Febuxostat (Uloric), A New Treatment Option for Gout

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INTRODUCTION

Gout is a rheumatic condition resulting from the deposition of monosodium urate crystals (tophi) in the joints or soft tissues. It is usually associated with elevated serum uric acid levels (greater than 7 mg/dL). The diagnosis is based on uric acid crystals found in the joints, tissues, or body fluids, as well as on gouty attacks or flares characterized by intense pain, swelling, redness, and heat.1–4 The peak incidence of gout occurs between 30 and 50 years of age. Approximately 1% to 2% of Americans are affected, with an equal prevalence in men and women; however, men are more likely to have elevated serum uric acid levels (hyperuricemia).2,4,5

Hyperuricemia results from the accumulation of uric acid, the end product of purine metabolism, which possesses no physiological role.2,6 It has been associated with a high-purine diet (i.e., meats, seafood), alcohol use, diuretic therapy, and analgesics are commonly used in the acute treatment of gout. Goals of therapy include controlling acute attacks, preventing recurrent attacks, and preventing or reversing complications.5,8

Chronic management of gout may include the long-term use of urate-lowering agents after an attack is treated and prophylactic therapy has been considered. Antihyperuricemic therapy is indicated in patients who have had two or more gouty attacks per year, tophaceous gout, erosive arthritis on radiographs, or uric acid kidney disease.9,10 In most patients, a serum uric acid level of below 6 mg/dL is the initial target for therapy. Urate-lowering agents should be started after the complete resolution of a gouty attack because a rapid decrease in serum urate levels sometimes exacerbates a subsequent attack.2,8

Underexcretion of uric acid is responsible for gout in approximately 90% of patients; therefore, uricosuric agents should be used in most patients after ongoing urate deposition has been confirmed and attempts to correct or reverse other causes of hyperuricemia have been made.6,7,9 Inhibitors of uric acid synthesis are also used, particularly for patients who produce excessive amounts of urate (more than 800 mg in 24 hours).8

Allopurinol (Zyloprim, Prometheus), a potent purine xanthine oxidase (XO) inhibitor, is the most commonly used drug in the treatment of hyperuricemia. Until recently, it was the only available inhibitor of uric acid synthesis. In February 2009, the FDA approved febuxostat (Uloric, Takeda Pharmaceuticals America), a structurally unrelated non-purine XO inhibitor, for the chronic management of hyperuricemia in patients with gout.12,13

PHARMACOLOGY AND MECHANISM OF ACTION6,12,14–17

Patients with gout can be categorized into two groups: (1) overproducers of uric acid or (2) underexcreters of uric acid. Hyperuricemia can thus result from the endogenous production of uric acid, a high rate of renal urate reabsorption, or a diet high in purines. XO inhibitors are effective in treating patients with both categories of gout as a result of their inhibition of uric acid synthesis by impairing the conversion of hypoxanthine to xanthine, which results in uric acid formation.

As a non-purine selective XO inhibitor, febuxostat inhibits both oxidized and reduced types of XO. It does not inhibit enzymes involved in purine or pyrimidine metabolism, as does allopurinol. Febuxostat is also structurally unrelated to allopurinol; its structure does not resemble a pyrimidine or a purine. The drug’s active ingredient is 2-(3-cyano-4-[2-methylpropoxy] phenyl)-4-methylthiazole-5-carboxylic acid. The empirical formula is C16H16N2O3S, with a molecular weight of 316.38. As a result of its selectivity and structural differences, febuxostat tends to cause fewer adverse events when compared with allopurinol.

PHARMACOKINETICS AND PHARMACODYNAMICS12,14,18,19

Febuxostat is administered orally and is quickly absorbed; it reaches its maximum plasma concentration in 1 to 1.5 hours after the dose is taken. Following oral absorption, approximately 85% of the drug is absorbed. Although the rate and extent of absorption may decrease with food intake and antacid use, no clinically significant change in the effect of febuxostat has been reported; therefore, it may be taken without regard to food or antacid consumption. There is no accumulation when it is given in therapeutic doses in daily intervals (once every 24 hours). It is approximately 99.2% protein-bound, primarily to albumin.

