REVIEW ARTICLE

Febuxostat – A New Treatment for Hyperuricaemia in Gout – A Review Article

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ABSTRACT

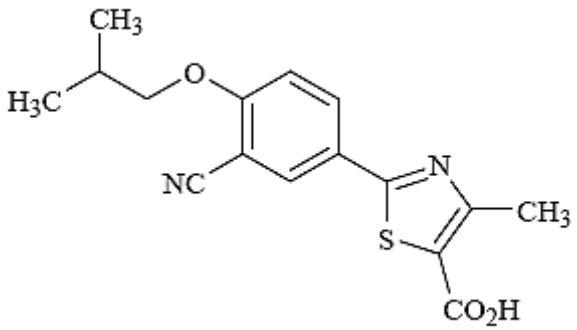
Febuxostat, a novel, orally administered, potent, non–purine analogue, xanthine oxidase / xanthine dehydrogenase inhibitor in the management of hyperuricemia in patients with gout & chronic tophaceous gout. It completely inhibits activity of xanthine oxidase enzyme by obstructing substrate binding but has minimal effects on activity of other enzymes in purine metabolism. It inhibits both oxidized and reduced forms of xanthine oxidase. Febuxostat is more potent than allopurinol in inhibiting xanthine oxidase. Recommended dosage in hyperuricemia and gout is 40 mg or 80 mg OD. Febuxostat, at a daily dose of 80 mg or 120 mg, was more effective than allopurinol at the commonly used fixed daily dose of 300 mg in lowering serum urate, significant number of patients achieves target levels of serum uric acid (< 6 mg/dl) with febuxostat as compared to allopurinol and uric acid ↓ effect is sustained with febuxostat. No dose adjustments are required in hepatic impairment, renal impairment or elderly patient

KEY WORDS: Febuxostat; Hyperuricaemia; Gout; New Treatment

Hyperuricemia is defined as a serum urate concentration exceeding the limit of solubility (about 6.8 mg per deciliter). The clinical manifestations of gout (acute gouty arthritis, gouty arthropathy, chronic tophaceous gout, uric acid urolithiasis, and gouty nephropathy) result from deposition of monosodium urate or uric acid crystals from supersaturated body fluids.[1] The solubility of monosodium urate in extracellular fluids is influenced by a variety of factors; including pH, temperature, and sodium ion and protein concentrations.[2,3,6] The most frequently used pharmacologic urate-lowering strategies involve reducing urate production with a xanthine oxidase inhibitor and enhancing urinary excretion of uric acid with a uricosuric agent. Urate-lowering agents are limited and allopurinol, a xanthine oxidase inhibitor, is the most commonly prescribed of these agents.[4] The average dose is 300 mg per day, although dosing recommendations range from 100 to 800 mg per day, titrated to serum urate and creatinine clearance. The side effects of allopurinol, although uncommon, may be severe or life-threatening and occur more often in patients with renal insufficiency.[5,7] Febuxostat is a potent xanthine oxidase inhibitor, has minimal effects on other enzymes involved in purine and pyrimidine metabolism[8], and is metabolized mainly by glucuronide formation and oxidation in the liver.[9]

CHEMICAL PROPERTIES

Active ingredient in febuxostat is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, with a molecular weight of 316.38. The empirical formula is $C_{16}H_{16}N_2O_3S$. The chemical structure is:



Febuxostat is a non-hygroscopic, white crystalline powder that is freely soluble in dimethylformamide; soluble in dimethylsulfoxide; sparingly soluble in ethanol; slightly soluble in methanol and acetonitrile; and practically insoluble in water. The melting range is 205°c to 208°c.

Tablets for oral use contain the active ingredient, febuxostat, and are available in two dosage strengths; 40 mg and 80 mg. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, and silicon dioxide and magnesium stearate.

MECHANISM OF ACTION

Febuxostat, a xanthine oxidase inhibitor completely inhibits activity of xanthine oxidase (XO) enzyme by obstructing substrate binding and inhibits both oxidized and reduced forms of xanthine oxidase (XO). Activities of other enzymes in purine and pyrimidine synthesis and metabolism at therapeutic concentrations is affected by < 4%

PHARMACODYNAMICS

Effect on Uric Acid and Xanthine Concentrations: In healthy subjects, febuxostat resulted in a dose dependent decrease in 24-hour mean serum uric acid concentrations, and an increase in 24-hour mean serum xanthine concentrations. Febuxostat in dose of 80 & 120 m significantly reduces uric acid levels within 2 weeks after initiation of therapy and the effect is seen to be sustained as compared to allopurinol 300 mg in various studies. In addition, there was a decrease in the total daily urinary uric acid excretion. Also, there was an increase in total daily urinary xanthine excretion.[10,11-15]

***Effect on Cardiac Repolarization*:** The effect of febuxostat on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy subjects and in patients with gout. Febuxostat in doses up to 300 mg daily, at steady

state, did not demonstrate an effect on the QTc interval.[10]

PHARMACOKINETICS [10,13]

In healthy subjects, maximum plasma concentrations & AUC of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life (t½) of approximately 5 to 8 hours.

