Febuxostat for treatment of chronic gout

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Febuxostat, a chemically engineered, nonpurine, selective inhibitor of xanthine oxidase,1 received labeling approval in February 2009 from the Food and Drug Administration.2 It is the first drug marketed in 40 years for the long-term management of hyperuricemia in patients with gout.2,3

Gout is one of the oldest metabolic diseases described, frequently categorized as a type of inflammatory arthritis.4 Gout is associated with the metabolic syndrome of insulin resistance, obesity, hypertension, and hypertriglyceridemia.5

Background

According to the National Health and Nutrition Examination Survey III (NHANES III), an estimated 5.1 million Americans suffer from gout.6 The self-reported National Health Interview Survey (NHIS) documented the frequency of gout as 0.9%.6,7 The NHIS found that 2.24% of people age 45–64 years and 3.08% of people age 65 years or older had gout.7,8 In 2008, Lawrence et al.9 estimated that 3 million adults age 18 years or older had gout in the previous year and that 6.1 million adults age 20 years or older had an occurrence of gout in their lifetime, though these values are likely overestimates, as self-reported data were not verified.

Hyperuricemia, defined as a serum concentration of uric acid that exceeds the limit of solubility (approximately 7.0 mg/dL), can manifest clinically as the deposition of uric acid crystals in joints and surrounding tissues.10,11 Individuals with hyperuricemia are usually asymptomatic and do not always have gouty symptoms. In the Normative Aging Study, Campion et al.12 detailed the risk of gout development relative to serum uric acid levels. The 5-year cumulative risk of gout development in subjects whose serum uric acid concentration was less than 7...
mg/dL was 0.6%; for subjects whose serum uric acid concentration was 10 mg/dL or greater, it was 30.5%. Asymptomatic hyperuricemia is not currently managed with pharmacologic agents. Acute gout attacks are attributed to episodes of hyperuricemia in which monosodium urate monohydrate precipitates out of serum and is deposited in joints and tendons, causing local inflammation. Symptoms of acute gout, also known as gouty flare, include sudden onset of pain, fever, limited range of motion, and warmth of the affected area. Hyperuricemia and the presence of monosodium urate monohydrate crystals can occur without an inflammatory response. Persistent or uncontrolled hyperuricemia and repeated acute attacks are categorized as chronic gout. Tophi may appear at any site, typically as firm swellings. Ulcerated tophi may appear as a visible whitish chalky material, while chronic tophaceous gout usually develops after 10 or more years of acute intermittent gout. Progressive joint and bone destruction and renal impairment due to gouty nephropathy and tophaceous deposits can result if gout is left untreated. Disease progression is not sufficiently prevented by treating acute flare-ups alone.

**Diagnosis and treatment of gout.** Gout is characterized by elevated serum uric acid levels, deposits of monosodium urate monohydrate crystals in the joints and soft tissue, and inflammation. A definitive diagnosis of gout depends on the finding of characteristic crystals. In 1977, the American College of Rheumatology published preliminary criteria for the classification of gout for use in either clinical settings or population-based epidemiologic studies. Criteria included monosodium urate monohydrate crystals in synovial fluid during attack, more than one attack of acute arthritis, maximum inflammation developing within one day, monarthritic attack, redness observed over joints, pain or swelling in the first metatarsal joint, unilateral first metatarsophalangeal joint attack, unilateral tarsal joint attack, tophus (proven or suspected), hyperuricemia, asymptomatic swelling within a joint on radiograph, subcortical cysts without erosions on radiograph, and joint fluid culture negative for organisms during attacks. Study subjects were classified as having gout if they had monosodium urate monohydrate crystals in synovial fluid, a proven tophus, or at least 6 of the other 11 criteria.

Treatment goals for gout are often aimed at alleviating inflammation and associated pain, stopping the acute flare-up, preventing future flare-ups, preventing deposition of monosodium urate monohydrate crystals, and reducing serum uric acid to target level. Uricosuric agents were used to treat gout near the end of the 19th century and included salicylates, sulfispyrazone (not widely used due to its unfavorable adverse-effect profile), and benzbroamarone. Other agents that treat gout include losartan, fenofibrate, amlodipine, sevelamer, and ascorbic acid, though none of these agents are currently approved for treatment of hyperuricemia or gout.

**Current therapies.** Gout flares typically begin abruptly, with red, hot, or tender joints. Individuals may also be febrile during gouty attacks. Attacks may be polyarticular and can intensify quickly. Colchicine in combination with probenecid or allopurinol is frequently used to treat gouty flares. For acute attacks refractory to or in individuals with contraindications to colchicine and nonsteroidal antiinflammatory drugs (NSAIDs), systemic corticosteroids are typically given.

