

Febuxostat (Uloric) for Hyperuricemia in Gout

NDA #21-856

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Overview of Presentation

- Brief background on Gout
- Regulatory History
- Summary of Safety Concerns noted in the Second Cycle Review
- Summary of New Trial Data
 - Brief summary of efficacy
 - Summary of safety
- Conclusion

Gout

- A *common* disorder
 - 3-5 million in US
 - Self-reported prevalence of 1.4% in men and 0.6% in women
 - Prevalence increases with age: 9% in men & 6% in women over 80
- A crystalline arthropathy due to hyperuricemia
- When serum uric acid > 6 mg/dL, monosodium urate crystals can precipitate and deposit in joints and soft tissue causing an inflammatory response

Gout

- Chronic vs Acute
- Current treatments include:
 - For acute gout attacks
 - NSAIDS, Colchicine, Corticosteroids
 - For chronic gout
 - Allopurinol, Probenecid
- *Comorbidities*: hypertension, diabetes, chronic renal failure, metabolic syndrome, cardiovascular disease
 - Risk of CAD > 1.5

Febuxostat for Chronic Gout

- Uric acid is the end product of purine metabolism
- The last step involves conversion of xanthine to uric acid
- This conversion is the result of the activity of xanthine oxidase
- Febuxostat inhibits the activity of xanthine oxidase and in so doing, decreases the production of uric acid

Regulatory History

- **First Cycle:** original NDA submitted 12/2004:
 - FDA review confirmed efficacy of 80-mg dose
 - FDA review noted febuxostat's potential to result in cardiovascular adverse events.
 - Due to concern about the safety profile, an Approvable letter was issued.
- **Second cycle:** A Complete Response (CR) was submitted 2/2006 → a second Approvable letter because of continued concern about a cardiovascular signal
- **Third cycle:** current submission with results of a new study comparing febuxostat 40 mg and 80 mg to allopurinol

Second Cycle Review

Summary of Findings Suggesting Cardiovascular Safety Signal



Studies Reviewed at Time of Second Cycle

- *Phase 3 Randomized Controlled Trials:*
 - *010 (FACT):* 52 wk, 760 subjects F- 80, 120, allopurinol
 - *009 (APEX):* 6 mos, 1072 subjects, F-80, 120, 240, allopurinol, placebo
- *Phase 2 dose-ranging trial:*
 - *004: RCT*, 28-day dose-finding, 153 subjects, F-40, 80, 120, placebo
- *Long-term extension studies:*
 - *021 (EXCEL):* 1086 subjects, open-label, F-80, 120, allopurinol; up to 40 months
 - *005 (FOCUS):* 5-year, open-label extension with 116 subjects who had completed #004 - F-80 \pm 40

Safety Review, Second Cycle

- **To assess cardiovascular safety, several categories of events were analyzed:**
 - **All-cause mortality**
 - **Cardiovascular mortality**
 - **Investigator-reported cardiovascular events**
 - **Adjudicated cardiovascular events**
- **FDA review of data in these categories concluded that there was a cardiovascular safety signal.**

Mortality

All-Cause Mortality: Second Cycle

All-Cause Mortality: Second Cycle*				
Treatment	Patient-Years of Exposure	Number of Deaths	Rate Per 100 Patient-Years	95% Confidence Interval
<i>Phase 3 Randomized Controlled Studies</i>				
Febuxostat Total	671	4	0.6	0.16 - 1.52
Allopurinol 300/100 mg QD	334	0	0	0.00 - 1.11
<i>Long-Term Extension Studies</i>				
Febuxostat Total	2121	8	0.4	0.16 - 0.74
Allopurinol 300/100 mg QD	145	0	0	0.00 - 2.54
*Adapted from FDA Clinical Review, July 2006				
Note: No subjects died in Phase 1 studies or during treatment in the Phase 2 controlled trial.				

Cardiovascular Mortality: Second Cycle

Cardiovascular Mortality: Second Cycle							
	<i>Treatment</i>						
	<i>Placebo</i>	<i>Febuxostat</i>					<i>Allopurinol</i>
	(N=134) (PY=60)	Total (N=1692) (PY=2792)	40 mg (N=12) (PY=35)	80 mg (N=1221) (PY=1697)	120 mg (N=909) (PY=1006)	240 mg (N=134) (PY=54)	300/100 mg (N=642) (PY=479)
Number of CV Deaths	0	9	0	5	4	0	0
Per 100 PY	0	0.3	0	0.3	0.4	0	0
95% CI	(0-6.2)	(0.1-0.6)	(0-10.7)	(0.1-0.7)	(0.1-1.0)	(0-6.8)	(0-0.8)

Adapted from FDA Clinical Review, July 2006. Due to reclassification during FDA review, the number of CV deaths differs from that found in Applicant's original submission.

