CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-856

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	February 13, 2009
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
NDA#	21-856
Applicant Name	Takeda Pharmaceuticals North America, Inc
Date of Submission	July 17, 2008
PDUFA Goal Date	January 18, 2009
Proprietary Name / Established (USAN) Name	Uloric febuxostat
Dosage Forms / Strength	Immediate-release tablets, 40 mg and 80 mg
Proposed Indication	For the management of hyperuricemia in patients with gout
Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Jane L. Gilbert, M.D., Ph.D.
Statistical Review	Joan Buenconsejo, Ph.D.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	Asoke Mukherjee, Ph.D.; R. Daniel Mellon, Ph.D.
CMC Review	Olen M. Stephens, Ph.D.; Ali Al-Hakim, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Lei K. Zhang, Ph.D.; Suresh Doddapaneni, Ph.D.
DDMAC	Mathilda Fienkeng, Pharm.D; Michael Sauers
DSI	Susan Leibenhaut, M.D.; Constance Lewin, M.D.
CDTL Review	Jeffrey Siegel, M.D.
OSE/DMEPA	Walter Fava, Pharm.D.; Kellie Taylor, Pharm.D., M.P.H.; Carole Holquist, R.Ph.
OSE/DAEA	N/A
OSE/DRISK	LaShawn Griffiths, MSHS-PH, BSN, RN; Jodi Duckhorn, MA; Mary Dempsey; Claudia Karwoski, Pharm.D.
OSE/DEPI	N/A
SEALD	Jeanne M. Delasko, RN, MS; Laurie Burke, RPh, MPH

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DAEA=Division of Adverse Event Analysis
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology
SEALD=Study Endpoints and Label Development group

1. Introduction

Uloric is a xanthine oxidase inhibitor developed as an alternative to allopurinol in the treatment of gout. The proposed indication is for the management of hyperuricemia in patients with gout. This is the third cycle review of Uloric. This novel xanthine oxidase inhibitor received approvable letters on the last two review cycles based predominantly on a signal of cardiovascular toxicity which had not been adequately evaluated to allow for a complete risk-benefit assessment of the available doses of the proposed drug product. The history of the Agency's interactions with the sponsor regarding this application has been documented in my previous reviews dated October 14, 2005 and July 31, 2006. Those reviews are appended to this document as Appendix 1 and Appendix 2, respectively.

2. Background

The outstanding deficiencies cited in the initial approvable letter of October 14, 2005 were:

1. Due to the finding that exposure to Uloric appeared to increase the risk of cardiac thromboembolic events compared to placebo or allopurinol, the sponsor was asked to either provide further comparative controlled clinical safety data or to reanalyze the original database and demonstrate that the apparent signal of increased risk is not predictive of clinically important differences. Should a differential signal of cardiac thromboembolic events persist, the sponsor was encouraged to consider proposing the use of lower doses of Uloric.

2. Due to the potential for drug-drug interactions when co-administered with other commonly used drug products for which xanthine oxidase plays a role in metabolism, the sponsor was asked to perform drug-drug interaction studies with theophylline, azathioprine and mercaptopurine. It was noted, however, that should they choose to not perform these studies, co-administration of Uloric and these drugs would need to be contraindicated and risk minimization strategies might be needed to assure that concomitant use did not occur.

3. Due to the finding of hemorrhagic adverse events and elevated INRs in patients on Uloric and warfarin in the original database for the application, and questions concerning the reliability of the results of a pharmacokinetic study that specifically looked at warfarin interaction with Uloric, the sponsor was asked to further evaluate the potential for concomitant administration of warfarin and Uloric to result in hemorrhagic adverse events, and to further evaluate the potential for exposure to Uloric alone to result in these types of events.

4. Due to an absence of data to evaluate the induction potential of Uloric on human CYP P450 enzymes, the sponsor was asked to perform a study to provide this data either in vitro or in vivo.

5. Due to an inadequate methodology for the 80- and 120-mg strength tablets, the sponsor was asked to revise their dissolution testing and specific parameters were provided.

Items 2 through 5 were adequately addressed in the sponsor's complete response to this letter as described in Appendix 2. In regard to the cardiovascular safety concern, the sponsor submitted a reanalysis that included readjudication of adverse events by an expert consultant. The clinical team reviewed this reanalysis and also requested consultation by our own experts in the Division of Cardio-Renal Products (DCRP). As described in Appendix 2, the review team concluded that the sponsor's reanalysis was inadequate to address our concerns regarding the cardiovascular toxicity of Uloric.

The second approvable letter dated August 2, 2006, cited the following deficiency to be addressed prior to approval:

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

In addition, the letter requested that the sponsor conduct a new warfarin-febuxostat interaction study and reminded them of their commitment to perform a clinical study of Uloric's effect on the incidence of gout flares, a pharmacokinetic interaction study with theophylline and an in vitro assessment of the induction potential of febuxostat in primary human hepatocytes.