The current strategy for managing chronic gout is the use of uric-acid-lowering drugs to reduce urate production or of a uricosuric agent to promote renal uric acid excretion. Probenecid is indicated for the management of hyperuricemia associated with chronic gout. By preventing the reabsorption of serum uric acid in the proximal tubule, probenecid corrects underexcretion of uric acid. Xanthine oxidase inhibitors block uric acid production, as xanthine oxidase catalyzes the oxidation of hypoxanthine to xanthine and xanthine to uric acid. Allopurinol has become the most frequently used pharmacologic therapy to lower uric acid and manage chronic gout, demonstrating effectiveness in individuals who overproduce or underecrete uric acid.

The pharmacologic options to treat gout are fairly limited, and each option has benefits and potential adverse effects. These limited options, coupled with the lack of symptoms outside of those associated with a flare-up, contribute to inconsistent treatment. In addition to adherence challenges, discontinuation of prescription treatment due to adverse effects is also a challenge in the management of gout.

**Pharmacology**

The therapeutic effect of febuxostat is achieved via the lowering of serum uric acid. The primary mechanism of action of febuxostat evaluated in trials was the inhibition of xanthine oxidase, evidenced by the increase in serum and urine xanthine concentrations, decrease in serum and urine uric acid levels, and lack of significant reduction in total purine synthesis. In the purine metabolism cascade, xanthine oxidase converts hypoxanthine to xanthine and xanthine to uric acid. Animal studies have demonstrated that febuxostat had a greater uric-acid-lowering effect than did allopurinol. Febuxostat’s chemical structure does not resemble a pyrimidine or purine and is unlike that of allopurinol. It does not inhibit other enzymes involved in purine or pyrimidine metabolism. In vitro metabolism studies of febuxostat found no significant effect on the activity of cytochrome P-450 (CYP) isoenzymes 1A2, 92C9,
Febuxostat is rapidly absorbed after oral administration, with peak plasma concentrations occurring in 0.5–1.3 hours. After multiple oral 40- and 80-mg once-daily doses of febuxostat, the mean ± S.D. maximum plasma drug concentration (C_{max}) was 1.6 ± 0.6 μg/mL (n = 30) and 2.6 ± 1.7 μg/mL (n = 227), respectively. The mean terminal elimination half-life (t_{1/2}) of febuxostat is approximately 5–8 hours. Febuxostat is 99.2% protein bound, primarily to albumin, with an apparent volume of distribution at steady state of 0.7 L/kg.

Based on a four-week treatment phase in which 10 patients with gout or hyperuricemia or both received febuxostat 20 mg daily, serum uric acid concentrations decreased by 33% (from 8.7 to 5.8 mg/100 mL), with mean ± S.D. maximum and minimum serum uric acid concentrations differing by 0.84 ± 0.34 mg/100 mL for the 24-hour period before administration of the first dose and by 0.96 ± 0.25 mg/100 mL for the 24-hour period after the final administration. There was a steady decrease in the mean serum uric acid levels, which were linearly related to the dosage up to 120 mg per day, at which point the levels plateaued. At dosages exceeding 120 mg per day, the area under the concentration-time curve (AUC) increased with increasing dosages. At steady state, about 1–6% of the orally administered daily dose was excreted into the urine as unchanged drug, and 25–45% of the dose was excreted as total (unchanged plus febuxostat conjugate) drug. The acyl-glucuronide metabolite of febuxostat comprised 22–44% of the dose excreted in the urine due to conjugation by uridine diphosphate glucuronosyl transferase and oxidation via CYP1A2, CYP2C8, and CYP2C9, resulting in 2–8% of the dose excreted in the urine comprising the active metabolites 67M-1, 67M-2, and 67M-4.

Febuxostat has been evaluated in patients with renal and hepatic dysfunctions, men and women, and the elderly. In one study, febuxostat 80 mg daily was administered orally for seven days to patients with normal renal function (CL_{cr} of >80 mL/min), mild renal impairment (CL_{cr} of 50–80 mL/min), moderate renal impairment (CL_{cr} of 30–49 mL/min), and severe renal impairment (CL_{cr} of 10–29 mL/min). Regression analysis showed that the time to reach peak plasma concentration (t_{max}) and the C_{max} in patients with renal impairment were similar to those in patients with normal renal function, but the AUC and the t_{1/2} increased linearly by severity of renal impairment. By day 7, the mean serum uric acid concentrations decreased by 55–64%, regardless of renal function. The authors suggested that conjugated febuxostat underwent enterohepatic cycling and increased biliary excretion, resulting in a lower renal clearance and higher AUC and t_{1/2} without affecting the overall decrease in serum uric acid. Thus, the 80-mg dose of febuxostat did not appear to require adjustment based on renal function.

