Febuxostat for the treatment of hyperuricemia in patients with gout

Febuxostat (Takeda Pharmaceuticals North America, Inc., IL, USA) is a novel, nonpurine selective inhibitor of xanthine oxidase, approved for the treatment of hyperuricemia in patients with gout. There have been four randomized, double-blind controlled trials and two open-label extension studies evaluating the safety and efficacy of febuxostat in lowering serum urate concentration among patients with gout, including those with mild-to-moderate renal insufficiency. These trials compared febuxostat with placebo or allopurinol 200–300 mg daily; although, notably, the maximum US FDA approved dose of allopurinol is up to 800 mg daily for patients with a creatinine clearance >20 ml/min. Febuxostat may be a safe and effective alternative for treating gout patients where allopurinol 300 mg/day is neither safe nor effective. Owing to imbalances in cardiovascular event frequency between allopurinol- and febuxostat-treated patient groups in earlier studies, the manufacturer of febuxostat has initiated a large, FDA-mandated study of cardiovascular safety of febuxostat. Future research is expected to provide additional data on febuxostat in combination with other urate-lowering therapies for better serum urate control.

KEYWORDS: allopurinol ■ febuxostat ■ gout ■ hyperuricemia ■ Uloric® ■ uric acid ■ xanthine oxidase

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Summary of disease process & therapeutic targets

Hyperuricemia, as defined by a serum urate ≥6.8 mg/dl, is necessary but not sufficient to produce the clinical manifestations of gouty arthritis (gout) [1]. Hyperuricemia develops whenever there is a relative imbalance of production and excretion of urate. There are several other risk factors associated with the development of gout, mostly related to the effects on uric acid production or excretion. Common modifiable risk factors associated with increased uric acid production are obesity, high intake of meat and seafood and alcohol use, especially beer. Many drugs are associated with decreased uric acid excretion, including thiazide diuretics, low-dose aspirin and cyclosporine [2].

Therapeutic strategies for gout include treatment of inflammation and reduction of serum urate. There are three broad classes of drugs for urate-lowering therapy: xanthine oxidase (XO) inhibitors, uricosuric agents and the recombinant forms of the enzyme urate oxidase (uricase) [3]. XO inhibitors act by blocking the human enzyme XO. During purine metabolism, XO catalyzes the conversion of hypoxanthine to xanthine, and then xanthine to uric acid. Inhibition of XO leads to reduced levels of serum urate and increased levels of the more soluble precursor molecules, xanthine and hypoxanthine [4]. Allopurinol has been the classic XO inhibitor in use over the past 40 years, and has been recommended as a safe and cost-effective therapy for long-term urate reduction in patients with gout [5]. While allopurinol is generally well-tolerated, its side-effect profile includes the possibility of allopurinol hypersensitivity syndrome, a rare but life-threatening skin rash, which seems to be more common in patients with renal insufficiency [6]. In this article, we discuss the data on febuxostat, a novel XO inhibitor approved for urate reduction in patients with gout in the USA, Canada, Europe, South Korea and Japan.

Clinical pharmacology of febuxostat

■ Pharmacodynamics

There are important differences between febuxostat and oxypurinol, the active metabolite of allopurinol. Allopurinol is a structural isomer of hypoxanthine. Febuxostat (2-[3-cyano-4-(2-methylpropoxy)-phenyl]-4-methylthiazole-5-carboxylic acid) is a novel, nonpurine selective inhibitor of XO. Febuxostat can bind both to the oxidized and reduced form of XO, whereas oxypurinol can only bind to the reduced form, limiting its ability to persistently inhibit the enzyme. Additionally, since allopurinol is a purine analog, it interferes with other enzymes involved in purine and pyrimidine metabolism, including purine nucleoside phosphorylase and orotidine-5′-monophosphate decarboxylase,

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whereas febuxostat is selective for XO [7,8]. It is still unclear whether these differences in pharmacodynamics have any clinical relevance.

