CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-856

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	February 13, 2009
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	N 21-856
Applicant Name	Takeda, Inc.
Proprietary / Established (USAN) Names	Uloric febuxostat
Dosage Forms / Strength	Tablet 40 mg, 80 mg
Proposed Indication(s)	For the management of hyperuricemia in patients with gout
Action:	*Approval*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding febuxostat and the reader should refer to the reviews in the action package, and in particular Drs. Siegel's and Gilbert's, for a more detailed discussion. Febuxostat is a xanthine oxidase inhibitor that lowers uric acid levels by inhibiting the conversion of xanthine to uric acid.

This is the third review cycle for febuxostat. During the first review cycle, it was determined that the 80 mg and 120 mg doses demonstrated efficacy, but a cardiovascular safety signal was noted which was felt to give an unfavorable risk benefit so that marketing was not allowed and the sponsor was requested to conduct more exploration of the existing database. This re-analysis of existing data was submitted during the second cycle and failed to assuage the cardiovascular concerns. For this cycle, the sponsor conducted a safety study to further characterize the potential cardiovascular signal as well as to determine the efficacy of a 40 mg dose. Please refer to Dr. Rappaport's reviews (co-signed by Dr. Robert Meyer as the memorandum of record) for details regarding the efficacy and safety signal noted during the first two cycles, but in brief, regarding the safety signal there was a higher incidence of Anti-Platelet Trialists Consortium (APTC) events of combined cardiovascular death, MI, CVA and non-fatal cardiac arrest in febuxostat treated subjects compared to those treated with allopurinol (as an example, one of many different analyses demonstrated APTC events with febuxostat 120 mg and 80 mg of 1.1% and 0.9% respectively compared to allopurinol 0.2%). The imbalance observation was based on small numbers of events which resulted in wide confidence intervals surrounding the point estimates, but was maintained after various attempts at post-hoc adjudication and re-evaluation.

With this submission, the sponsor has conducted Study F-153 was a six-month randomized study which enrolled 2269 subjects randomized to febuxostat 40 mg or 80 mg and allopurinol. I will detail this study a little further below, but for the most part, this study did not

demonstrate a concerning cardiovascular risk signal when compared to allopurinol. However, as with the original submission, this study had very few events so interpretations of the safety results are not definitive and fragile at best.

During this review cycle, consultation was sought from the Division of Cardiovascular and Renal Products (DCRP), and the data was presented at an advisory committee meeting. DCRP felt that there was not an increased cardiovascular risk with febuxostat when compared to allopurinol. The advisory committee met on November 24, 2008 and voted 12-0 with 1 abstention that febuxostat could be approved, but qualified this by saying that further study of cardiovascular safety was needed post-approval.

I agree that the present evaluation of efficacy and safety for febuxostat is satisfactory to allow for approval with a post-marketing requirement for a cardiovascular outcome study. This recommendation of approval is contingent upon satisfactory resolution of labeling.

Efficacy

Febuxostat had clearly demonstrated efficacy for the 80 mg and 120 mg dosages as reviewed in the first cycle. In addition, febuxostat at these dosages has demonstrated efficacy in reducing uric acid levels in subjects with high serum urate levels and in patient with mild or moderate renal insufficiency. These groups may be more refractory to current therapies. Therefore, febuxostat may be an advance in the therapy of gout, although this should be viewed in the context that clinicians are hesitant to advance the dose of allopurinol beyond 300 mg a day, even though it is labeled for a maximal dose of 800 mg a day.

Study F-153 evaluated whether 40 mg dose of febuxostat was non-inferior to allopurinol. Febuxostat was non-inferior to allopurinol overall and was superior to allopurinol in subjects with renal impairment, although the dose of allopurinol was 200mg in this group. Please see Dr. Siegel or Gilbert's reviews for further details.

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Safety

As discussed above, during the first two cycles, an imbalance of APTC events was noted. This is demonstrated in the table below from Dr. Siegel's review (this table reflects one of the post-hoc evaluations performed during the second cycle review, although all the analysis revealed an imbalance).

Table 1: Investigator-reported primary APTC events in randomized controlled trials, N (%)

Primary APTC Events	*Placebo*	*Febuxostat*				*Allopurinol*
		Total	80 mg	120 mg	240 mg	300/100 mg
	N=134	N=1177	N=523	N=520	N=134	N=521
Overall	**0**	**9 (0.8)**	**4 (0.8)**	**5 (1.0)**	**0**	**1 (0.2)**
CV Death	0	3 (0.3)	2 (0.4)	1 (0.2)	0	0
Non-fatal MI	0	5 (0.4)	2 (0.4)	3 (0.6)	0	1 (0.2)
Non-fatal stroke	0	1 (0.1)	0	1 (0.2)	0	0
Non-fatal cardiac arrest	0	1 (0.1)	0	1 (0.2)	0	0

Source: Complete Response to October 14, 2005 Approvable Letter

It should be noted that this imbalance is based on very few events, and is therefore very unstable by its very nature. This imbalance led to the request for more data which led the sponsor to perform Study F-153 which had 2269 subjects randomized 1:1:1 to febuxostat 40 mg or 80 mg and allopurinol. This study was conducted for 6 months and had the cardiovascular safety results noted in the table below from Dr. Siegel's review.

