

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**NDA 21-856**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

1/29/09



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: January 27, 2009

To: Bob Rappaport, M.D., Director  
**Division of Analgesics, Anesthetics and Rheumatology  
Products**

Through: Jodi Duckhorn, MA, Team Leader  
**Patient Labeling and Education Team  
Division of Risk Management**

From: LaShawn Griffiths, MSIS-PH, BSN, RN  
Patient Product Information Reviewer  
**Patient Labeling and Education Team  
Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Uloric (febuxostat)

Application Type/Number: NDA 21-856

Applicant/sponsor: Takeda Pharmaceuticals North America, Inc.

OSE RCM #: 2008-2031

## 1 INTRODUCTION

TAP Pharmaceuticals Products Inc. submitted a New Drug Application (NDA 21-856) for Uloric tablet (febuxostat) on December 14, 2004. An Approval Letter was sent to TAP Pharmaceutical Products, Inc. on August 2, 2006. The sponsor submitted the Prescribing Information which had been converted to PLR format on July 2, 2008. On July 17, 2008 Takeda Pharmaceuticals North America, Inc. submitted an amendment notifying the FDA of the merger of TAP Pharmaceutical Products, Inc. into the Takeda corporate entity.

The Division of Analgesics, Anesthetics and Rheumatology Products (DAARP) requested that the Division of Risk Management's Patient Labeling and Education Team review the proposed Patient Package Insert (PPI) for this product. This review was written in response to that request.

## 2 MATERIAL REVIEWED

- Draft Uloric (febuxostat) Prescribing Information (PI) submitted July 2, 2008 and revised by the Review Division throughout the current review cycle.
- Draft Uloric (febuxostat) Patient Package Insert (PPI) submitted July 2, 2008 and revised by the Review Division throughout the current review cycle.

## 3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 7.7, and a Flesch Reading Ease score of 59.6%. To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8<sup>th</sup> grade reading level). The reading scores as submitted by the sponsor are acceptable.

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible,
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI.

We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

#### 4 CONCLUSIONS AND RECOMMENDATIONS

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Please let us know if you have any questions.

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\_\_\_\_\_ Draft Labeling (b4)

\_\_\_\_\_ Draft Labeling (b5)

\_\_\_\_\_ Deliberative Process (b5)

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LaShawn Griffiths  
1/29/2009 11:40:29 AM  
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn  
1/29/2009 11:42:12 AM  
DRUG SAFETY OFFICE REVIEWER

12/23/08



Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology

**Date:** December 23, 2008

**To:** Bob Rappaport, M.D., Director  
Division of Analgesics, Anesthetics, and Rheumatology  
Products (DAARP)

**Through:** Claudia Karwoski, Pharm.D., Director (Acting)  
Division of Risk Management (DRISK)

**From:** OSE Febuxostat Risk Management Team

**Scientific Lead:**  
LCDR Kendra Worthy, Pharm.D., Drug Risk Management  
Analyst (DRISK)

**Team Members:**  
Suzanne Berkman, Pharm.D., Senior Drug Risk Management  
Analyst (Acting) Team Leader (DRISK)  
Mary Dempsey, Risk Management Program Coordinator  
(DRISK)  
Christopher Wheeler, Pharm.D., Regulatory Project Manager  
(OSE)

**Subject:** 3<sup>rd</sup> Cycle Review Risk Management Update

**Drug Name(s):** Uloric<sup>®</sup> (Febuxostat)

**Application  
Type/Number:** NDA 21-856

**Applicant/sponsor:** Takeda Pharmaceuticals

**OSE RCM #:** 2008-1486

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## 1 INTRODUCTION

This review follows the inclusion of the Office of Surveillance and Epidemiology (OSE) in team meetings with the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) regarding the 3<sup>rd</sup> review cycle of Febuxostat (Uloric<sup>®</sup>), NDA 21-856. Although the Division of Risk Management (DRISK) was not formally consulted by DAARP, we are providing comments, as the sponsor did submit a proposed risk management plan with this review cycle.

Febuxostat is a non-purine selective inhibitor of xanthine oxidase with the proposed indication for the treatment of hyperuricemia in patients with gout. It is supplied as a 40 mg and 80 mg tablet. The proposed dosing regimen is 40 mg or 80 mg once daily.

Febuxostat 80mg and 120 mg tablets were approved as Adenuric<sup>™</sup> in the European Union on April 21, 2008.