Pharmacokinetics in humans

In humans, febuxostat is administered orally and rapidly absorbed (T_{max}= 1 h) with >80% oral absorption; 99% is bound to albumin and it has a relatively low volume of distribution at steady state (0.7 l/kg). Febuxostat is highly metabolized in the liver, to its acyl-glucuronide and oxidative metabolites [9]. Less than 6% of the active drug is excreted in the urine, and the small remainder of non-metabolized active drug is eliminated through the gastrointestinal tract [10,11]. Concomitant food or antacid intake does not alter the pharmacokinetics of febuxostat [12].

Clinical efficacy of febuxostat

There are four randomized, double-blind controlled trials and two open-label extension studies that have investigated the clinical efficacy of febuxostat, looking at the effect on serum urate lowering, as well as clinical outcome of gout (see TABLE 1). The primary end point in all studies was serum urate level, but secondary end points included reduction in gouty flares and tophus area (see TABLES 2 & 3). All of the studies were conducted by Takeda Pharmaceuticals, Inc. (Deerfield, IL, USA), the manufacturer and marketer of febuxostat in the USA.

Phase II dose-ranging study with placebo control

In 2005, Becker *et al.* published the first Phase II randomized, placebo-controlled trial of febuxostat at three different doses versus placebo in 153 patients with gout and hyperuricemia (serum urate level ≥8 mg/dl) [13]. The primary end point in this study was the proportion of patients with a serum urate level <6 mg/dl at 28 days; this was achieved in 56% of patients taking the 40-mg dose, 76% at the 80-mg dose and 94% at the 120-mg dose. The primary end point was not achieved in any of the patients taking placebo. Gout flares occurred with similar frequency in the placebo and low-dose febuxostat groups, and with increased frequency in the two higher doses of febuxostat.

Phase III studies

Febuxostat Versus Allopurinol Control Trial in Subjects With Gout (FACT)

Febuxostat Versus Allopurinol Control Trial in Subjects With Gout (FACT), also published in 2005, was a multicenter, randomized controlled trial of febuxostat versus allopurinol comparing the serum urate lowering effects of the two drugs in 762 patients with gout and hyperuricemia [14]. The primary end point of serum urate <6 mg/dl during the last 3 months of treatment was achieved in 53% of patients taking 80 mg of febuxostat, 62% at the 120-mg dose, and in 21% of patients taking allopurinol 300 mg once daily. Over the average follow-up of 52 weeks, there was no significant difference in gout flares or reduction in tophi between treatment groups. There was increased frequency of gout flares in the first 8 weeks of high-dose febuxostat, which was expected given the precipitous reduction in serum urate levels.

Phase III, Febuxostat, Allopurinol & Placebo-Controlled Study in Gout Subjects (APEX)

Phase III, Febuxostat, Allopurinol and Placebo-Controlled Study in Gout Subjects (APEX), a larger Phase III randomized controlled trial,

Table 1. Summary of study design, Phase II and III clinical trials.

Phase	Study acronym	Design	Duration	Size (n)	Febuxostat dose, mg (n)				Control (n)		Ref.
					40	*80*	*120*	*240*	*Allopurinol*[†]	*Placebo*	
II	–	RCT	4 weeks	153	37	40	38	N/A	N/A	38	[13]
III	FACT	RCT	52 weeks	760	N/A	256	251	N/A	253	N/A	[14]
III	APEX	RCT	28 weeks	1072	N/A	267	269	134	268	134	[15]
III	CONFIRMS	RCT	6 months	2269	757	756	N/A	N/A	756	N/A	[16]
II	FOCUS	OLES	5 years	116	8	79	29	N/A	N/A	N/A	[13,17]
III	EXCEL	OLES	40 months	1086	N/A	606	388	N/A	92	N/A	[18]

[†]*Allopurinol dose of 300 mg daily.*

APEX: Effects of Febuxostat versus Allopurinol and Placebo in Reducing Serum Urate in Subjects with Gout; CONFIRMS: The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout; EXCEL: Open-label extension of subjects from the APEX and FACT Phase III studies; FACT: Febuxostat Versus Allopurinol Control Trial in Subjects With Gout; FOCUS: 5-year open-label extension of the Phase II dose-ranging study; N/A: Not applicable; OLES: Open-label extension study; RCT: Randomized clinical trial.