Febuxostat is metabolized primarily by uridine diphosphate glucuronosyltransferase (UGT) enzymes by means of conjugation. A small portion also undergoes oxidation via cytochrome P (CYP) 450 isoenzymes. However, oxidation via
CYP 450 is clinically insignificant in terms of the drug’s pharmacokinetics. Febuxostat does not inhibit any major CYP isoenzymes, other than CYP 2D6, to which it exerts a mild inhibitory effect for which no dose adjustments are required.

Febuxostat is eliminated by both renal and hepatic pathways. However, renal clearance is not significant. Only a small amount of unchanged drug or metabolites is excreted in the urine. The half-life is approximately five to eight hours. Over a 24-hour period, febuxostat results in a dose-dependent decrease in serum uric acid concentrations. As a result, total daily urinary uric acid excretions are reduced with an increase in total daily urinary xanthine excretion.

CLINICAL EFFICACY

The FDA’s approval of febuxostat was based on three randomized, double-blind, controlled clinical trials involving patients with hyperuricemia (i.e., 8 mg/dL or higher) and gout.

FACT

The Febuxostat versus Allopurinol Controlled Trial (FACT) was conducted to compare the safety and efficacy of febuxostat with that of allopurinol. In this phase 3, 52-week, multicenter trial, 762 patients were randomly assigned to receive either febuxostat 80 mg, febuxostat 120 mg, or allopurinol 300 mg once daily for the study period. All participants receiving any urate-lowering therapy were required to undergo a two-week washout period prior to randomization. During this two-week period, as well as during the first eight weeks of the trial, patients were given either naproxen or colchicine as prophylaxis for gout flares. Any subsequent flares were treated at the discretion of the investigators. Serum urate levels, laboratory testing, gout flares, adverse events, concomitant medication use, and the number and size of palpable tophi were evaluated at the every-four-week visit.

The primary endpoint was the proportion of patients with the last three monthly serum urate levels of below 6 mg/dL. Secondary endpoints included the proportion of patients with a serum urate level of below 6 mg/dL at each visit, the percentage of reduction of serum urate from the baseline value at each visit, the proportion of patients requiring treatment for gouty attacks.

Of the 756 patients who were included in the final analysis, 53% of patients receiving 80 mg of febuxostat, 62% of those receiving 120 mg of febuxostat, and 21% of those receiving allopurinol reached the primary efficacy endpoint. Higher proportions of patients treated with febuxostat (as opposed to allopurinol at all ranges of initial urate levels tested) also reached this endpoint.

All results were determined to be statistically significant. The secondary endpoints were also achieved more frequently with febuxostat than with allopurinol. However, no statistically significant differences among the groups were seen in the percentage reduction in tophus area or in the reduction in number of tophi or gouty flares.

Adverse event rates were similar in all treatment groups. The most frequently reported adverse events among all patients included liver function abnormalities, diarrhea, headaches, joint-related signs and symptoms, and musculoskeletal and connective tissue signs and symptoms. Four deaths were reported in the two febuxostat groups, but they were determined to be unrelated to the drug.

APEX

The Allopurinol and Placebo-Controlled, Efficacy Study of Febuxostat (APEX) was a phase 3, 28-week, multicenter trial designed to compare the efficacy and safety of febuxostat, allopurinol, and placebo in patients with normal and impaired renal function. Impairment was defined as a serum creatinine level of 1.5 to 2 mg/dL.

A total of 1,072 patients received once-daily febuxostat (80, 120, or 240 mg), allopurinol (100 or 300 mg, based on renal function), or placebo. Participants receiving any urate-lowering therapy underwent a two-week washout period prior to randomization. During this two-week period, as well as during the first eight weeks of the trial, patients were also given either naproxen or colchicine as prophylaxis for gout flares. Any subsequent flares were treated at the discretion of the investigators. Serum urate levels, laboratory testing, gout flares, adverse events, concomitant medication use, and the number and size of palpable tophi were evaluated at the every-four-week visit.

The primary endpoint was the proportion of patients with the last three monthly serum urate levels of below 6 mg/dL. Secondary endpoints included the proportion of patients with a serum urate level of below 6 mg/dL at each visit, the percentage of reduction of serum urate from the baseline value at each visit, the proportion of patients requiring treatment for gouty attacks.