The effect of hepatic impairment was assessed in three groups of individuals with normal hepatic function, mild hepatic impairment (Child-Pugh class A), and moderate hepatic impairment (Child-Pugh class B) who were given febuxostat 80 mg daily for seven consecutive days. No statistically significant differences in the C_{max} of unbound febuxostat, t_{max}, t_{1/2}, and AUC for unbound febuxostat and metabolites 67M-1, 67M-2, and 67M-4 were demonstrated when the mild and moderate hepatic impairment groups were compared with the group with normal hepatic function. After giving febuxostat 80 mg daily, the change in serum uric acid concentrations from baseline was statistically but not clinically significant (p ≤ 0.05) for each group, with decreases of 62.5% (from 4.77 to 1.83 mg/dL) in the normal hepatic function group, 48.9% (from 4.95 to 2.66 mg/dL) in the mild hepatic impairment group, and 47.8% (from 5.45 to 2.85 mg/dL) in the moderate impairment group. A decrease in biliary clearance of uric acid in patients with mild or moderate hepatic impairment may be the result of xanthine, febuxostat, or febuxostat metabolites using the same biliary transport system, which is more easily saturable in patients with hepatic impairment. Khosravan et al. concluded that no dosage adjustment is necessary in patients with mild-to-moderate hepatic impairment, as there is increased renal excretion and decreased biliary excretion of uric acid with febuxostat.

To determine the effect of age and sex on febuxostat pharmacokinetic and pharmacodynamic parameters, Khosravan and colleagues studied 48 patients, divided into four groups of 12: men age 18–40 years, women age 18–40 years, men age 65 years or older, and women age 65 years or older. Each person was given febuxostat 80 mg once daily for seven days. The C_{max} was 31.5 ng/mL in women and 23.6 ng/mL in men (p ≤
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0.01), and the AUC was 62.8 ng·hr/mL in women and 53.9 ng·hr/mL in men (p ≤ 0.05); when body weight at baseline was analyzed as a covariate, these parameters were no longer statistically significant.14 In women, the percentage decrease in the 24-hour mean serum uric acid concentration was 59% versus 52% in men (p ≤ 0.01), but this was not clinically significant. There were no statistically significant differences between the younger age groups and those 65 years or older in regard to serum uric acid, AUC, and C_{\text{max}} for febuxostat and its metabolites 67M-1, 67M-2, and 67M-4.14 Dosage adjustments were not necessary based on age or sex.

Clinical efficacy

The therapeutic goals of uric-acid-lowering therapy are to prevent crystal formation and to promote crystal dissolution by maintaining the serum uric acid at ≤6 mg/dL or less, which is below the saturation point for monosodium urate monohydrate.34 The ability of febuxostat to decrease serum uric acid production through selective inhibition of enzyme xanthine oxidase has been established in short-term Phase II and III clinical trials and long-term open-label studies.

Short-term studies

Febuxostat versus placebo. In a randomized, double-blind, placebo-controlled trial with 153 patients age 23–80 years with gout and hyperuricemia, Becker et al.10 compared the efficacy and safety of febuxostat 40 mg (n = 37), 80 mg (n = 40), and 120 mg (n = 38) once daily with placebo (n = 38) for 28 days with colchicine prophylaxis for 14 days before and after randomization. The efficacy analysis was based on an intent-to-treat population of 140 patients. Thirteen patients were excluded because their serum uric acid level was collected outside of the specified time frame. All 153 patients were analyzed for adverse effects and gout flares. The target serum uric acid concentration of <6.0 mg/dL at each visit was achieved by a greater percentage of patients in the febuxostat 40-mg group (50%, n = 19; 56%, n = 21; 59%, n = 22; and 56%, n = 21), 80-mg group (59%, n = 24; 68%, n = 27; 76%, n = 30; and 76%, n = 30), and 120-mg group (91%, n = 35; 94%, n = 36; 97%, n = 37; and 94%, n = 36) on days 7, 14, 21, and 28, respectively, compared with those in the placebo group (3%, n = 1; 0%; 0%; 0%; p < 0.001 for each comparison). Gout flares were similar in the placebo and febuxostat 40-mg/day groups (37% [n = 14] versus 35% [n = 13], respectively), with increasing flare frequency in the 80-mg (43%, n = 17) and 120-mg (55%, n = 21) groups. With colchicine prophylaxis, the rates of gout flares were 8% (n = 3), 8% (n = 3), 13% (n = 5), and 11% (n = 4) for febuxostat 40, 80, and 120 mg and placebo, respectively, versus 30% (n = 11), 40% (n = 16), 42% (n = 16), and 34% (n = 13) for febuxostat 40, 80, and 120 mg and placebo, respectively, when febuxostat or placebo was administered alone. Gout flares occurred more frequently in patients receiving the higher febuxostat dosages, implying that extended prophylaxis may be appropriate with more potent antihyperuricemic agents.10 The number of adverse effects with febuxostat and placebo was similar, with diarrhea being the most common adverse effect, occurring in 0%, 10% (n = 4), 8% (n = 3), and 8% (n = 3) of patients receiving febuxostat 40, 80, and 120 mg and placebo, respectively.