Table 2. Summary of efficacy data (primary outcome: serum urate lowering).

Study acronym	Phase	Primary outcome: % of subjects with serum urate level <6.0 mg/dl at study completion (n)						Ref.
		Dose or drug						
		40 mg	*80 mg*	*120 mg*	*240 mg*	*Allopurinol*[†]	*Placebo*	
–	II	56 (19)	76 (28)	94 (32)			0 (0)	[13]
FACT	III		74 (185)	80 (193)		36 (88)		[14]
APEX	III		72 (183)	79 (209)	92 (116)	39 (102)	1 (1)	[15]
CONFIRMS	III	45 (342)	67 (507)			42 (318)		[16]
FOCUS	II	100 (8)	82 (65)	81 (22)				[17]
EXCEL	III		83 (496)	75 (283)		53 (47)		[18]

[†]*Allopurinol dose of 300 mg daily.*
APEX: Effects of Febuxostat versus Allopurinol and Placebo in Reducing Serum Urate in Subjects with Gout; CONFIRMS: The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout; EXCEL: Open-label extension of subjects from the APEX and FACT Phase III studies; FACT: Febuxostat Versus Allopurinol Control Trial in Subjects With Gout; FOCUS: 5-year open-label extension of the Phase II dose-ranging study.

investigated the effects of febuxostat versus allopurinol or placebo in 1072 patients with gout and hyperuricemia, including patients with mild renal insufficiency (defined as a serum creatinine level >1.5 to ≤2 mg/dl) [15]. Three different doses of febuxostat (80, 120 and 240 mg once daily) were compared with allopurinol (300 or 100 mg once daily, in renal insufficiency) or placebo over a 28-week treatment period. Colchicine or naproxen was given as flare prophylaxis. The primary end point was defined as a serum urate level <6 mg/dl during the last 3 months of treatment; secondary end points included self-reported gout flares and reduction in number or size of tophi. Significantly higher percentages of patients in the febuxostat group, at all doses, achieved the primary end point compared with allopurinol or placebo: 48% at the 80-mg dose, 65% at 120-mg dose and 69% at 240-mg dose compared with 22% in the allopurinol group and 0% with placebo. In the group with renal insufficiency, over 44% of patients receiving febuxostat achieved the primary end point compared with no patients in the allopurinol group (100 mg once daily). After week 8, there was no significant difference in the rates of gout flares between treatment groups; however, prior to week 8, there were significantly more gout flares in the 120- and 240-mg febuxostat groups. There was not a significant decrease in tophi size or number between treatment groups. Notably, the withdrawal rates in the febuxostat 80- and 240-mg groups were significantly higher than the allopurinol group (35–36 vs 21%; $p < 0.05$).

Table 3. Summary of efficacy data (secondary outcome: incidence of gout flares).

Study acronym	Phase	Secondary outcome: % of subjects with gout flares (n)						Ref.
		Dose or drug						
		40 mg	*80 mg*	*120 mg*	*240 mg*	*Allopurinol*[†]	*Placebo*	
–[‡]	II	35 (13)	43 (17)	55 (21)			37 (14)	[13]
APEX[§]	III		28 (73)	36 (97)	46 (69)	23 (61)	20 (27)	[15]
FACT[§]	III		22 (55)	36 (90)		21 (52)		[14]
CONFIRMS[‡¶]	III	31 (757)	31 (756)			25 (755)		[16]
FOCUS[‡]	II	75 (6)	47 (37)	41 (12)				[17]
EXCEL[¶#]	III		15 (79)	20 (58)		23 (13)		[18]