## 2 MATERIALS REVIEWED

The following materials were reviewed:

- Medical Officer Clinical Efficacy Review, Uloric (Febuxostat) NDA 21-856. Joel Schiffenbauer, M.D., Division of Anesthesia, Analgesia, and Rheumatology Products. Dated December 15, 2004.
- Medical Officer Clinical Safety Review, Uloric (Febuxostat) NDA 21-856. Tatiana Oussova, M.D., Division of Anesthesia, Analgesia, and Rheumatology Products. Dated December 15, 2004.
- Division Director Summary Review and Basis for Approvable Action. Bob Rappaport, M.D., Director, Division of Anesthesia, Analgesia, and Rheumatology Products. Dated October 14, 2005.
- Cover Letter, Resubmission: Complete Response to Deficiencies Identified in the Action Letter, submitted by TAP Pharmaceuticals, February 17, 2006.
- Medical Officer Clinical Efficacy Review (second cycle), Uloric (Febuxostat) NDA 21-856. Joel Schiffenbauer, M.D., Division of Anesthesia, Analgesia, and Rheumatology Products. Dated July 3, 2006.
- Medical Officer Clinical Safety Review (second cycle), Uloric (Febuxostat) NDA 21-856. Tatiana Oussova, M.D., Division of Anesthesia, Analgesia, and Rheumatology Products. Dated July 17, 2006.
- Office of Surveillance and Epidemiology Review of Proposed Risk Minimization Action Plan (RiskMAP) from TAP Pharmaceutical Products, Inc., by Joyce Weaver, Pharm.D., Office of Surveillance and Epidemiology. Dated July 20, 2006.
- Approvable Letter. Robert Meyer, M.D., Director, Office of Drug Evaluation II. Dated August 2, 2006.
- Cardiovascular Events with Febuxostat, NDA 21-856, Thomas Marciniak, M.D., Medical Team Leader, Division of Cardiovascular and Renal Products. Dated October 14, 2008.
- Proposed Uloric package insert by Takeda Pharmaceuticals. Submitted July 17, 2008.
- Proposed Risk Management Plan submitted for Uloric (febuxostat), NDA 21-856, submitted July 17, 2008, by Takeda Pharmaceuticals.

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*risk. The risks identified by the sponsor, a potential interaction associated with co-administration with azathioprine, mercaptopurine, and theophylline, could be managed routinely through product labeling.*

*...Because the MO has found that the risk-benefit profile of this drug is unfavorable, these [cardiovascular] risks are not appropriate for management with a RiskMAP. RiskMAPs are not intended to provide a pathway to market products with an unfavorable risk/benefit profile for the products' labeled indications under labeled conditions of use; rather, RiskMAPs provide a strategy to minimize risks of a product while preserving product benefits for products with favorable risk/benefit profiles.<sup>6</sup>*

The Agency issued an Approvable letter on August 2, 2006 that requested the sponsor to “provide further data to clarify the cardiovascular risks of the proposed doses and/or provide data on the safety and efficacy of lower doses of febuxostat in order to assure that a dose level(s) with favorable risk-benefit characteristics has been defined.”<sup>7</sup>

On July 17, 2008, another complete response was submitted by Takeda Pharmaceuticals, as TAP Pharmaceuticals was merged into Takeda.

## **4 RESULTS OF REVIEW**

### **4.1 CARDIOVASCULAR SAFETY CONCERN**

In the sponsor's third cycle submission, they submitted the results of an additional randomized clinical trial (F-153) to address the cardiovascular risk and to evaluate the efficacy and safety of febuxostat 40 mg and 80 mg daily in comparison with allopurinol in subjects with hyperuricemia and gout. This trial enrolled approximately 3 times the number of subjects than the previous trials. The study showed efficacy of febuxostat at both the 40 mg and 80 mg dose, and examination of the cardiovascular events in the study did not show a higher rate of events with febuxostat compared with allopurinol. Also, the overall mortality rate and cardiovascular mortality rate were not increased.<sup>8</sup> This conclusion was substantiated with a consultation from the Division of Cardiovascular and Renal Products.