***Absorption*:** The absorption of radio labeled febuxostat following oral dose administration was estimated to be at least 49% (based on total radioactivity recovered in urine). Maximum plasma concentrations of febuxostat occurred between 1 to 1.5 hours post-dose. Febuxostat may be taken without regard to food or antacid.

***Distribution*:** The mean apparent steady state volume of distribution of febuxostat was approximately 50 liters (CV ~40%). The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 40 mg and 80 mg doses.

***Metabolism*:** Febuxostat is extensively metabolized by both conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes and oxidation via cytochrome p450 (CYP) enzymes including and non-p450 enzymes. In urine and feces, acyl glucuronide metabolites of febuxostat (~35% of the dose), and oxidative metabolites (~10% of the dose) and a secondary metabolite form, (~14% of the dose) appeared to be the major metabolites of febuxostat *in vivo*.

***Elimination*:** Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of ^{14}c-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the drug (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the feces as the unchanged febuxostat (12%), the acyl glucuronide of the drug (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).[10]

The apparent mean terminal elimination half-life (t½) of febuxostat was approximately 5 to 8 hours.

DRUG-DRUG INTERACTIONS [10]

Effect of Febuxostat on Other Drugs

Xanthine oxidase substrate drugs – azathioprine, mercaptopurine and theophylline: Inhibition of xanthine oxidase (XO) may cause increased plasma concentrations of these drugs leading to toxicity. Theophylline is a CYP1A2 and xanthine oxidase (XO) substrate. Although no febuxostat drug interaction study with theophylline has been conducted. Because febuxostat is a xanthine oxidase inhibitor and theophylline is a low therapeutic index drug, inhibition of the xanthine oxidase (XO) -mediated metabolism of theophylline leading to increased plasma concentrations of theophylline that could induce severe theophylline toxicity. Although interaction studies have not been performed with febuxostat, inhibition of xanthine oxidase (XO) may cause an increase in the theophylline level [inhibition of the metabolism of theophylline has been reported with other xanthine oxidase (XO) inhibitors)]. Hence caution is advised if these active substances are given concomitantly, and theophylline levels should be monitored in patients starting febuxostat therapy.

P450 substrate drugs: *in vitro* studies have shown that febuxostat does not inhibit p450 enzymes. As such, pharmacokinetic interactions with drugs metabolized by these CYP enzymes are unlikely.

Effect of Other Drugs on Febuxostat

Febuxostat is metabolized by conjugation and oxidation via multiple metabolizing enzymes. The relative contribution of each enzyme isoform is

not clear. A drug interaction between febuxostat and a drug that inhibits or induces one particular enzyme isoform is in general not expected.

In Vivo Drug Interaction Studies

Colchicine: no dose adjustment is necessary for either febuxostat or colchicine when the two drugs are co-administered. Administration of febuxostat (40 mg once daily) with colchicine (0.6 mg twice daily) resulted in an increase of 12% in Cmax and 7% increase in AUC of febuxostat.These changes were not considered clinically significant.
Naproxen: no dose adjustment is necessary when the two drugs are coadministered. Administration of febuxostat (80 mg once daily) with naproxen (500 mg twice daily) resulted in a 28% increase in Cmax and a 40% increase in AUC of febuxostat. The increases were not considered clinically significant.

Indomethacin: no dose adjustment is necessary for either febuxostat or indomethacin when these two drugs are co-administered. Administration of febuxostat (80 mg once daily) with indomethacin (50 mg twice daily) did not result in any significant changes in Cmax or AUC of febuxostat or indomethacin (less than 7%).

Hydrochlorothiazide: No dose adjustment is necessary for febuxostat when co-administered with hydrochlorothiazide. Administration of febuxostat (80 mg) with hydrochlorothiazide (50 mg) did not result in any clinically significant changes in Cmax or AUC of febuxostat (less than 4%), and serum uric acid concentrations were not substantially affected.