[†]*Allopurinol dose of 300 mg daily.*
[‡]*Incidence over the entire study period.*
[§] *Incidence during first 8 weeks, while on gout prophylaxis.*
[¶]*These figures were obtained from the published reports as well as from the authors.*
[#]*Incidence after 1 year on treatment.*
APEX: Effects of Febuxostat versus Allopurinol and Placebo in Reducing Serum Urate in Subjects with Gout; CONFIRMS: The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout; EXCEL: Open-label extension of subjects from the APEX and FACT Phase III studies; FACT: Febuxostat Versus Allopurinol Control Trial in Subjects With Gout; FOCUS: 5-year open-label extension of the Phase II dose-ranging study.

Efficacy & Safety of Oral Febuxostat in Subjects with Gout (CONFIRMS)

In 2010, an even larger Phase III randomized clinical trial of 2269 patients with gout and hyperuricemia evaluated the efficacy of febuxostat 40 or 80 mg once daily compared with allopurinol 200 or 300 mg once daily over a 6-month period [16]. This study was designed to evaluate a larger population, including patients with mild-to-moderate renal insufficiency (creatinine clearance of 60–89 ml/min, or 30–59 ml/min, respectively), with a lower dose of febuxostat and also to revisit concerns about cardiovascular (CV) safety, raised in previous studies. The primary end point was serum urate <6 mg/dl at the final visit, achieved in 67.1% of patients taking 80 mg of febuxostat, which was significantly higher than the 40-mg group (45.2%) or the allopurinol group (42.1%). The lower dose of febuxostat demonstrated noninferiority with respect to the primary outcome. In patients with renal insufficiency, both the 40- and 80-mg doses of febuxostat were significantly more effective in achieving the primary outcome (49.7 and 71.6%, respectively), compared with allopurinol 200 or 300 mg daily (42.3%). There was no significant difference in gout flares between groups, although all participants who had previously received urate-lowering therapy had lower rates of gout flares compared with those who had not.

Febuxostat Versus Allopurinol Control Trial in Subjects with Gout (FOCUS)

A 5-year, open-label extension of the 28-day Phase II clinical trial of febuxostat versus placebo assessed the durability of response in lowering serum urate levels, as well as changes in gout flares and reduction of tophi [13,17]. Of the initial 145 patients enrolled in the 28-day study, 116 enrolled in the open-label extension, with 59 patients still enrolled in the trial at 5 years. The maintenance dose of febuxostat was 40, 80 or 120 mg, with initial dose adjustment allowed before week 24. At the end of the study period, 83% of patients had maintained a serum urate level <6 mg/dl. Overall, 47% of patients had gout flares requiring treatment while on the study drug: 75% in the 40-mg group, 47% in the 80-mg group and 41% in the 120-mg group. During the fifth year of the study, patients still enrolled in the study had no gout flares. Of the 26 patients with a palpable tophus at enrollment, 18 had resolution of the tophus by the final visit. Patients with a serum creatinine level >1.5 mg/dl were excluded from the study.

Clinical Efficacy & Safety of Successful Long-term Urate Lowering with Febuxostat or Allopurinol in Subjects with Gout (EXCEL)

Clinical Efficacy and Safety of Successful Long-term Urate Lowering with Febuxostat or Allopurinol in Subjects with Gout (EXCEL) was an open-label extension study of 1086 patients from two of the Phase III clinical trials comparing febuxostat and allopurinol, FACT and APEX, designed to assess the long-term efficacy of serum urate lowering, as well as clinical benefits and safety [18]. Febuxostat was dosed at 80 mg or 120 mg once daily, and allopurinol at 300 mg once daily; the follow-up period was up to 40 months. After initial randomization, patients were allowed to switch between treatment groups during the first 6 months; guidelines for treatment change are not explicit, but most changes were due to failure to achieve a serum urate level <6 mg/dl. Approximately 30% of patients made at least one treatment switch, most of these were away from the allopurinol group. Notably, an increase in the dose of allopurinol was not allowed. After 6 months, no further changes in treatment were permitted and after month 12, 75–100% of patients in all treatment groups maintained a serum urate level <6 mg/dl. As goal urate levels were achieved in the majority of patients, gout flares by month 18 were <4% overall. Tophus reduction occurred in 46, 36 and 29% of patients receiving febuxostat 80 mg, 120 mg and allopurinol, respectively. **Tables 2 & 3** summarize the efficacy data for the above mentioned studies.