Of the 1,067 patients who were included in the final analysis, higher and statistically significant percentages of patients attained the primary endpoint. Forty-eight percent of the febuxostat 80-mg group, 65% of the 120-mg group, and 69% of the 240-mg group achieved serum urate levels below 6 mg/dL at the last three monthly visits, compared with the 22% of patients in both allopurinol groups and none (0%) of the patients in the placebo group.

A significantly higher percentage of patients with impaired renal function who received febuxostat 80 mg (44%), 120 mg (45%), and 240 mg (60%) also achieved the primary endpoint, compared with patients receiving allopurinol 100 mg (0%). The febuxostat-treated patients also attained the secondary endpoints more often compared with the allopurinol or placebo patients.

Higher and significant proportions of patients with serum urate levels of below 6 mg/dL at week 28 (or at the final visit) were observed with febuxostat therapy than with allopurinol or placebo. None of the patients with renal impairment who received allopurinol 100 mg reached this endpoint.

All febuxostat groups also experienced
significantly greater decreases in serum urate levels from baseline at week 28 (or at the final visit) compared with patients receiving allopurinol or placebo. However, no significant differences among the groups were seen in the proportion of patients requiring treatment for gout flares between weeks 8 and 28, in the number of tophi, or in the percentage of reduction in tophus area.

The occurrence of adverse events was similar for all study groups. As in FACT, liver function abnormalities, diarrhea, headaches, joint-related signs and symptoms, and musculoskeletal and connective tissue signs and symptoms, as well as upper respiratory infections, were the most frequently experienced events. Cardiovascular events were also similar in all groups. No deaths were reported during the study period.

CONFIRMS®

A study called The Efficacy and Safety of Oral Febuxostat in Subjects with Gout (CONFIRMS) was the largest phase 3, 28-week, multicenter trial to compare daily febuxostat with allopurinol. A total of 2,269 patients received febuxostat 40 mg, febuxostat 80 mg, or allopurinol 300 mg. Patients with an estimated creatinine clearance (CrCl) of 30 to 59 mL/minute received 200 mg. Prophylaxis of gout flares was provided at the investigators’ discretion throughout the study.

The primary endpoint was the proportion of patients who achieved final serum urate levels below 6 mg/dL. The secondary endpoint was the proportion of patients with mild chronic kidney disease (CrCl, 60–89 mL/minute) or moderate chronic kidney disease (CrCl, 30–59 mL/minute) who achieved final serum urate levels of less than 6 mg/dL.

Forty-five percent of patients who received febuxostat 40 mg, 67% of those receiving febuxostat 80 mg, and 42% of those receiving allopurinol achieved the primary endpoint. Urate-lowering efficacy was similar for the febuxostat 40-mg and allopurinol groups, although the 80-mg dose was superior to both the 40-mg dose and allopurinol.

In patients with chronic kidney disease (n = 1,483), febuxostat 80 mg had greater urate-lowering efficacy compared with the 40-mg dose and allopurinol; however, febuxostat 40 mg provided greater urate-lowering efficacy than allopurinol in these patients. Overall, patients with baseline tophi or serum urate levels higher than 10 mg/dL had a greater response to the 80-mg dose than the 40-mg dose and allopurinol. All data were determined to be statistically significant.

The rates of adverse events (including cardiovascular events) were comparable for all groups and levels of renal function. During the study, one patient in each febuxostat group died and three allopurinol patients died.

ADVERSE DRUG REACTIONS

Compared with allopurinol and placebo in clinical trials, febuxostat at doses of 40 mg and 80 mg daily was associated with a higher percentage of liver function abnormalities, the most common adverse reaction that resulted in discontinuation of therapy. Of those subjects taking febuxostat 40 mg, 1.2% experienced liver abnormalities, compared with 1.8% of patients who were receiving 80 mg. In the allopurinol group, 0.9% discontinued therapy because of hepatic abnormalities, compared with 0.7% of patients in the placebo group.

Other common adverse reactions that were experienced in 1% or more of subjects taking febuxostat and that occurred at least 0.5% more often than in those receiving placebo were nausea, arthralgia, and rash.