Febuxostat versus allopurinol. Febuxostat has been compared with allopurinol and has demonstrated increased efficacy in lowering serum uric acid levels.

Febuxostat versus Allopurinol Controlled Trial. Becker et al.35 conducted a randomized, double-blind, 52-week trial at 112 centers in the United States and Canada. This study, known as the Febuxostat versus Allopurinol Controlled Trial (FACT), compared the efficacy and safety of daily febuxostat 80 mg (n = 256) or 120 mg (n = 251) with allopurinol 300 mg daily (n = 253) in 760 adults with gout and hyperuricemia (serum uric acid concentration of ≥8.0 mg/dL). Before randomization, patients already receiving a uric-acid-lowering therapy underwent a two-week washout period. Prophylaxis with naproxen 250 mg twice daily or colchicine 0.6 mg once daily was administered to all patients during the washout period and the first eight weeks of double-blind treatment. The primary endpoint was the percentage of patients achieving a serum uric acid concentration of <6.0 mg/dL based on measurements during each of the preceding three months. Baseline characteristics, including mean serum uric acid concentration, history or presence of tophi, age, sex ratio, and racial distribution, were similar in all three groups. Most subjects were white men age 50 years or older who reported drinking alcohol. Subjects had gout for a mean ± S.D. 11.9 ± 9.6 years, 24% (n = 186) had tophi or a history of tophi, 16% (n = 123) had a history of urolithiasis, and 44% (n = 331) had previously taken a uric-acid-lowering therapy. A serum uric acid concentration of <6.0 mg/dL during the preceding three months was attained by 53% (n = 136), 62% (n = 154), and 21% (n = 53) of patients receiving febuxostat 80 mg, febuxostat 120 mg, and allopurinol, respectively (p < 0.001 for febuxostat groups versus allopurinol group). A significantly higher percentage of patients treated with febuxostat (80 mg: 80%, n = 196; and 120 mg: 88%, n = 211) achieved a serum uric acid concentration of <6.0 mg/dL by week 2 and maintained this concentration through week 52 (p < 0.001) compared with those treated with allopurinol (42%, n = 98). During weeks 9–52, the overall frequency of gout flares was similar.
of patients had experienced a gout flare within the past year. Tophi had been present for a mean of 5.7 years, and 29% of patients had a palpable tophus. The primary endpoint—a serum uric acid concentration of <6 mg/dL—was assessed over 28 weeks and attained by 48% (n = 126), 65% (n = 175), 69% (n = 92), 22% (n = 60), and 0% of patients receiving febuxostat 80 mg, febuxostat 120 mg, febuxostat 240 mg, allopurinol, and placebo, respectively (p < 0.001 for all groups versus placebo). In patients with impaired renal function, the primary endpoint was reached by 44% (n = 4), 46% (n = 5), and 60% (n = 3) of those receiving febuxostat 80, 120, and 240 mg, respectively, and 0% in the allopurinol and placebo groups. At week 28 and the final visit (after baseline visit), there were significant decreases (p ≤ 0.05) from baseline in serum uric acid levels in all febuxostat groups (48% and 45% for 80 mg, 55% and 52% for 120 mg, and 68% and 66% for 240 mg, respectively) versus allopurinol (34% and 34%, respectively) and placebo (4% and 3%, respectively).

The number of patients requiring treatment for gout flares decreased with continued treatment. Overall, there were no statistically significant differences between the groups regarding patients requiring treatment for gout flares in week 8 (after the prophylaxis period) through week 28. During the prophylaxis period, more patients receiving febuxostat 120 mg (36%, n = 97) and 240 mg (26%, n = 69) required treatment for gout flares (p ≤ 0.05) compared with those receiving febuxostat 80 mg (28%, n = 73), allopurinol (23%, n = 61), or placebo (20%, n = 27). A decrease in the number of tophi observed with febuxostat 120 mg (1.2) versus placebo (0.3) was significant (p ≤ 0.05) at week 28, but no significant differences were noticed with the other treatment groups. Adverse effects were similar across all treatment groups, except diarrhea (3% [n = 4] versus <1% [n = 1]) and dizziness (7% [n = 9] versus 2% [n = 6], respectively) with febuxostat 240 mg versus allopurinol (p ≤ 0.05).