Febuxostat efficacy & safety in special populations

Renal & hepatic impairment

The CONFIRMS trial included 1483 subjects with mild-to-moderate renal insufficiency, who received either allopurinol 200 or 300 mg daily, or febuxostat 40 or 80 mg daily. Febuxostat was superior in achieving the primary end point of a serum urate level <6 mg/dl (71% in 80-mg group, 49% in 40-mg group and 42% with allopurinol, $p < 0.001$). The rate of serious adverse events was not higher in the febuxostat group [16].

A Phase I study of febuxostat 80 mg in patients with mild-to-moderate hepatic impairment did not demonstrate any clinically significant differences in pharmacokinetics, when compared with healthy controls. The percentage decrease in serum urate levels was lower in patients with hepatic impairment, but this was not statistically significant [19].

Women & the elderly

A *post-hoc* analysis of 226 female patients enrolled in the Phase III clinical trials found that the primary end point of serum urate <6 mg/dl was achieved in over 80% of patients taking febuxostat (superior to allopurinol, $p < 0.05$), and was well tolerated [20]. A similar subgroup analysis of 374 elderly patients (age ≥65 years) from the CONFIRMS trial found that febuxostat was well tolerated and superior to allopurinol in lowering serum urate [21]. There were no clinically significant differences in pharmacokinetics, pharmacodynamics or safety based on age or gender [22].

Choice of febuxostat dose & efficacy

The four randomized controlled clinical trials have used doses from 40–240 mg daily. All doses have proven efficacy in lowering serum urate to <6.0 mg/dl. In general, the higher doses of febuxostat were more effective in lowering serum urate levels (see TABLE 2) [13]. The US FDA has approved febuxostat at the 40-mg dose for the chronic management of hyperuricemia in patients with gout; the 80-mg dose is recommended for patients who fail to achieve a serum urate level <6 mg/dl after 2 weeks on therapy [101]. In Europe, both the 80- and 120-mg doses are approved.

It should be noted that the maximum dose of allopurinol used in the comparator groups for these trials was 300 mg/day. Allopurinol is approved in doses up to 800 mg/day, and if up-titrated slowly, 600 mg/day is a common maintenance dose in patients with moderately severe gout and normal renal function [102]. There is still significant debate regarding the safest yet most effective dosing of allopurinol in patients with renal insufficiency [23].

Safety & tolerability

CV effects

In the initial clinical trials, APEX and FACT, there was a nonsignificant increase in the absolute number of CV events in the febuxostat groups, compared with allopurinol. In APEX, there were two adverse CV events in the febuxostat group compared with none in the allopurinol group [15]. In FACT, there were five adverse CV events, compared with one in the allopurinol group [14]. In FOCUS, CV events occurred in 5% of patients (combined data from three doses, 40, 80 and 120 mg), however, there was no placebo or control group [17]. In EXCEL, there were five adverse cardiac events and 14 adverse vascular events in the treatment groups, compared with three and one, respectively, in the allopurinol group [18]. However, as FOCUS and EXCEL were open-label extension studies, it is hard to make direct comparisons about adverse events with the much smaller allopurinol group. Notably, there was not a dose-dependent increase in adverse CV events. While overall rates of CV events in these studies were low, the FDA required a larger study to assess CV safety before drug approval.