Cardiovascular Adverse Events

Cardiovascular SAEs

- **Sponsor summarized cardiovascular events using two different categorization schemes.**
 - **Investigator-reported APTC events**
 - **Adjudicated APTC events**

APTC: Antiplatelet Trialists' Collaboration

- **A collaborative group that devised classification criteria to perform a meta-analysis involving over 100 trials of antiplatelet therapy. The purpose was to analyze CV thromboembolic events.**
- **Defined outcome measures**
 - **Non-fatal MI**
 - **Non-fatal stroke**
 - **Vascular death**

Investigator-Reported APTC Events: Definitions

- *Primary APTC Events:*
 - Cardiovascular death
 - Non-fatal MI
 - Non-fatal stroke
 - Non-fatal cardiac arrest
- *Secondary APTC Events:*
 - Angina
 - Revascularization
 - Transient ischemic attack
 - Venous and peripheral arterial vascular thrombotic event
 - Non-fatal congestive heart failure

Adjudicated APTC Events

Method of adjudication, second cycle

- **A single cardiologist adjudicated cardiovascular events**
 - reviewed all deaths and SAEs and events with any cardiovascular or cerebrovascular diagnosis
 - reviewed data from all Phase 3 controlled trials and long-term safety extension studies
 - reviewed these blinded to treatment group and type of study

Adjudicated APTC events: *definition*

- **113 events were adjudicated**
- **Categories:**
 - **Cardiovascular Death**
 - **Non-fatal MI**
 - **Non-fatal stroke**

- *Turning to investigator reported APTC events.....*

Investigator-Reported Primary APTC events: RCTs, *second cycle*

Investigator-Reported Primary APTC Events: RCTs, N (%)						
Primary APTC Events	<i>Placebo</i>	<i>Febuxostat</i>				<i>Allopurinol</i>
		Total	80 mg	120 mg	240 mg	300/100 mg
	N=134	N=1177	N=523	N=520	N=134	N=521
Overall (CI)	0 (0.0-2.7)	9 (0.8) (0.4-1.5)	4 (0.8) (0.2-2.0)	5 (1.0) (0.3-2.2)	0 (0.0-2.7)	1 (0.2) (0.0-1.0)
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

Risk Ratio

Investigator-Reported APTC Events

- The risk ratio for febuxostat 80 mg, compared to allopurinol, is 4 (0.8/0.2).
- The 95% CI for this ratio is (0.5-32).
- This interval includes the null value, 1, as well as values less than 1, which would correspond to a more favorable outcome with febuxostat.
- Therefore, not possible to determine direction or magnitude of risk with a great amount of confidence.

Investigator-Reported Primary APTC events: *long term extension studies*

Investigator-Reported Primary APTC Events: LTES, N (%)

Events per 100 Patient-Years of Exposure

Primary APTC Events	<i>Febuxostat</i>				<i>Allopurinol</i>
	Total	40 mg	80 mg	120 mg	300/100 mg
	N=1143	N= 12	N=910	N=522	N=178
	<i>PY= 1934</i>	<i>PY=33</i>	<i>PY= 1265</i>	<i>PY=635</i>	<i>PY=133</i>
Overall	29 (1.5)	1 (3.0)	18 (1.4)	10 (1.6)	1 (0.8)
CV Death	5 (0.3)	0	1 (<0.1)	4 (0.6)	0
Non-fatal MI	15 (0.8)	0	12 (0.9)	3 (0.5)	1 (0.8)
Non-fatal stroke	9 (0.5)	1 (3.0)	5 (0.4)	3 (0.5)	0

Source: FDA Clinical Review, July, 2006.

