: A phase 3, randomized, multicenter, allopurinol-controlled study assessing the efficacy and safety of febuxostat in patients with gout.

Objective: To assess the efficacy and safety of febuxostat compared to allopurinol in patients with gout.

Inclusion and exclusion criteria: Similar to the Phase 3 pivotal studies; allopurinol doses stratified by renal function. Subjects who participated in one of the previous febuxostat studies can be enrolled, washout period is 30 days.

Treatments:
At baseline, 2000 subjects will be randomized to one of 3 fixed-dose treatment groups in a 1:1:2 ratio:

1. Febuxostat 40 mg QD
2. Febuxostat 80 mg QD
3. Allopurinol (200 mg QD for subjects with mild-moderate renal impairment and 300 mg QD for subjects with normal renal function)

Subjects will be stratified by renal impairement (mild to moderate or normal) such that a total of 50% of subjects will have mild to moderate renal impairement.

Total treatment duration is 6 months.

All subjects will receive prophylactic treatment with colchicine 0.6 mg BID[1]. Alternatively, in case colchicine is not tolerated by a subject, subjects will receive naproxen 250 mg BID / lansoprazole 15 mg QD.

Efficacy: Primary endpoint will be the proportion of subjects with serum urate level <6 mg/dL at the Final Visit.

Safety: Safety evaluations: adverse events including cardiovascular adverse events such as APTC events, physical exam, laboratory evaluation and vital signs. An adjudication committee consistent of 3 cardiologists will adjudicate each cardiovascular adverse event.
The primary treatment comparison for the safety endpoint of primary APTC will be comparing the febuxostat total (40 mg QD and 80 mg QD groups combined) and the allopurinol group. Assuming the incidence rate for primary APTC events is 0.8% for both the febuxostat combined groups and allopurinol group, the sample size of 1000 subjects per group for this comparison will provide a 95% probability to expect that the observed relative risk in this study is within 0.377 and 2.654.

References
1. **Borstad GC, et al. Colchicine for Prophylaxis of Acute Flares When Initiating Allopurinol for Chronic Gouty Arthritis. J Rheumatology. 31:2429-32, 2004.**

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/s/

Sara Stradley
9/8/2006 01:50:55 PM
CSO

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Complete the information below and check form into DFS.

Application Type	☐ P-IND ☐ IND X NDA
Application Number	21 856
DATE Meeting Granted	August 7, 2006
Sponsor was informed of: • date/time & meeting location • expected FDA attendees • meeting briefing package due date • number of copies	X Yes ☐ No X Yes ☐ No ☐ Yes (date:_____) X No X Yes ☐ No ☐ Other: please indicate Sponsor informed this would be an informal telcon only. Meeting was informally granted on Aug 3, 2006 over the phone. Sponsor's request was received Aug 7, 2006.
Project Manager	Matt Sullivan

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/s/

Matthew Sullivan
8/24/2006 03:39:01 PM

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Monday, July 10, 2006 3:41 PM
To: 'binita.kwankin@tap.com'
Subject: febuxostat information request

7/10/06
IR

Hi Binita –

I have another information request:

Please clarify the discrepancies in the numbers for events in tables 3.6e and 3.6g. For example, the numbers in the "overall" category do not appear to match the numbers of individual events if you add up all events.

Obviously, we're starting to run short on time, so please let me when you'll be able to address this.

Thanks
matt

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/s/

Matthew Sullivan
7/17/2006 05:13:51 PM
CSO

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Wednesday, May 17, 2006 12:04 PM
To: 'binita.kwankin@tap.com'
Subject: Information Request NDA 21-856

5/17/06
IR

Binita –

Here is the information request that I mentioned in my voicemail this morning.

Thanks for your attention to this matter.

Matt

1. In your response to the Division's information request dated April 11, 2006, you submitted tables 3.1.1 (List of Investigator Reported Primary APTC Events) and 3.2.1 (List of Adjudicated APTC Events). Comparing the 2 lists, patients #4167 and 4249 appear on the Investigator list but not on the Adjudicated list. However, Dr. White does not list these patients in Table 2 of his review. Please explain this discrepancy.

2. Our estimate is that there are total of 10 CV deaths in combined Phase 3 and long-term extension studies as of February 8, 2006. However, Table 4.0a of the Supplement to the Safety Update lists only 9 CV deaths. Please clarify this discrepancy.

3. Please let us know whether there were more deaths or APTC/other serious adverse events in ongoing studies since the cut-of date of February 08, 2006

4. In your response to previous FDA request you stated that "since there is no MedDRA term of ischemic stroke, subject numbers are provided based on the MedDRA terms that were classified as non-fatal stroke in the February 2006 Safety Update: brain stem infarction, cerebral haemorrhage, cerebrovascular accident, and lacunar infarction". Table 3.8.2 (among other tables) of ISS contains a preferred term ISCHAEMIC STROKE under HLT central nervous system haemorrhages and cerebrovascular accidents under SOC Nervous System Disorders. This particular table, in addition to cerebrovascular accidents, lists one case of an ischaemic stroke in Febuxostat 120 mg group. Please provide an identifying number for that patient, the result of your adjudication and help us locate his narrative.

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Tuesday, April 11, 2006 10:28 AM
To: 'binita.kwankin@tap.com'
Subject: Information request/ N21856

4/11/06
IR

Binita –

Please find attached five items to be addressed with regard to NDA 21-856.

1. Provide a Kaplan-Meier analysis of cardiovascular events defined as meeting Anti-Platelet Trialists Collaboration (APTC) criteria for the safety database included with your February 17, 2006 submission. You should graph investigator-reported and adjudicated events separately.

2. Provide patient-years of exposure for tables 2.3.c and 2.3.l.

3. Provide the case number for each patient included in the categories "overall" and "CV deaths" in tables 2.3.c, 2.3.e, 2.3.l and 2.3.p. This listing should be provided separately for investigator-reported and adjudicated events.

4. Provide adjudication for case number 4665.

5. Provide the case number for each case of ischemic stroke, pulmonary embolism and deep venous thrombosis.

As always, please provide an advance electronic copy directly to me in addition to your official regulatory submission.

Please let me know if you have any questions.

Thanks
Matt

PS Since we haven't communicated via email previously, please confirm receipt of this email.

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
Bldg 22 Rm 3167
10903 New Hampshire Ave
Silver Spring MD 20903-0002

Phone 301-796-1245
Fax 301-796-9722 / 9723

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/s/

Matthew Sullivan
7/7/2006 03:29:09 PM
CSO