Warfarin: no dose adjustment is necessary for warfarin when co-administered with febuxostat. Administration of febuxostat (80 mg once daily) with warfarin had no effect on the pharmacokinetics of warfarin in healthy subjects. INR and factor VII activity were also not affected by the co-administration of febuxostat.

Desipramine: co-administration of drugs that are CYP2d6 substrates (such as desipramine) with febuxostat are not expected to require dose adjustment. Febuxostat was shown to be a weak inhibitor of CYP2d6 *in vitro* and *in vivo*. Administration of febuxostat (120 mg once daily) with desipramine (25 mg) resulted in an increase in Cmax (16%) and AUC (22%) of desipramine.

SIDE EFFECTS

Treatment-related adverse events included nausea, vomiting, abdominal pain, abnormal liver-function test results, headaches, and musculoskeletal signs and symptoms. Most adverse events were mild to moderate in severity and most of them were seen in patients receiving high dosage of febuxostat (120/ 240 mg/d).[10]

PRECAUTIONS [10]

Gout Flare: After initiation of febuxostat, an increase in gout flares is frequently observed. This increase is due to reduction in serum uric acid levels resulting in mobilization of urate from tissue deposits. In order to prevent gout flares when febuxostat is initiated, concurrent prophylactic treatment with an NSAID or colchicine is recommended.[10]

Cardiovascular Events: In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with febuxostat than allopurinol. A causal relationship with febuxostat has not been established. Monitor for signs and symptoms of myocardial infarction and stroke.

Liver Enzyme Elevations: Laboratory assessment of liver function is recommended at, for example, 2 and 4 months following initiation of febuxostat and periodically thereafter.

Carcinogenesis: Two-year carcinogenicity studies were conducted in f344 rats and b6c3f1 mice. Increased transitional cell papilloma and carcinoma of urinary bladder was observed at 24 mg per kg (25 times the human plasma exposure at maximum recommended human dose of 80 mg per day) and 18.75 mg per kg (12.5 times the

human plasma exposure at 80 mg per day) in male rats and female mice, respectively. The urinary bladder neoplasms were secondary to calculus formation in the kidney and urinary bladder.

Mutagenesis: Febuxostat showed a positive mutagenic response in a chromosomal aberration assay in a Chinese hamster lung fibroblast cell line with and without metabolic activation *in vitro*.

Impairment of Fertility: Febuxostat at oral doses up to 48 mg per kg per day (approximately 35 times the human plasma exposure at 80 mg per day) had no effect on fertility and reproductive performance of male and female rats.

USE IN SPECIFIC POPULATIONS [10]

Pregnancy (Category C): There are no adequate and well-controlled studies in pregnant women. Febuxostat should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Febuxostat is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when febuxostat is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric Use: No dose adjustment is necessary in elderly patients.

Renal Impairment: No dose adjustment is necessary in patients with mild or moderate renal impairment (ClCr 30-89 ml per min). The recommended starting dose of febuxostat is 40 mg once daily. For patients who do not achieve a serum uric acid less than 6 mg per dl after 2 weeks with 40 mg, febuxostat 80 mg is recommended.

There are insufficient data in patients with severe renal impairment (ClCr less than 30 ml per min); therefore, caution should be exercised in these patients.

Hepatic Impairment: No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh class C); therefore, caution should be exercised in these patients.

Secondary Hyperuricemia: No studies have been conducted in patients with secondary hyperuricemia (including organ transplant recipients); febuxostat is not recommended for use in patients whom the rate of urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). The concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract.

OVERDOSE

No overdose was reported in clinical studies. Patients should be managed by symptomatic and supportive care should there be an overdose.

CONTRAINDICATIONS

Febuxostat is contraindicated in patients being treated with azathioprine, mercaptopurine, or theophylline.

INDICATIONS

Chronic management of hyperuricemia in patients with gout & tophi

Febuxostat is not recommended for the treatment of asymptomatic hyperuricemia.

DOSAGE AND ADMINISTRATION

Recommended Dose: For treatment of hyperuricemia in patients with gout, febuxostat is recommended at 40 mg or 80 mg once daily.

The recommended starting dose of febuxostat is 40 mg once daily. For patients who do not achieve a target serum uric acid (sUA) less than 6 mg per dl after 2 weeks with 40 mg, febuxostat in a higher dose of 80 mg is recommended.

Follow-up: Testing for the target serum uric acid level of less than 6 mg per dl may be performed as early as 2 weeks after initiating febuxostat therapy.

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