The FDA Arthritis Advisory Committee met on November 24, 2008 to discuss this application for the proposed treatment of hyperuricemia in patients with gout. The committee voted 12-0, with 1 abstention to recommend approval of febuxostat for the treatment of chronic gout. The committee members also agreed that further studies should be conducted post-approval to further assess the safety of febuxostat.<sup>9</sup>

### **4.2 OTHER SAFETY CONCERNS<sup>10</sup>**

The proposed labeling has a contraindication in patients being treated with azathioprine, mercaptopurine, or theophylline. Concomitant administration of allopurinol, another xanthine oxidase inhibitor, with azathioprine, mercaptopurine, or theophylline has been reported to

<sup>6</sup> Office of Surveillance and Epidemiology Review of Proposed Risk Minimization Action Plan (RiskMAP) from TAP Pharmaceutical Products, Inc., by Joyce Weaver, Pharm.D., Office of Surveillance and Epidemiology. Dated July 20, 2006.

<sup>7</sup> Approvable Letter. Robert Meyer, M.D., Director, Office of Drug Evaluation II. Dated August 2, 2006.

<sup>8</sup> Background Materials for FDA Arthritis Advisory Committee Meeting, November 24, 2008.

<sup>9</sup> Summary Minutes of FDA Arthritis Advisory Committee, November 24, 2008.

<sup>10</sup> Proposed Uloric package insert by Takeda Pharmaceuticals. Submitted July 17, 2008.

substantially increase plasma concentrations of these drugs. Increased plasma concentrations of azathioprine, mercaptopurine, or theophylline could result in severe toxicity. Drug interaction studies have not been conducted with febuxostat.

The following are listed in the Warnings and Precautions section of the proposed labeling:

- **Gout Flare:**

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- **Cardiovascular Events:**

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- **Liver Enzyme Elevations:**

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#### **4.3 SPONSOR'S CURRENT RISK MANAGEMENT PROPOSAL**

Takeda's proposed risk management plan for febuxostat focuses on the potential risks of cardiovascular effects, elevation of liver function enzyme(s), and drug-drug interactions with theophylline, azathioprine, and mercaptopurine. They propose to manage these potential risks with routine labeling and pharmacovigilance. The sponsor states that safety information is collected and communicated globally, and that Periodic Safety Update Reports that also contain a review of the Risk Management Plan will be submitted at designated reporting intervals.

#### **5 DISCUSSION AND CONCLUSION**

The Sponsor has proposed routine labeling and routine pharmacovigilance to address the risks associated with febuxostat, which also include cardiovascular effects and elevation of liver function enzyme(s). According to the previous OSE review of the proposed risk minimization plan, both DAARP and OSE believe that routine pharmacovigilance and product labeling are appropriate measures to mitigate drug-drug interactions with theophylline, azathioprine, and mercaptopurine. Based on the risks (particularly the cardiovascular data) reviewed and presented at the Advisory Committee meeting, DRISK believes that this approach is reasonable at this time and is consistent with the management of other xanthine oxidase inhibitors. Additional strategies such as a Medication Guide, Communication Plan, and/or Elements to Assure Safe Use do not appear to be warranted to minimize any of the risks described. Should DAARP raise further concerns with the risks outlined above or identify additional risks associated with febuxostat warranting more extensive risk mitigation or a formal risk evaluation and mitigation strategy (REMS), please send a consult to OSE Division of Risk Management.

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Mary Dempsey  
12/23/2008 08:14:27 AM  
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski  
12/23/2008 08:16:19 AM  
DRUG SAFETY OFFICE REVIEWER

7/20/06



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

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**DATE:** July 20, 2006

**TO:** Bob Rappaport, M.D., Director  
Division of Analgesics, Anesthetics, & Rheumatology Products, HFD 170

**FROM:** Joyce Weaver, Pharm.D.,  
Senior Drug Risk Management Analyst  
Office of Surveillance and Epidemiology, HFD-400

**DRUG:** Uloric (Febuxostat)

**NDA:** 21-856

**SPONSOR:** TAP Pharmaceutical Products, Inc.

**SUBJECT:** OSE Review of Proposed Risk Minimization Action Plan (RiskMAP)  
submitted February 17, 2006

**PID #:** D060533

**Summary**

Uloric (febuxostat) is a non-purine selective inhibitor of xanthine oxidase with a proposed indication for the management of hyperuricemia in patients with gout. The Sponsor submitted an application for Uloric 12/14/2004. An approvable (AE) action was taken on 10/14/2005 pending additional information on cardiovascular safety, the potential for hemorrhagic events, the potential for drug-drug interactions with commonly co-administered products, and the dissolution of tablets under some conditions.<sup>1</sup> The Sponsor submitted a complete response to the AE letter on 2/21/2006, with a user fee goal date of 8/21/2006.