The sponsor submitted their complete response to the second approvable letter on July 17, 2008. This submission included documentation of the results of an additional clinical efficacy and safety study comparing doses of Uloric 40 mg and 80 mg with allopurinol 200/300 mg.

One additional concern that arose during the review of this second resubmission was the finding that, upon attempting to inspect the drug substance manufacturing plant, the plant had been closed and demolished. However, this problem has been resolved as discussed below in Section 3.

3. CMC

The only outstanding CMC issue addressed in the current submission was the discriminatory ability of the proposed dissolution method for the two strengths. The current submission revises the method and the acceptance criterion to conditions that can discriminate between the 40-mg and 80-mg tablets by changing the pH of the media used in the method. Dr. Stephens reviewed the new method validation and deemed it adequate. The CMC review team recommended approval on this cycle, but initially noted that this recommendation was pending adequate facilities inspections. As noted above the inspectors found the single drug substance manufacturing site to have been demolished upon arrival for inspection. However, although the original Abbot manufacturing site for the drug substance encompasses several buildings and the specific building used to manufacture drug substance batches for launch was demolished, Takeda is in agreement with Abbott, that they can perform drug substance manufacturing at the same establishment site in a different building. In addition, Takeda has reserves of GMP drug substance from the original site to launch the drug product to market, and plans to qualify an additional drug substance supplier post-approval. This arrangement was discussed with Office of Compliance which indicated that the site is acceptable based on profile. Based on this plan, the CMC team is now recommending approval.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical concerns were raised during this review cycle and the nonclinical pharmacology/toxicology review team has recommend approval.

5. Clinical Pharmacology/Biopharmaceutics

The sponsor submitted their new warfarin-febuxostat interaction study in this response. The review team evaluated that study and concurred with the sponsor that it demonstrated that there was no interaction of multiple 80-mg doses of febuxostat with warfarin. Additionally, an in vitro induction potential study performed in primary human hepatocytes demonstrated a low potential to induce the major isoforms of cytochrome P450.

As noted above, the sponsor has agreed to perform a post-marketing study of the interaction between febuxostat and theophylline. Until those results are available, the Uloric label will contain a contraindication for the concomitant use of theophylline.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

In the previous submissions to this application the sponsor provided adequate evidence to support the efficacy of doses of 80 and 120 mg of Uloric as treatments for gout. However, due to the cardiovascular signal seen in association with those doses, they were asked to provide additional data to support the safety of these doses and to consider evaluating the efficacy and safety of the lower, 40-mg dose. This submission does contain an additional study which evaluates the efficacy and safety of 40 and 80 mg of Uloric compared to 200/300 mg of allopurinol. Drs. Gilbert and Siegel have reviewed the details of this study and, therefore, I will briefly summarize the results.

Study F-GT06-153 (Study 153) was a six-month, randomized, double-blind, active-controlled trial that compared the efficacy of Uloric 40 mg and 80 mg to allopurinol 300 mg (200 mg in renal impairment) in patients with gout and hyperuricemia. Randomization was stratified by renal function with normal vs. mild/moderate renal impairment. The primary endpoint was the proportion of subjects with a serum uric acid of less than 6 mg/dL at the final study visit. The initial statistical evaluation compared Uloric 80 mg to allopurinol in a superiority design. A non-inferiority comparison was then employed to compare Uloric 40 mg to allopurinol. This comparison utilized a margin of 10% which had been determined would preserve at least 75% of the effect size of the active comparator. The clinical review team thought that this degree of effect would be clinically relevant.

The following is reproduced from pages 15 and 16 of Dr. Buenconsejo's review and summarizes the efficacy findings for Uloric:

In all Phase 3 studies (Applicant's results), the proportions of ITT subjects in the febuxostat 80 mg QD arm with Final Visit sUA levels <6.0 mg/dL were higher compared to the proportion of subjects in the allopurinol arm. Based on a test of superiority, the difference in the response rates of febuxostat 80 mg versus allopurinol is statistically significant.

Allopurinol is a commonly prescribed agent and is effective (compared to placebo) for managing hyperuricemia in patients with gout. In Study FGT06-153, a test of non-inferiority was applied to show febuxostat 40 mg QD is not worse than that of allopurinol on the basis of a minimally important clinical effect (i.e. a difference of -10%). The proportion of subjects in the febuxostat 40 mg with final visit sUA levels < 6.0 mg/dL was slightly higher compared to the proportion of subjects in the allopurinol. The difference in the proportions is 3% with the lower bound of the 95% confidence interval (-2%) greater than the pre-specified margin of -10%. This implies that febuxostat 40 mg QD is effective in reducing serum urate level in patients with gout.