**Confirmation of Febuxostat in Reducing and Maintaining Serum Urate trial.** The Confirmation of Febuxostat in Reducing and Maintaining Serum Urate (CONFIRMS) trial compared the safety and efficacy of febuxostat 40 mg (n = 757) and 80 mg (n = 756) with allopurinol (n = 755) dosed based on renal function in 2268 patients with hyperuricemia and gout.38 Patients with normal renal function or mild impairment (CLcr of 60–89 mL/min) received a 300-mg dose of allopurinol, and patients with moderate renal impairment (CLcr of 30–59 mL/min) received a 200-mg dose. Prophylaxis for gout was given in the form of colchicine 0.6 mg daily or naproxen 250 mg daily with lansoprazole 15 mg daily for a 30-day washout period for subjects receiving prior uric-acid-lowering therapy and throughout the six-month treatment period for all subjects. The primary endpoint was the percentage of patients who achieved a final serum uric acid concentration of <6 mg/dL. The secondary endpoint was the percentage of patients with mild or moderate renal impairment who achieved a final serum uric acid concentration of <6 mg/dL. There were no significant differences in regard to demographics or gout-related or comorbid characteristics across the treatment groups. Most subjects were white (82%, n = 1860), men (94%, n = 2133), and obese (body mass index of ≥30 kg/m2; 64%, n = 1452) and reported drinking alcohol (68%, n = 1543). A three- to five-year open label uric-acid-lowering therapy trial with either febuxostat or allopurinol had been previously completed by 276 of the patients participating in the CONFIRMS trial.38 When compared with patients who had not previously participated in either long-term study, patients from the prior trial.
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had fewer tophi at baseline (22.3% [n = 444] versus 12.5% [n = 34], respectively; p < 0.001). The primary endpoint was achieved by 45.2% (n = 342), 67.1% (n = 507), and 42.1% (n = 318) of patients in the febuxostat 40-mg, febuxostat 80-mg, and allopurinol groups, respectively. Febuxostat 80 mg was superior to febuxostat 40 mg and allopurinol in lowering serum uric acid levels (p < 0.001). In patients with mild or moderate renal impairment (n = 1483), febuxostat 80 mg lowered serum uric acid levels more than did febuxostat 40 mg (71.6% [n = 360] versus 49.7% [n = 238], p < 0.0001), and febuxostat 80 and 40 mg lowered serum uric acid levels more than did allopurinol (42.3% [n = 212] for allopurinol, p < 0.0001 compared with febuxostat 80 mg and p = 0.021 compared with febuxostat 40 mg). Adverse-event rates were similar across all treatment groups. The CONFIRMS study demonstrated that febuxostat 80 mg was more effective at lowering serum uric acid levels than were febuxostat 40 mg and allopurinol. In patients with renal impairment, febuxostat was more effective than allopurinol, with a comparable adverse-effect profile.

Long-term studies

Two long-term, open-label studies, which were extensions of previously published trials, assessed the clinical efficacy, safety, and tolerability of serum uric acid lowering and maintenance with febuxostat in patients with gout. Febuxostat Open-Label Clinical Trial of Urate-Lowering Efficacy and Safety. The Febuxostat Open-Label Clinical Trial of Urate-Lowering Efficacy and Safety (FOCUS) is a five-year extension of the previously discussed febuxostat versus placebo 28-day Phase II trial. The number of patients achieving and maintaining a serum uric acid concentration of <6.0 mg/dL was the primary endpoint; the percent reduction from the baseline serum uric acid level was a secondary endpoint. A total of 116 patients in the extension study received febuxostat 80 mg daily for 4 weeks followed by febuxostat 40 mg (n = 8), 80 mg (n = 79), or 120 mg (n = 29) daily for weeks 4–24 in order to keep their serum uric acid concentration between 3.0 and <6.0 mg/dL; then, a stable dose was maintained beyond week 24. Most patients (62%, n = 72) remained on the initial febuxostat 80-mg/day dose. Study subjects were primarily Caucasian (85%, n = 99) and men (91%, n = 105) with a mean age of 53.3 years. Tophi were present in about one fourth of the subjects at baseline. Antiinflammatory medications and analgesics were among the most commonly used concomitant medications, as 98% (n = 114) of patients used medications other than febuxostat and prophylactic colchicine.