A risk minimization action plan (RiskMAP) was submitted by the Sponsor to mitigate the potential risk associated with co-administration of febuxostat with azathioprine, mercaptopurine, and theophylline. The Sponsor propose: \_\_\_\_\_

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<sup>1</sup> Approvable letter NDA 21-856, 10/14/2005. Available in DFS.

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The reviewing Medical Officer (MO) in the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) has proposed an approvable action pending resolution of unresolved safety issues with the product, especially cardiovascular safety.

DAARP has communicated to OSE that they believe that the potential risk of concomitant administration with interacting drugs would be appropriately managed with a contraindication for concomitant use in the product labeling. We agree with DAARP that a RiskMAP would not be needed to manage this risk. The risks identified by the Sponsor, a *potential* interaction associated with co-administration with azathioprine, mercaptopurine, and theophylline, could be managed routinely through product labeling.

The MO has identified a number of safety risks that suggest an unfavorable risk/ benefit profile. Because the MO has found that the risk-benefit profile of this drug is unfavorable, these risks are not appropriate for management with a RiskMAP. RiskMAPs are not intended to provide a pathway to market products with an unfavorable risk/benefit profile for the products' labeled indications under labeled conditions of use; rather, RiskMAPs provide a strategy to minimize risks of a product while preserving product benefits for products with favorable risk/ benefit profiles.

### Safety Risks

The Sponsor identified co-administration of febuxostat with azathioprine, mercaptopurine, or theophylline with the resultant potential for increased serum levels of these drugs as the risk to be mitigated with a RiskMAP. The Sponsor has not studied this interaction in clinical trials, but the interaction is expected based on the mechanism of action of xanthine oxidase inhibition.

Regarding other safety risks, DAARP raised a concern in the first cycle for this application about the occurrence of hemorrhage with concomitant use of warfarin. In clinical testing, two patients died of retroperitoneal hemorrhage while being treated concomitantly with febuxostat and warfarin. The data that were submitted in the first cycle to study the interaction of warfarin and febuxostat did not allay the reviewer's concern, although the conduct of the study made interpretation difficult. Additionally, the most compelling safety risk identified in the first cycle was a higher incidence of cardiovascular thromboembolic events with febuxostat. Dr Sharon Hertz noted a higher incidence of combined myocardial infarction, cerebral vascular accident, and cardiac arrest in febuxostat-treated patients.<sup>2</sup>

The reviewing MO in DAARP for the resubmission noted that the febuxostat safety issues

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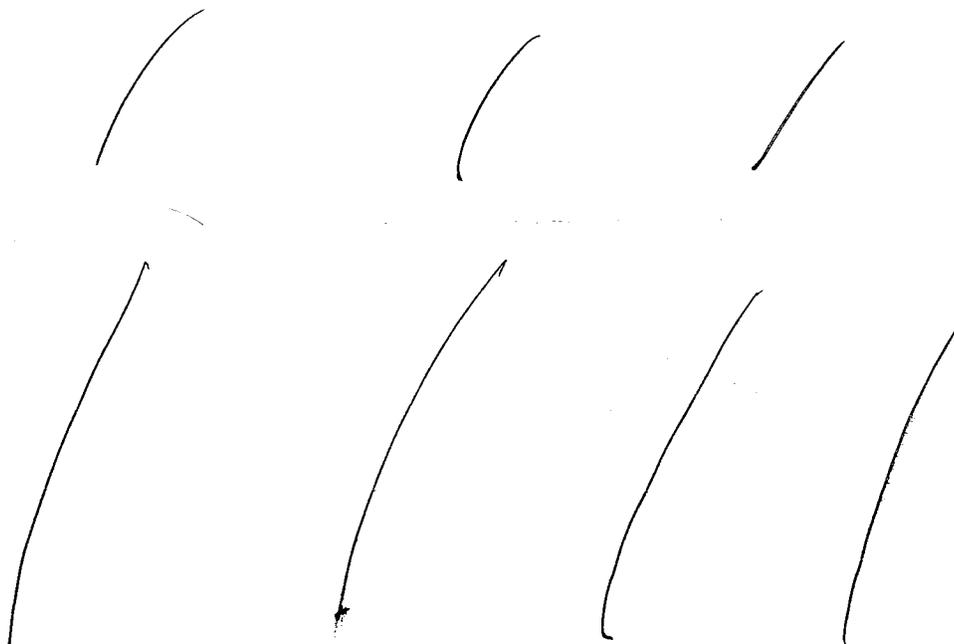
<sup>2</sup> Summarized in *Division Director Summary Review and Basis for Approvable Action*, 10/14/2005; available in DFS.