Applying "non-responder" status to patients who discontinued treatment prior to end of the study and including all subjects randomized as denominator (as shown with symbol ‡) did not change the primary efficacy conclusions.

Table 1: Proportion of Subjects with Final Visit Serum Urate Levels < 6.0 mg/dL

Study	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Allopurinol	Placebo
C02-009				
N (ITT)		262	268	134
n/N_1(%) †		183/253 (72%)	102/263 (39%)	1/127 (1%)
95% CI*		33% (25%, 41%)		
p-value**		<0.0001		
n/N(%) ‡		126/262 (48%)	85/268 (32%)	1/134 (1%)
95% CI*		16% (8%, 24%)		
p-value**		<0.0001		
C02-010				
N (ITT)		255	250	
n/N_1(%) †		185/249 (74%)	88/242 (36%)	
95% CI*		38% (30%, 46%)		
p-value**		<0.0001		
n/N(%) ‡		133/255 (52%)	72/250 (29%)	
95% CI*		23% (15%, 31%)		
p-value**		<0.0001		
FGT06-153				
N (ITT)	757	756	755	
n/N_1(%) †	342/757 (45%)	507/756 (67%)	318/755 (42%)	
95% CI*	3% (-2%, 8%)	25% (20%, 30%)		
p-value**	0.233	<0.0001		
n/N(%) ‡	310/757 (41%)	452/756 (60%)	289/755 (38%)	
95% CI*	3% (-2%, 8%)	22% (17%, 26%)		
p-value**	0.288	<0.0001		
TMX-00-004	34	37		35
n/N(%)§	19/34 (56%)	28/37 (76%)		0/35 (0%)
p-value**	<0.0001	<0.0001		

† Source: Clinical Study report Study C02-009, Table 14.2.2.1 page 589, Study C02-010, Table 14.2.2.1 page 437, and Study FGT06-153 Table 14.2.1.2 page 526

‡ Reviewer's: In order for a subject to be considered a responder, the 'final' serum urate levels must have been <6.0 mg/dL. If a subject prematurely discontinued from the study before the 'final' serum urate level was obtained, the subject was considered a nonresponder. The denominator is all subjects randomized to treatment.

* 95% confidence interval comparing febuxostat versus allopurinol: $(p_1 - p_2) \pm 1.96 * se$

** p-value based on Fisher's exact test comparing febuxostat versus allopurinol

§ The primary endpoint is defined as the proportion of subjects whose serum urate level decreased to <6.0 mg.dL after treatment with study drug (Day 28).

8. Safety

I have discussed the cardiovascular adverse events noted in the earlier clinical studies in my two previous reviews. The reader is referred to appendices 1 and 2. The data from the first two review cycles showed a small, but consistent elevation in incidence of these events in the Uloric-treatment arms compared to the placebo-treatment arms. However, this imbalance was based on a low number of events, particularly in the placebo arm, which was likely due, at least in part, to the uneven randomization strategy employed by the sponsor. Additional data were requested and Study 153 again looks at the cardiovascular safety profile of the 80-mg dose, but now includes the 40-mg dose for evaluation as well, and the study includes a larger number of subjects with a 1:1:1 randomization pattern for Uloric 40 mg, 80 mg and allopurinol 200/300 mg. While allopurinol is approved for doses up to 600 mg, the clinical rheumatology community is generally reluctant to use doses greater than 300 mg in most cases. Therefore, it was reasonable for the sponsor to choose this dose as the comparator. This study was conducted for 6 months and the table below, reproduced from page 16 of Dr. Siegel's review, summarizes the cardiovascular safety results:

Table 2: Analysis of adjudicated APTC cardiovascular adverse events (Study F-153)

Variable	Treatment Group n (%)		
	Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=756)
All APTC Events			
Number of subjects with events	0	3	3
Rate (%)	0.00	0.40	0.40
95% Confidence Interval (%)[a]	(0.000, 0.486)	(0.082, 1.155)	(0.082, 1.155)
Fisher's exact test p-value			
Versus Allopurinol 300/200 mg QD	0.125	>0.999	
Versus Febuxostat 40 mg QD		0.125	
Relative Risk (95% CI)[b]			
Versus Allopurinol 300/200 mg QD	0.14 (0.01, 2.76)	1.00 (0.20, 4.94)	
Versus Febuxostat 80 mg QD	0.14 (0.01, 2.76)		
APTC Events Summarized by Criterion			
Cardiovascular Death	0	0	2 (0.26)
Nonfatal Myocardial Infarction	0	1 (0.13)	1 (0.13)
Nonfatal Stroke	0	2 (0.26)	0

CI=confidence interval; N=number of subjects dosed; QD=once daily.
a Exact confidence interval based on Binomial Distribution.
b Continuity correction of 0.5 was used if either treatment group had zero APTC events.
Source: Clinical Study Report, F-GT06-153, p. 168.