The serum uric acid concentration was <6.0 mg/dL in 93% (n = 54) of all patients at year 5 who remained in the study and in 83% (n = 95) of all patients at the final visit defined as the last visit on study drug at any point during the study. After 12 months of treatment, patients with baseline tophi reported gout flare rates as high as 31% (n = 8) compared with 10% (n = 9) for patients without baseline tophi, but flares did decrease to less than 10% (n = 2) in the former group by year 4. FOCUS demonstrated the ability of febuxostat to lower and maintain the serum uric acid concentration of <6.0 mg/dL for up to five years. The number of gout flares declined to zero in subjects who remained in the study after five years of therapy with febuxostat. Of the 116 patients who were enrolled in the study, 58 discontinued prematurely, with 38 discontinuing enrollment in year 1. Personal reasons (19%, n = 22) and adverse events (11.2%, n = 13) were the most common reasons for discontinuation. Although most adverse events were mild or moderate in severity, 13 patients cited an adverse event (e.g., abnormal liver function test value, cancer, increased SCR value) as a primary reason for premature discontinuation.

Febuxostat/Allopurinol Comparative Extension Long-Term study. The Febuxostat/Allopurinol Comparative Extension Long-Term (EXCEL) study included 1086 participants of either FACT or APEX, both of which were double-blind Phase III trials. Patients initially received febuxostat 80 mg daily (n = 351), but the protocol was modified to randomly assign patients in a 2:2:1 ratio to febuxostat 80 mg daily (n = 299), febuxostat 120 mg daily (n = 291), or allopurinol (dosed according to renal function) (n = 145). Patients could change febuxostat dosages during the first six months of the trial, but dosages were to be stabilized and maintained by month 6. Subjects received colchicine (0.6 mg daily) or naproxen (250 mg daily) during the first two months of the study to reduce gout flares. The number of patients achieving and maintaining a serum uric acid concentration of <6.0 mg/dL at each visit was the primary endpoint, and the percent reduction from the baseline serum uric acid level was a secondary endpoint.

Most patients were Caucasian (80%, n = 519) with a mean age of 51.34 years. Alcohol use (1–14 drinks imbibed weekly) was reported by 68% of patients (n = 433). At baseline, defined as entry into either previous Phase III trial, normal renal function (SCR of <1.5 mg/dL) was present in 98% of patients (n = 1066). At least one palpable tophus was present in 214 patients (20%). Concomitant medication use (i.e., antiinflammatory drugs and anti-rheumatics, analgesics, antibiotics, and antihyperlipidemics) was reported by 95% (n = 1086) of patients. Premature study discontinuation occurred in 32% (n = 194), 44.1% (n = 171), and 62% (n = 57) of patients in the febuxostat 80-mg,
febuxostat 120-mg, and allopurinol groups, respectively. Reasons for withdrawal included adverse events, personal reasons, lost to follow-up, and therapeutic failure.

Patients receiving febuxostat 80 mg (81%, n = 501) and 120 mg (87%, n = 241) achieved the primary endpoint after one month of therapy, and at least 80% of patients in both groups maintained the primary endpoint for the duration of treatment. Only 46% of patients (n = 64) in the allopurinol group achieved the primary endpoint after one month of therapy, but this increased to 82% (n = 37) of patients by month 12. The mean reductions from baseline serum uric acid levels were 47% (n = 291), 53% (n = 147), and 32% (n = 44) with febuxostat 80 mg, febuxostat 120 mg, and allopurinol, respectively. The number and size of tophi decreased across all treatment groups. Complete resolution of tophi was achieved by 46% (n = 299) of patients in the febuxostat 80-mg group, 36% (n = 104) of patients in the febuxostat 120-mg group, and 29% (n = 42) of patients in the allopurinol group.

Adverse events were similar across all treatment groups but were summarized according to the treatment the patient was receiving at the time of the event. Adverse events adjusted for duration of exposure were reported as 227, 216, and 245 events per 100 patient-years of exposure, and serious adverse events were 11, 9, and 12 events per 100 patient-years of exposure for the febuxostat 80-mg, febuxostat 120-mg, and allopurinol groups, respectively. Serious adverse events were reported by 161 patients, with cardiac disorders being reported most frequently by 48 patients, all of whom had a history of cardiovascular disease or other underlying risk factors. Ten patients died during the study while receiving febuxostat (80 mg, n = 7; 120 mg, n = 3). Cardiovascular events were associated with the death of 6 patients, all of whom had an extensive history of cardiovascular disease. Two deaths were due to cancer, one was due to postsurgical sepsis, and one was due to a bleeding event in a patient receiving warfarin and heparin. Four patients who died were 65 years of age or younger, two were age 65–74 years, and four were age 75 years or older. When the deaths were assessed by the investigators, no evident relationship between the drug dose or length of therapy was identified.