- *Turning to Adjudicated APTC Events*

Adjudicated APTC Events: RCTs

Adjudicated APTC Events: RCTs, N (%)						
	Placebo N=134	Febuxostat				Allopurinol
		Total	80 mg	120 mg	240 mg	300/100 mg
		N=1177	N=523	N=520	N=134	N=521
APTC Events	0	7 (0.6)	4 (0.8)	3 (0.6)	0	1 (0.2)
CV Death	0	3 (0.3)	2 (0.4)	1 (0.2)	0	0
Non-fatal MI	0	4 (0.3)	2 (0.4)	2 (0.4)	0	1 (0.2)

Source: Complete Response to October 14, 2005 Approvable Letter

Risk Ratio

Adjudicated APTC Events

- **The risk ratio for febuxostat, 80 mg, is 4 (0.8/0.2).**
- **The 95% CI for this is (0.4-36)**
- **There are limitations to how confident we can be about the direction or magnitude of risk.**

Adjudicated APTC Events: *long term extension studies*

Adjudicated APTC Events: LTES, N (%)					
<i>Events per 100 Patient-years of Exposure</i>					
	<i>Febuxostat</i>				<i>Allopurinol</i>
	Total	40 mg	80 mg	120 mg	300/100 mg
N	1143	12	910	522	178
PY	1934	33	1265	635	133
APTC Events	21 (1.1)	1 (3.0)	12 (1.0)	8 (1.3)	1 (0.8)
CV Death	4 (0.2)	0	1 (0.1)	3 (0.5)	0
Non-fatal MI	9 (0.5)	0	7 (0.6)	2 (0.3)	1 (0.8)
Non-fatal Stroke	8 (0.4)	1 (3.0)	4 (0.3)	3 (0.5)	0

Source: Complete Response to October 14, 2005 Approvable Letter

Summary of Second Cycle Review

- Analyses identify a higher rate of events with febuxostat 80 mg and 120 mg doses in the following categories: all cause mortality, cardiovascular mortality, investigator-reported APTC events and adjudicated APTC events.
- *These data suggest a possible cardiovascular safety signal.*
- However, there are limitations in the data that raise uncertainty about this conclusion.

Limitations of Analysis: Second Cycle

- Numerically, there were small numbers of events.
- Exposure to allopurinol was limited in the long-term extension studies
- No consistent dose response was observed.

Limitations of Analysis: Second Cycle

In the calculation of relative risk, the confidence intervals are broad and include one. This makes it difficult to determine the direction and magnitude of risk with much confidence.

FDA Action Following Second Cycle: Approvable Letter

- Based upon the higher rate of cardiovascular events observed in febuxostat-treated patients compared to allopurinol-treated patients FDA could not rule out a clinically important increase in cardiovascular thromboembolic adverse events in patients exposed to febuxostat compared to allopurinol or placebo.
- FDA issued an Approvable letter requiring additional data to:
 - clarify the cardiovascular risks of the proposed doses, and/or
 - assess the safety and efficacy of lower doses. The purpose was to identify a dose (or doses) with a favorable risk-benefit profile.

- ***Third Cycle: Current Submission***

FDA Advice on Subsequent Trial

- In preparation for a new trial, the Applicant submitted a draft protocol (for Study F-153) to assess the safety of 40 and 80 mg doses of febuxostat compared to allopurinol.
- The Agency agreed with the definition of APTC events, the proposed adjudication process, and the size and associated power of the proposed trial to analyze febuxostat 40 mg.

Advice

- The Agency further indicated that interpretation of the safety of the 40 and 80 mg febuxostat doses would be difficult if the new study does not show a safety signal with the higher dose.
- However, if an adequate number of events were observed in the allopurinol arm and a similar or lower rate was seen in the febuxostat 40 and 80 mg arms that would be potentially reassuring.

New Study: F-GT06-153 (*CONFIRMS*)

- Randomized double-blind placebo-controlled trial (RDBCT); six month duration
- Subjects had a history of gout and $sUA \geq 8$ mg/dL.
- Active comparator allopurinol dosed at either 300 mg or 200 mg each day
- *Primary endpoint: sUA < 6 mg/dL at 6 months*
- 2269 subjects with 1:1:1 randomization to febuxostat 40 mg, 80 mg, or allopurinol
- *Randomization stratified by baseline renal function*
 - Estimated creatinine clearance used to determine whether renal function was normal (≥ 90 mL/min), mildly impaired (60 mL/min-89 mL/min) or, moderately impaired (30 mL/min to 59 mL/min)

F-GT06-153: *continued*

- Non-inferiority design to assess efficacy of 40 mg dose vs allopurinol
 - 10% non-inferiority margin
 - *Earlier trials demonstrated a response rate for allopurinol of approximately 40% vs 0-1% for placebo*
 - *Therefore, specification of a 10% non-inferiority margin preserves 75% of this benefit*

F-GT06-153: *continued*

- Cardiovascular safety endpoints prespecified:
 - Investigator-reported APTC outcomes
 - Adjudicated APTC outcomes
- Cardiovascular endpoints committee established to adjudicate events
 - A multidisciplinary group of clinicians serving in an advisory role
 - Included two cardiologists and one neurologist
 - Evaluated all deaths and cardiovascular adverse events in a blinded fashion