Again, however, we are dealing with a limited number of events which raised the same questions as the first set of results. Additionally, an assessment of the relative risk of APTC events for Uloric 40 mg and 80 mg doses were 0.1 and 1, respectively, with confidence intervals that do not provide assurance that the risk is greater than or less than allopurinol. Dr. Siegel's table, reproduced below from page 16 of his review, summarizes this analysis:

Table 3: Relative risk (RR) with 95% confidence intervals (CI) for adjudicated APTC events

	F-40	F-80	F-120	F-240	Total: Febuxostat treated
N	757	1279	520	134	2690
C02-009					
RR		3.01	2.99	2.00	2.00
CI		(0.1, 73.6)	(0.1,73.1)	(0.04, 100.1)	(0.1, 41.6)
C02-010					
RR		2.96	2.02		2.5
CI		(0.3, 28.3)	(0.2, 2.1)		(0.3, 21.2)
F-GTO6-153					
RR	0.1	1			0.5
CI	(0.01, 2.76)	(0.2, 4.9)			(0.1, 2.5)
All Phase 3					
RR	0.2	1.75	1.8	1.06	1.19
CI	(0, 3.5)	(0.5, 5.95)	(0.4, 8.2)	(0.1, 19.5)	(0.4, 3.8)

Source: Response to FDA Information Request of 25 August 2008

As such, the Division decided to present all of the data to a meeting of the Arthritis Advisory Committee. In addition to presentations on gout and the need for new treatments of this debilitating disease, presentations were included on the efficacy and safety data, specifically focusing on the cardiovascular adverse events, and a specific presentation was provided on the difficulties associated with the evaluation of safety when the event number is low. The results of the meeting are summarized below. In addition, we re-consulted the DCRP, and they concluded that there was no value to performing additional studies.

9. Advisory Committee Meeting

As per Section 8 above, an advisory committee meeting was held during this cycle to discuss the cardiovascular signal seen in the Uloric studies. Based on the paucity of data, most members felt that trying to draw firm conclusions was not possible. While the general consensus was that the benefits of the product outweigh the risks (indeed, they voted 12 to 0 in favor of approval, with one abstention), the committee members also recommended that this issue be further evaluated after approval and a study designed and conducted that would assure an adequate number of events upon which to draw firm conclusions. It is of some note that some committee members expressed the opinion that they were only willing to recommend approval due to the recent passage of FDAAA, which provides the Agency with regulatory authority to require studies and to implement strict time-lines for completion. There was considerable discussion regarding whether an observational study and/or an outcome study would be the most appropriate to undertake. As documented by Drs. Gilbert and Siegel, no specific conclusion or recommendation derived from this discussion. Although I appreciate that Dr. Gilbert's recommendation to perform both types of studies has some merit, I concur with Dr. Siegel that there is little value to performing the observational study as the outcome study is necessary to achieve accurate results, is possible to perform and its results will trump those of an observational study.

10. Pediatrics

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 necessary studies are impossible or highly impracticable. 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 plan was concurred with by the Pediatric Review Committee on December 10, 2008.

11. Other Relevant Regulatory Issues

There are no additional regulatory issues.

12. Labeling

There are no outstanding labeling concerns. The review team and the sponsor have reached agreement on all aspects of the product labeling.

13. Decision/Action/Risk Benefit Assessment

- Recommended Regulatory Action

  I recommend approval.

- Risk Benefit Assessment

  The sponsor has provided adequate evidence to support the efficacy, safety and quality of their product. While the cardiovascular safety risk of Uloric has not been fully elucidated, there is at this time adequate data to write appropriate warnings and cautions into the label while the sponsor initiates an outcome study to, hopefully, clarify the true cardiovascular risk. In light of the need for alternative treatments for gout, an extremely painful and often debilitating disease, the current level of understanding of the cardiovascular risks once included in the product label and the product ——— will allow for a reasonable risk-benefit balance for now. In addition to the cardiovascular outcome study, the sponsor also needs to initiate a clinical efficacy study to assure that the surrogate outcome used to date, lowering of serum uric acid, truly represents a clinical improvement, particularly in light of the possible toxicities associated with the drug. b(4)

Recommendation for Postmarketing Risk Management Activities

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (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), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

The sponsor has agreed to the following postmarketing studies and timelines:

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

- Recommendation for other Postmarketing Study Commitments

There are no postmarketing study commitments.

Appendix 1

The Reviews in this Appendix appear in the Medical Reviews section of this approval package.