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.

This study also had limited events, which makes any results fragile and conclusions speculative at best. An overall relative risk with 95% confidence intervals of febuxostat compared to allopurinol combining all events from across studies for each dosage strength was performed and is demonstrated in the table below from Dr. Siegel's review.

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 can be seen above, when all the dosages are combined, using all the available data shows a febuxostat risk that is close to unity (19% increase) with a confidence interval that demonstrates that the true effect can be anything from cardioprotective to a four-fold increase.

As mentioned above, a consult was obtained from DRCP, who after analysis stated that they did not recommend further studies of CV risk for febuxostat.

As mentioned above, an Advisory Committee meeting was held during this cycle to discuss febuxostat. As discussed by Dr. Siegel, there was discussion concerning the need for new agents for gout. There was also a great deal of discussion concerning the paucity of data with which to try to evaluate if there was a true cardiovascular signal and most member felt that trying to draw firm conclusions was not possible. The general consensus was that as it stands and considering the instability of the data, the benefits of this drug would outweigh the risks, but that this issue should 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. Some committee members expressed they were only willing to allow approval

as, thanks to FDAAA, we now have the regulatory authority to require studies and have strict time-lines for completion, such that sponsors cannot 'run out the clock'. Some members also expressed that they were only willing to consider approval prior to having a cardiovascular study because, again thanks to FDAAA, the agency has the ability to require certain protocol design features to assure that the relevant question is actually being answered.

Conclusions and Recommendations

Febuxostat has demonstrated that the 40 mg and 80 mg dosages are effective in decreasing serum uric acid levels. This drug may be advancement from present therapies with the caveats I describe above, but it would clearly be a favorable addition from an efficacy standpoint.

The question we have to confront with this application is how to approach a potentially serious safety issue, one that has a background rate that is not rare such that it may not be evident in post-marketing reporting, when we just have a few events so the results are fragile. Dr. Siegel's review cites that there are few events resulting in wide confident intervals and instability of conclusion, which combined with lack of biologic plausibility and dose ordering to the events or any preclinical signals make the data less than conclusive (he further states that cardiovascular safety is a concern and additional information is necessary). I would agree with the above, but would like to comment on how those elements weigh in my decision making.

The lack of biological plausibility and dose ordering do not figure strongly in my decision. We have had several drugs now, which have had 'off-site' activity causing adverse events that was not originally recognized, such that they would have not had recognized biological plausibility. The prime example is terfenadine, which as an antihistamine, would have been thought to not have biological plausibility in causing arrhythmias, and it was only upon witnessing clinical events that it was recognized that it did cause arrhythmias, and after several years the true mechanism was discovered such that we even knew what the biological plausibility could be. I think we are very primitive in our understanding of the potential for drugs to have off-site activity, and lack of biological plausibility should not weigh heavily in our conclusions. The same would go for dose ordering, as if we do not recognize potential biological systems or yet have an understanding of a drug's full biological effect, we would not know if there was a threshold effect, above which we would not expect any increase, or if we should expect more cases with higher doses. As far as lack of preclinical effects, I am reminded that several drugs that are now recognized hepatotoxins did not have any preclinical indication of this effect and at least one diabetic drug that did not receive approval did not have any pre-clinical effects but in studies did have increased cardiovascular toxicity.

I have considered what we have asked for, pre-approval, for diabetes drugs to rule out an adverse cardiovascular effect. I think there are several differences between this drug and those used in the diabetes population. First, the background rate of cardiovascular events would be lower is this population than in the diabetic population (unless of course it was used in someone with diabetes). We also do not have a large body of evidence of several years (decades actually) of evidence that has questioned drugs used in the treatment of diabetes and their effects on cardiovascular risks, although of course lack of evidence is not evidence of

lack. Finally, there are a limited number of drugs for use in this indication, and this does seem to be advancement in the field.

Even with all of that however, had we not had the new authorities given under FDAAA which gives me some confidence that we can dictate a study such that we can get a definitive answer, my conclusion on whether to approve or not may have been different. As it stands though, I agree that febuxostat should be approved with a PMR for a cardiac outcome study.

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/s/

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