DRUG INTERACTIONS

Inhibition of XO by febuxostat may cause increased plasma concentrations of drugs that are metabolized by this enzyme, although studies have not been conducted to confirm this effect. Azathioprine (e.g., Imuran, GlaxoSmithKline), theophylline (Theo-Dur, Key), and mercaptopurine (e.g., Purinethol, Gate) undergo some metabolism, mediated by XO, which has the potential to result in toxic levels of these drugs. Therefore, the manufacturer identifies this possibility as a contraindication for use.

There are no interactions between febuxostat and CYP 450 enzymes or CYP 1A2, 2C9, 2C19, 2D6, or 3A4. There appear to be no clinically significant effects of febuxostat on colchicine, indomethacin, or naproxen, medications that are commonly used to treat gout. Because hydrochlorothiazide (HCT) can cause an increase in uric acid levels, it was studied with febuxostat. When the two agents are used together, the increase in uric acid levels has been determined to be insignificant. No dose adjustment is necessary when febuxostat is used with HCT, warfarin (Coumadin, Bristol-Myers Squibb), or desipramine (Norpramin, Sanofi-Aventis).

It is speculated that febuxostat is a weak inhibitor of CYP 2D6, although this property does not seem to be clinically significant. Even though febuxostat is highly protein-bound, the available evidence is insufficient to verify the degree of displacement.

CONTRAINDICATIONS

Because of the possible increases in plasma concentrations with febuxostat, this agent is contraindicated in patients using azathioprine, mercaptopurine, or theophylline. As with other medications, febuxostat should not be administered to patients with any hypersensitivity to any component of the product.

PRECAUTIONS AND WARNINGS

Patients should be informed that an increase in gout flares is common after the commencement of febuxostat therapy. This is the result of the shift in urate from tissue deposits caused by the reduction in serum uric acid levels. To help avoid such flares, prophylactic treatment with an NSAID or colchicine is recommended when febuxostat is initiated. It may be beneficial to continue prophylactic therapy for up to six months. Febuxostat does not need to be discontinued if a flare occurs.

Although a causal relationship has not been established, patients should be monitored and counseled for signs and symptoms of myocardial infarction and stroke. In randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events with febuxostat than with allopurinol.

It is recommended that baseline liver function be assessed at two and four months and periodically after febuxostat is initiated. Increases in liver transaminase levels are not affected by the dose.

No adequate or well-controlled studies have been conducted on the use of febuxostat in pregnant women. Febuxostat is a Pregnancy Category C drug. Caution should be used when this agent is pre-
scribed to nursing mothers because the drug has been noted to be excreted in the milk of rats. Safety and effectiveness have not been established in patients 18 years of age or under.

Febuxostat is not recommended for patients who may have conditions that increase urate formation. No studies have been conducted in patients with secondary hyperuricemia; however, in rare instances, xanthine concentrations in the urine may increase and accumulate in the urinary tract.

**DOSE AND ADMINISTRATION**

Febuxostat is available in 40-mg and 80-mg tablets. For the treatment of gout, it is recommended that the drug be started at 40 mg by mouth once daily. Two weeks after initiation, if serum uric acid levels are not below 6 mg/dL, the dose can be increased to 80 mg daily. Febuxostat can be taken with or without food. Although not clinically significant in relation to its effects, there is a slight delay in absorption, of approximately one hour, if febuxostat is taken with antacids that contain magnesium and aluminum hydroxide.

No dose adjustment is necessary in elderly patients or in patients with mild or moderate renal or hepatic impairment. However, caution should be used when febuxostat is prescribed for patients with severe renal impairment or hepatic impairment, because the data available in this regard are inadequate.

**COST**

Febuxostat (Uloric) is sold as 40-mg and 80-mg light green to green tablets. The product should be protected from light and stored at room temperature (25°C, or 77°F). According to the 2009 edition of Red Book, the average wholesale price of a bottle of 30 tablets was $162, regardless of strength.

**CONCLUSION**

Febuxostat is the first drug approved and marketed for the treatment of gout in more than 40 years. It represents a new option for the management of hyperuricemia and gout, particularly in patients who are unable to use or to tolerate the less expensive and more extensively studied allopurinol.

**REFERENCES**