Safety
Febuxostat is approved only for use in adults. The safety and effectiveness of febuxostat in pediatric patients have not been established at this time. Based on data reported from clinical trials, febuxostat appears to be generally well tolerated. No Q-T interval prolongation was seen with febuxostat 80 or 300 mg daily for four days. The most common treatment-related adverse effects documented were headache, arthralgias, abdominal pain, nausea, abnormal liver function test values, flushing, and dizziness. Patients treated with febuxostat should be monitored for signs and symptoms of cardiovascular events (e.g., myocardial infarction [MI], stroke). In clinical trials there were higher rates of cardiovascular thromboembolic events, including cardiovascular death, nonfatal MI, and nonfatal stroke with febuxostat versus allopurinol. In their 28-week, Phase III trial, Schumacher et al. documented adverse cardiovascular events across all treatment groups. A total of 11 cardiovascular events occurred in the febuxostat group, with 5 (2%) occurring in the febuxostat 80-mg group, 5 (2%) in the 120-mg group, and 1 (<1%) in the 240-mg group. Two other cardiovascular events occurred, 1 (<1%) in the placebo group and 1 (<1%) in the allopurinol group. The difference in cardiovascular events among groups was not statistically significant. Cardiovascular events included chest pain, coronary artery disease, MI, and atrial fibrillation in subjects with a history of underlying cardiovascular disease or risk factors. A Phase III trial is currently being conducted to evaluate the cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular comorbidities.

Data suggest an increased risk of flares after the initiation of uric-acid-lowering therapy. The mechanism for this effect is poorly understood but has been attributed to sudden changes in uric acid concentrations. In addition to the initiation of uric-acid-lowering therapy, gouty flares can be caused by other precipitating factors, such as infection, surgery, alcohol consumption, and pharmacologic agents that increase uric acid concentrations. Prophylactic therapy has proved beneficial when administered before uric-acid-lowering pharmacotherapy. Febuxostat-treated patients had higher rates of acute gout flares and early study withdrawal in published comparative trials with allopurinol. Bruce detailed that up to 70% of patients had febuxostat-induced gout flares despite adequate prophylaxis. In a 28-day, Phase II study in which participants received febuxostat 40, 80, or 120 mg or placebo, the overall frequency of gout flares was similar in the 40-mg (35%) and placebo groups (37%) but higher in the 80-mg (43%) and 120-mg (55%) groups. Increased flares after initiation of febuxostat may be secondary to rapid reduction in serum uric acid levels and induced mobilization of uric acid stores.

As a xanthine oxidase inhibitor, febuxostat may interact with drugs that are metabolized by xanthine oxidase. Febuxostat is currently contraindicated in patients concurrently using azathioprine, mercaptopurine, or theophylline. Drug interaction studies with theophylline, mercapto-
purine, and azathioprine have not yet been completed. One of the methods of metabolism for azathioprine and mercaptopurine is mediated by xanthine oxidase, and theophylline is a xanthine oxidase substrate. Inhibition of xanthine oxidase in the presence of these drugs may cause increased plasma concentrations of these drugs and potentiate toxicity. Febuxostat is highly protein bound, and in vitro studies have demonstrated a minimal impact of other protein-bound medications on the binding of febuxostat.

Additional information is needed regarding the potential extent to which febuxostat displaces other protein-bound drugs in vivo. Most studies conducted with this novel agent evaluate medications commonly administered concurrently in patients with hyperuricemia and gout. Current findings suggest a low drug–drug interaction potential for febuxostat.

The most common adverse effect leading to discontinuation from febuxostat in clinical trials was abnormal liver function test values, occurring in up to 6.6% of patients taking febuxostat. In clinical trials, 2–3% of patients treated with febuxostat developed transaminase elevations of greater than three times the upper limit of normal. These studies did not establish a dose–effect relationship between febuxostat and abnormal liver function test values. Compared with other uric-acid-lowering agents, the serum uric-acid-lowering effects of febuxostat were unaltered in individuals with renal impairment. There are insufficient data in patients with severe renal impairment, as most studies did not evaluate individuals with a CLcr of <30 mL/min. Febuxostat pharmacodynamics or pharmacokinetics have not been investigated with respect to race.

Deaths in patients treated with febuxostat were reported in several clinical trials. Of 116 participants in FOCUS, 6 had occurrences of atrial fibrillation or atrioventricular block, determined to be unrelated to febuxostat. Serious cardiovascular events (chest pain, coronary artery disease, MI, and atrial fibrillation) occurred with similar frequency (3–4%) across all treatment groups in APEX. The EXCEL trial documented serious adverse events across all treatment groups. However, of the 10 documented deaths that occurred in participants receiving febuxostat, 6 were cardiovascular-related deaths. The 4 deaths reported in FACT and the 5 in the CONFIRMS trial were not related to febuxostat.