have not been resolved.<sup>3</sup> He noted increased mortality with febuxostat, and an increased incidence of cardiovascular thromboembolic events, congestive heart failure, and cardiac arrhythmias in the febuxostat-treated patients compared with the patients in the placebo group and/or in the allopurinol-treated patients. In addition to concerns about cardiovascular safety, the MO noted apparent increased incidence of pneumonia, skin adverse events, and liver toxicity in the febuxostat-treated patients. The MO's review states,

In summary, the totality of the safety profile for febuxostat is of concern. The overall mortality rate for febuxostat is higher than for allopurinol, even though there is no single cause of death that appears to stand out. Two cases of retroperitoneal hemorrhage in a data base of this size, is also disturbing (most likely related to changes in INR in patients on warfarin). Furthermore, in the context of the higher rate of CV related SAEs in the febuxostat group, the 2 deaths related to MIs are of greater concern. In addition to CV thromboembolic issues, there is an increase in SVT, and a higher rate of discontinuations due to skin and liver related events, some of which were labeled as severe, in the febuxostat group.

Therefore, based on the above assessments, the risk/benefit analysis is not favorable for this drug at this time.

#### Proposed RiskMAP



<sup>3</sup> *Febuxostat/complete response Clinical Review*; 7/17/2006; available in DFS.

<sup>4</sup> *Risk Management Assessment for Febuxostat*; TAP Pharmaceuticals; submitted 2/17/2006; available in EDR.

<sup>5</sup> The Sponsor did not explain how adverse events and outcomes would be ascertained.

**OSE Evaluation**

The Sponsor's proposed RiskMAP



We agree with DAARP that the risk of concomitant administration with these potentially interacting drugs could be managed routinely through product labeling.

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Because the MO has found that the risk-benefit profile of this drug is unfavorable, these risks are not appropriate for management with a RiskMAP. RiskMAPs are not intended to provide a pathway to market products with an unfavorable risk/benefit profile for the products' labeled indications under labeled conditions of use; rather, RiskMAPs provide a strategy to minimize risks of a product while preserving product benefits for products with favorable risk/ benefit profiles.

Should the reviewing division want OSE to review a future RiskMAP submission please send a consult to OSE and notify the OSE-IO Project Manager, Mary Dempsey, at 301-796-0147.

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Joyce Weaver  
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DRUG SAFETY OFFICE REVIEWER

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**MEMORANDUM**

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

**DATE:** April 7, 2005

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

**VIA:** Jane Dean, R.N., M.S.N., Regulatory Health Project Manager  
Division of Anti-Inflammatory, Analgesic, and Ophthalmologic  
Drug Products, HFD-550

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Gerald Dal Pan, M.D., M.H.S., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

**SUBJECT:** DSRCs Review of Patient Labeling for Uloric (feboxostat)  
Tablets, NDA 21-856

**Background and Summary**

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Uloric (feboxostat) Tablets, NDA 21-856. We have simplified the wording, made it consistent with the PI, removed other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on draft labeling submitted by the sponsor on December 14, 2004. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

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We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

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Jeanine Best  
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DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
4/7/05 03:59:29 PM  
DRUG SAFETY OFFICE REVIEWER  
for Gerald Dal Pan

5/23/05

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> April 5, 2005	<b>DESIRED COMPLETION DATE:</b> May 31, 2005	<b>ODS CONSULT #:</b> 04-0118-2
<b>DATE OF DOCUMENT:</b> March 30, 2005	<b>PDUFA DATE:</b> October 15, 2005	
<b>TO:</b> Bob Rappaport, MD Division of Anesthesia, Analgesia, and Rheumatology Products HFD-170		
<b>THROUGH:</b> Jane Dean Project Manager HFD-170		
<b>PRODUCT NAME:</b>  Uloric (Febuxostat Tablets) 80 mg and 120 mg  NDA# 21-856	<b>NDA SPONSOR:</b> Tap Pharmaceuticals	
<b>SAFETY EVALUATOR:</b> Linda M. Wisniewski, RN		
<b>COMMENDATIONS:</b>  DMETS recommends implementation of the label and labeling revisions outlined in section II of this review in order to minimize user error.		
Denise Toyer, PharmD Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242	Carol Holquist, RPh Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664	

Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

**DATE OF REVIEW:** May 13, 2005  
**NDA#** 21-856  
**NAME OF DRUG:** Uloric (Febuxostat Tablets)  
80 mg and 120 mg  
**NDA HOLDER:** Tap Pharmaceuticals

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550), for assessment of the proposed labels and labeling for Uloric, which can be found in the electronic document room, dated March 31, 2005. Draft container labels and carton labeling were provided for review and comment. Please note the proposed name Uloric was found acceptable by DMETS on February 25, 2005.

PRODUCT INFORMATION

Uloric is a non-purine, selective inhibitor of xanthine oxidase/dehydrogenase. The proposed indication of use is for the management of hyperuricemia in patients with gout. Uloric will be dosed as 80 mg or 120 mg taken orally as a single dose, once daily, in order to maintain serum uric acid below 6 mg/dL. Doses can be given without regard to timing of meals. In order to reduce the possibility of an acute gout attack, it is recommended that febuxostat therapy begin with a concomitant low dose of either a non-steroidal anti-inflammatory drug (NSAID) or colchicine. It is supplied in 80 mg and 120 mg tablets, each packaged in bottles of 30 tablets, 100 tablets, 1000 tablets, and institutional unit-dose blisters.

**II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES**

In the review of the container labels, carton and insert labeling of Uloric, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

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       Draft Labeling (b5)

       Deliberative Process (b5)

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**III. DMETS RECOMMENDATIONS:**

DMETS recommends implementation of the label and labeling revisions outlined in section II of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-827-1998.

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Linda M. Wisniewski, RN  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

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Linda Wisniewski  
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Denise Toyer  
5/23/05 11:59:15 AM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
5/23/05 04:12:56 PM  
DRUG SAFETY OFFICE REVIEWER

3/22/05

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> January 28, 2005	<b>DESIRED COMPLETION DATE:</b> March 31, 2005	<b>ODS CONSULT #:</b> 04-0118-1
<b>TO:</b> Brian Harvey, MD, PhD. Acting Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products HFD-550		
<b>THROUGH:</b> Jane Dean Project Manager HFD-550		
<b>PRODUCT NAME:</b>  Uloric (Febuxostat Tablets) 80 mg and 120 mg  NDA# 21-856	<b>NDA SPONSOR:</b> Tap Pharmaceuticals	
<b>SAFETY EVALUATOR:</b> Linda M. Wisniewski, RN		
<b>RECOMMENDATIONS:</b>  ETS recommends implementation of the label and labeling revisions outlined in section II of this review in order to minimize user error.		
Denise Toyer, PharmD Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242	Carol Holquist, RPh Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664	

**Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research**

**LABEL AND LABELING REVIEW**

**DATE OF REVIEW:** February 1, 2005  
**NDA#** 21-856  
**NAME OF DRUG:** **Uloric** (Febuxostat Tablets)  
80 mg and 120 mg  
**NDA HOLDER:** Tap Pharmaceuticals

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Anti-inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550), for assessment of the proposed labels and labeling for Uloric. Draft container labels, carton and insert labeling were provided for review and comment. Please note the proposed name Uloric was found acceptable by DMETS on February 25, 2005.

**PRODUCT INFORMATION**

Uloric is a non-purine, selective inhibitor of xanthine oxidase/dehydrogenase. The proposed indication of use is for the management of hyperuricemia in patients with gout. Uloric will be dosed as 80 mg or 120 mg taken orally as a single dose, once daily, in order to maintain serum uric acid below 6 mg/dL. Doses can be given without regard to timing of meals. In order to reduce the possibility of an acute gout attack, it is recommended that febuxostat therapy begin with a concomitant low dose of either a non-steroidal anti-inflammatory drug (NSAID) or colchicine. It is supplied in 80 mg tablets, each packaged in bottles of 30 tablets, 100 tablets, 1000 tablets, and institutional unit-dose blisters.

b(4)

**II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES**

In the review of the container labels, carton and insert labeling of Uloric, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

**A. GENERAL COMMENT**

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       Trade Secret / Confidential (b4)

  /   Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

### III. DMETS RECOMMENDATIONS:

DMETS recommends implementation of the label and labeling revisions outlined in section II of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

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Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

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/s/

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