The CONFIRMS trial was designed to evaluate a larger population of patients with a prescreening evaluation of CV disease or risk factors and overall CV events, defined by the Anti-Platelet Trialists' Collaboration (APTC) as CV death, nonfatal myocardial infarction or stroke [24]; non-APTC cardiac events, including unstable angina, CV revascularization, cerebral revascularization, transient ischemic attack, arterial peripheral vascular thrombosis, congestive heart failure and arrhythmia were also evaluated. A blinded CV end points committee evaluated all of the adverse events; they identified three APTC events in the febuxostat 80-mg group and three in the allopurinol group. There was no statistically significant difference between groups with respect to non-APTC events (ten, nine and seven in febuxostat 40 and 80 mg, and allopurinol groups, respectively) [16].

It should also be noted that 89% of the patients enrolled in the Phase III studies had one or more CV risk factors; 30% of the patients had three or more CV risk factors [14–16]. The Cardiovascular Safety of Febuxostat and Allopurinol in Patients With Gout and Cardiovascular Comorbidities (CARES) study is an ongoing clinical trial evaluating CV outcomes in high-risk subjects with a history of a major CV or cerebrovascular event [103].

The effect of febuxostat on the corrected QT interval on electrocardiogram was evaluated in a Phase I study of healthy controls, in doses up to 300 mg daily. There was no significant difference in the corrected QT interval between febuxostat and placebo; there was a significant difference in the active control group (moxifloxacin) [25].

Hepatic effects

Elevations in liver enzymes did occur in some treatment groups. When combining the data from the three Phase III clinical trials (APEX, FACT and CONFIRMS), approximately 4–6% of patients taking febuxostat and 4% of patients taking allopurinol experienced liver function test abnormalities, however, only 2–3% of patients in either group developed aspartate aminotransferase or alanine aminotransferase elevations greater than three times the upper limit of normal [14–16]. There was no clear relationship by drug dose.

All of the liver function abnormalities resolved with continued treatment or promptly after discontinuation of the drug. Notably, over 60% of subjects in the Phase III studies endorsed regular alcohol use [14–16].

Renal effects

There were no significant differences in renal adverse events between placebo, febuxostat and allopurinol. Edema was the most commonly reported adverse event, which occurred in approximately 2% of patients across all Phase III trials. New onset renal insufficiency occurred in <1% of patients, and was similar across all treatment groups [14–16].

Dermatologic effects

Mild or moderate skin rashes occurred with an incidence of 1–6% in the Phase III clinical trials, with a similar incidence reported in the allopurinol groups [14–16]. There was one report of a severe rash leading to study withdrawal in APEX [15]. None of the Phase III randomized clinical trials included patients with a history of allopurinol hypersensitivity syndrome, therefore it is unknown whether these patients would have similar reactions to febuxostat. As part of a subgroup analysis in FOCUS, six patients with a history of allopurinol intolerance (defined as a reaction precluding drug rechallenge, including rash/hives and gastrointestinal symptoms) were followed for 4 years and were able to safely tolerate febuxostat without significant reactions [26].

There have been postmarketing reports of rare serious and/or generalized skin rashes, and skin hypersensitivity reactions; most of these reactions occurred in the first month of therapy, some in patients who had prior hypersensitivity reactions to allopurinol [104].

Tolerability

The most frequently reported adverse events in the Phase III studies were upper respiratory tract infections, musculoskeletal symptoms and diarrhea, which occurred with similar frequency in the febuxostat and allopurinol groups [14–16].

Drug–drug interactions

There were no significant drug–drug interactions identified during Phase I trials. Specifically, febuxostat in combination with hydrochlorothiazide, cochicine, indomethacin, theophylline and naproxen did not reveal any clinically significant interactions or need for dose adjustment [27–30]. Desipramine, a cytochrome p450 2D6 substrate, had little inhibitory effect on febuxostat, and no need for dose adjustment [31]. *In vitro* and Phase I studies of warfarin and febuxostat show no safety concerns and no need for dose adjustment of warfarin [32,33].