While febuxostat is excreted in the milk of rats, it is unknown if febuxostat is excreted in human breast milk. Febuxostat is a pregnancy category C drug, as no well-controlled studies have included pregnant women. For patients for whom febuxostat is prescribed, it would seem prudent to complete laboratory assessments of liver function. Recommendations from the manufacturer include liver function assessment two and four months after the initiation of therapy and periodically thereafter. Serum uric acid concentration should also be monitored at treatment initiation and regular intervals.

Dosage and administration
Febuxostat was approved for the chronic management of hyperuricemia in patients with gout, with recommended dosages of 40 and 80 mg once daily. The recommended initial dosage of febuxostat is 40 mg orally once daily with or without food. The target serum uric acid concentration is <6 mg/dL. Prophylaxis is recommended due to the risk of an acute gouty flare. Prophylaxis may be warranted for an extended period of time as patients receiving febuxostat monotherapy developed flares frequently. The manufacturer recommends flare prophylaxis with NSAIDs or colchicine. If the target serum uric acid concentration is not reached after two weeks, the dosage of febuxostat may be increased to 80 mg orally once daily. Patients with mild-to-moderate hepatic or renal impairment do not require additional dosage adjustments. However, caution should be encouraged in patients with severe renal insufficiency (CLcr of <30 mL/min) or severe hepatic impairment (Child–Pugh class C). Although the 120-mg dose was evaluated in clinical trials, that dosage is not in the approved labeling. Dosages of febuxostat should be adjusted to achieve serum uric acid concentrations of <6 mg/dL.

Cost
In general, long-term uric-acid lowering therapy, such as allopurinol, probenecid, or febuxostat, may not be warranted in all patients but is most appropriate in patients with recurrent acute attacks, tophi, radiographic evidence of joint damage, and urate nephrolithiasis. The average wholesale price for febuxostat 80- and 120-mg tablets is $162 per 30 tablets ($5.40 per unit). Allopurinol and probenecid are currently available as generics, with prices of $0.24 per unit for allopurinol 100-mg tablets, $0.64 per unit for allopurinol 300-mg tablets, and $0.98 per unit for probenecid 500-mg tablets. Although the results of clinical trials suggest that febuxostat is more effective than allopurinol in lowering serum uric acid levels, its cost may limit its use to patients with renal impairment, those intolerant to allopurinol, and patients who do not achieve the targeted serum uric acid level while taking the maximum recommended dosage of allopurinol.

Role in therapy
Febuxostat 40 mg daily appears to be as efficacious as allopurinol in lowering serum uric acid levels. Both febuxostat 40 and 80 mg can be given to patients with mild-to-moderate renal impairment (CLcr of 30–89 mL/min) without dosage
adjustments and are as effective as allopurinol in achieving the serum uric acid level of <6.0 mg/dL in patients with renal impairment.30,31,37,38

There do not appear to be any significant advantages in the use of febuxostat over allopurinol in patients who already experience adequately lowered serum uric acid levels with allopurinol. Febuxostat is generally well tolerated but is significantly more expensive than allopurinol. Febuxostat is a second-line option for patients with gout who are unable to take allopurinol due to hypersensitivity, intolerance, or lack of efficacy in achieving a target serum uric acid concentration of <6.0 mg/dL.

There may be additional uses in individuals with concurrent renal function impairment; however, more data need to be provided on dosage titration in renal impairment. Febuxostat may also be an alternative therapy for patients with allopurinol sensitivity or those who are not candidates for uricosuric therapy with probenecid. Evaluation of rates of discontinuation and documented adverse effects, primarily cardiovascular events, compared with current therapeutic options provides reason for pause in the placement of febuxostat as a first-line agent. Additional studies are needed to evaluate if and to what degree febuxostat displaces other highly protein-bound drugs and its potential long-term effects on hepatic function. Trials that include dosage increases for allopurinol would also provide details relative to comparative efficacy with febuxostat.

Febuxostat is not recommended for the treatment of patients with secondary hyperuricemia, such as those being treated for Lesch-Nyhan syndrome or cancer or those receiving organ transplants.30

Conclusion

Febuxostat is efficacious as a second-line therapy in lowering serum uric acid levels in patients with gout. Febuxostat may be an alternative for patients with gout who are unable to take allopurinol due to hypersensitivity, intolerance, or lack of efficacy.

References

30. Uloric (febuxostat) prescribing information, Deerfield, IL: Takeda Pharmaceuticals North America; 2009.


