DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-856

NDA APPROVAL

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 (FDCA) for Uloric (febuxostat tablets), 40 mg and 80 mg.

We acknowledge receipt of your submissions dated July 17, August 6, September 3 and 25, October 17, 24, and 27, and December 8, 2008, and January 14, 22, and 28, and February 6 and 9, 2009.

The July 17, 2008, submission constituted a complete response to our August 2, 2006, action letter.

This new drug application provides for the use of Uloric in the chronic management of hyperuricemia in patients with gout.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-856."

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your January 22 and 28, 2008, submissions containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable. The approved indication for febuxostat is the management of hyperuricemia in patients with gout, which is extremely rare in individuals below 18 years of age.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) also amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)). This provision took effect on March 25, 2008.

Clinical trials of Uloric identified a possible signal of serious cardiovascular outcomes, with a higher rate of serious cardiovascular outcomes, including cardiac deaths, myocardial infarctions, and strokes, in patients treated with Uloric than in the control group.

We have also determined that it is necessary to evaluate the effect of Uloric on the medication theophylline, a narrow therapeutic index drug, to determine whether it is safe to co-administer these two drugs. Since Uloric is a xanthine oxidase inhibitor and theophylline is a xanthine oxidase substrate, co-administration of Uloric with theophylline may result in elevated theophylline exposure and associated serious adverse events.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of serious risk of cardiovascular outcomes in patients treated with Uloric or to identify the a serious risk of a drug-drug interaction between Uloric and theophylline.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established and is therefore not sufficient to assess these serious risks.

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trials. Your February 6, 2009, submission provided the timetables.

1. A randomized, controlled trial of adequate size and duration to determine whether the use of Uloric is associated with a moderate increase in the risk of serious adverse cardiovascular outcomes as compared to allopurinol.

Final Protocol Submission Date:	August 31, 2009
Trial Start Date:	January 31, 2010
Trial Completion Date:	January 31, 2014
Final Report Submission:	January 31, 2015

2. A drug-drug interaction trial to evaluate the effect of Uloric on the pharmacokinetics of a single, oral dose of theophylline.

Final Protocol Submission Date:	April 30, 2009
Trial Start Date:	June 30, 2009
Trial Completion Date:	July 31, 2009
Final Report Submission:	May 31, 2010

Submit the protocols to IND 58,229, with a cross-reference letter to NDA 21-856. Submit all final reports to your NDA. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

OTHER

We also remind you of your December 8, 2008, agreement to submit a CMC Prior Approval Supplement adding **(b) (4)** as the supplier of future drug substance within two months of the date of this letter.

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

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure
Content of Labeling dated February 9, 2009
Carton and Container Labeling dated January 22 and 28, 2009

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

/s/

Curtis Rosebraugh

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