Demographics and Disease Activity at Baseline

- **No significant imbalance between study arms in terms of the demographic composition**
- **Serum Uric Acid: 9.6, 9.6 and 9.5 for febuxostat 40-mg, febuxostat 80-mg, and allopurinol**
- **CV history: present in 57% of those randomized to febuxostat and 58% of those randomized to allopurinol**
- **Moderate renal impairment: present in 18% in both groups**

Efficacy

Efficacy: Proportion with sUA < 6 mg/dL at Final Visit

Study	Febuxostat 40 mg	Febuxostat 80 mg	Allopurinol 300 mg	Placebo
<i>F-153</i>	45%* (342/757)	67%# (507/756)	42% (318/755)	N/A
<i>C02-009</i>	N/A	72%# (183/253)	39% (102/263)	1% (1/127)
<i>C02-010</i>	N/A	74%# (185/249)	36% (88/242)	N/A
<i>TMX - 004</i>	56% (19/34)	76% (28/37)	N/A	0% (0/35)

Source: Complete Response to August 2006 Approvable Letter

*non-inferior to allopurinol

#indicates statistical significance vs allopurinol at $p < 0.0001$.

Efficacy in Renally Impaired

Efficacy: Proportion of Moderate/Mild Renally Impaired Subjects with sUA < 6.0 mg/dL at Final Visit

	Febuxostat 40 mg	Febuxostat 80 mg	Allopurinol 300/300 mg
	N=479	N=503	N=501
sUA < 6.0 mg/dL	238 (49.7%)	360 (71.6%)	212 (42.3%)
	Difference in Proportions	95% CI	p-value
Feb 40 vs Allo	7%	(1% - 14%)	0.021
Feb 80 vs Allo	29%	(23% - 35%)	<0.001
Feb 40 vs Feb 80	22%	(16% - 28%)	<0.001

Source: Complete Response to August 2006 Approvable Letter

Safety Issues Identified during the Second Cycle.

- ***Four categories of events were involved:***
 - ***all cause mortality***
 - ***cardiovascular mortality***
 - ***investigator-reported APTC events***
 - ***and adjudicated APTC events***

Mortality

All Cause Mortality

All-Cause Mortality: F-153 and Combined Phase 3 Randomized Controlled Trials

	N	# of Deaths	Proportion	95% CI
Treatment				
<i>Study F-153</i>				
Febuxostat Total	1513	2	0.13%	(0.02 - 0.48)
Allopurinol	756	3	0.40%	(0.08 - 1.16)
<i>All Phase 3 RCTs</i>				
Febuxostat Total	2690	6	0.22%	(0.08 - 0.49)
Allopurinol	1277	3	0.23%	(0.05 - 0.69)

Source: Integrated Summary of Safety, July 2008.

Cardiovascular Mortality

Cardiovascular Mortality*: Previous RCTs compared with F-GT06-153

	Febuxostat-treated patients	Allopurinol-treated patients
Previous RCTs**		
N	1177	521
<i>Number (%) with CV Mortality</i>	3 (0.25)	0
F-GT06-153		
N	1513	755
<i>Number (%) with CV Mortality</i>	0	2 (0.26)
* From Investigator- Reported APTC category: Cardiovascular Death **C0-009 and C0-010		

Source: Complete Response to October 2005 Approvable letter, Clinical Study report F-GT06-153

Cardiovascular Adverse Events

Investigator-Reported APTC events: *randomized controlled trials*

Investigator- Reported Primary APTC events in RCTs: Previous RCTs vs F-153

	Febuxostat - total	Allopurinol
Prior RCTs		
N	1177	521
events (%)	9 (0.8)	1 (0.2)
New: F-153		
N	1513	756
events (%)	1 (0.1)	3 (0.4)
Source: Complete Response to October 2005 Approvable Letter; Clinical Study Report F-GT06-153.		

Investigator Reported APTC events: Updated results from long term extension studies

Investigator-Reported Primary APTC events in Long Term Extension Studies *						
	<i>Febuxostat 80 mg</i>		<i>Febuxostat -total</i>		<i>Allopurinol 300/100</i>	
	2006	2008	2006	2008	2006	2008
N	910	917	1143	1143	178	178
Patient years	1265	1746	1934	2661	133	172
# of subjects	18	21	28	31	1	1
Rate /100 patient years	1.4	1.2	1.5	1.2	0.75	0.6
95% CI	0.96 - 2.1	0.75 - 1.8	0.96 - 2.1	0.78 - 2.65	0.02 - 4.2	0.02 - 3.2
*Studies include TMX-01-005 and C02-021:						
taken from table 3.6.1.2 and 3.6.1.3, 2008 NDA Amendment						

Adjudicated APTC Events: Prior vs New Trial

Adjudicated APTC Events: Prior vs. New RCTs

	Febuxostat Total	Allopurinol
Prior RCTs		
N	1177	521
Number of events	7	1
%	0.6	0.2
New RCT: F-153		
N	1513	756
Number of events	3	3
%	0.2	0.4

Source: Complete Response to October 2005 Approvable letter; Clinical Study Report, F-GT06-153

Adjudicated APTC events: updated results for long term extension studies

Adjudicated APTC Events: Updated Results for Long-Term Extension Studies					
	<i>Febuxostat</i>				<i>Allopurinol</i>
	Total	40 mg	80 mg	120 mg	all doses
N	1143	12	917	524	178
PY	2661	38	1746	878	172
All Events: #					
	27	1	17	9	1
rate/100 PY	1.0	2.7	1.0	1.0	0.6
CV Death: #					
	7	0	4	3	0
rate/100 PY	0.3	0.0	0.2	0.3	0.0
Non-fatal MI: #					
	11	0	8	3	1
rate/100 PY	0.4	0.0	0.5	0.3	0.6
Non-fatal Stroke: #					
	9	1	5	3	0
rate/100 PY	0.3	2.7	0.3	0.3	0.0
Source: Integrated Summary of Safety, July, 2008					

Overview: Study F-153

Study F-153: Overview				
	<i>F-40</i>	<i>F-80</i>	<i>Total</i>	<i>Allopurinol</i>
N	756	756	1513	756
Mortality #	1	1	2	3
%	0.1	0.1	0.1	0.4
CV Mortality #	0/1*	0	0/1*	2
%	0/0.1	0	0/0.1	0.3
Primary Investigator-Reported APTC Events #	0	1	1	3
%	0	0.1	0.06	0.4
Secondary Investigator-Reported APTC Events	7	3	10	6
%	0.9	0.4	0.7	0.8
Adjudicated APTC Events #	0	3	3	3
%	0	0.4	0.2	0.4

* The number is "1" if the disputed subject is included as a cardiovascular event.

Relative Risk: Febuxostat vs Allopurinol

Relative Risks (RR) and Confidence Intervals(CI) of 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, 22.1)		(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)

Cardio-Renal Consult

- FDA review division (DAARP) consulted the cardio-renal division to assess whether the overall pattern of cardiovascular events presented in the febuxostat trials suggests an increased cardiovascular (CV) risk.
- Consultants did not identify a pattern suggesting an increased CV risk with febuxostat in Study F-153.
- Consultants noted that Applicant's analyses of combined trial data did not suggest greater rates of CV events with febuxostat than with allopurinol.
- No further cardiovascular studies were recommended.

Special Populations

- **Important to consider population likely to take febuxostat if approved**
 - **One FDA question to the Committee involves unmet medical need population**
- **Potential Unmet Medical Needs**
 - **Refractory to Currently Available Treatment**
 - **Renal Impairment**
 - **No specific safety signal identified in renally impaired population**

Summary

- Review of earlier data suggested a cardiovascular safety signal
 - However, the interpretation was complicated by uncertainty due to: small numbers of events, absence of a consistent dose response, lack of prespecified endpoints, post-hoc analysis, and broad confidence intervals that were consistent with either an increased or a decreased risk compared to allopurinol.
- Study F-153 provides additional information regarding cardiovascular safety:
 - 3-fold more patients per arm than previous studies
 - Prespecified cardiovascular endpoints
 - An adjudication committee established
 - Baseline cardiovascular risk similar to earlier trials

Summary, *continued*

- Data support efficacy of the 80-mg dose of febuxostat based on superiority to allopurinol.
- Efficacy of the 40-mg dose of febuxostat was demonstrated based on non-inferiority to allopurinol in study F-153.
- Cardiovascular events in study F-153 were few in number, both in total and in individual arms. For events that were seen, the rate was not higher with febuxostat 40 or 80 mg than with allopurinol.
- However, statistical analysis based upon calculation of confidence intervals does not enable one to exclude the possibility of an increased risk with febuxostat.

Issue for Discussion

- Taking into account the totality of the data, including the older as well as the new trial, and, considering their respective strengths and limitations, the FDA is asking the committee to provide its assessment of the risk/benefit relationship of the 40 mg and 80 mg doses of febuxostat.