There are no published data on the interaction between febuxostat and azathioprine or 6-mercaptopurine; however, there is significant evidence that allopurinol increases the bioavailability of these thiopurines, potentially leading to severe toxicity, including bone marrow suppression, nausea and vomiting [34]. Therefore, until there are data to suggest otherwise, the combination of febuxostat and azathioprine or 6-mercaptopurine should be avoided.

Dose-related adverse events

As discussed above, doses from 40 to 240 mg daily all have proven efficacy in lowering serum urate to <6.0 mg/dl. In general, the higher doses of febuxostat were more effective in lowering serum urate levels [15]. Higher doses of febuxostat were associated with a significant increase in the rate of diarrhea and dizziness, as well as acute gout flares during initiation of treatment. There was not a dose-related difference in abnormal liver function tests [14–16].

Pharmacoeconomics

The current retail price for febuxostat in the USA is $184.99 for a 30-day supply of 40-mg tablets. A 30-day supply of generic allopurinol 300-mg tablets is approximately $5.60 [105]. The UK National Institute for Health and Clinical Excellence (NICE) recently published a cost–effectiveness analysis of febuxostat versus allopurinol, based on pooled data from the FACT and APEX trials. The ultimate conclusion of the study group was that the comparison of febuxostat and allopurinol could not be adequately assessed, as the clinical trials relied on fixed dosing of allopurinol (100 or 300 mg daily), rather than a gradual upward titration to the maximum dose of 600–800 mg daily. Despite this limitation, the NICE appraisal committee recommended that febuxostat be considered as an option for the management of chronic hyperuricemia in patients with gout who are intolerant of allopurinol, or have contraindications to its use [35].

Conclusion

Febuxostat is the first new drug to be approved for hyperuricemia in over 40 years. It demonstrates noninferiority to allopurinol at low dose and superiority at higher doses for lowering serum urate levels. However, it should be noted that the maximum dose of allopurinol used in these

studies was 300 mg daily, which is well below the FDA-approved maximum dose for moderate-to-severe gout. After continued treatment, subjects experienced an overall reduction in acute gout flares, as well as a reduction in tophi in some individuals. As febuxostat has a different mechanism of action and pharmacokinetics from allopurinol, it may occupy a niche for patients with gout and hyperuricemia who cannot tolerate allopurinol, particularly patients with renal insufficiency.

Future perspective

The pharmacoepidemiologic studies of febuxostat are likely to reveal more data on safe use, especially as related to CV outcomes. The CARES study is an ongoing clinical trial enrolling subjects with hyperuricemia, gout and a history of major CV or cerebrovascular disease, evaluating the incidence of new major CV events while taking febuxostat or allopurinol [102]. Other ongoing clinical trials with febuxostat include: safety and efficacy in subjects with moderate-to-severe renal insufficiency, effects on renal blood flow in patients with hypertension, outcomes in patients with hyperurcosiuria and calcium oxalate stones, and modifying effect on joint damage in patients with early gout [106]. Combination therapy of febuxostat with allopurinol and/or uricosuric agents is a promising avenue for further exploration.

Financial & competing interests disclosure

E Krishnan has consultant/advisor/grant recipient relationships with Takeda Pharmaceuticals International Inc. (Deerfield, IL, USA). In the past E Krishnan has been a shareholder of Savient Pharmaceuticals. E Krishnan is an investigator for a clinical trial performed by ARDEA, Inc. and Metabolex, Inc. E Krishnan serves on advisory boards for Takeda, URL Pharma and UCB, Inc. In order to ensure accuracy, the factual data were verified with the authors and sponsors of the original febuxostat papers reviewed here. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Approved indication

- Febuxostat is US FDA approved for the chronic management of hyperuricemia in patients with gout.

Therapeutic targets in gout

- Involves the treatment of acute inflammation and reduction of risk factors, especially serum urate.
- Three classes of drugs are approved for urate-lowering therapy: xanthine oxidase (XO) inhibitors, uricosuric agents and recombinant uricase preparations.

Mechanism of action

- Febuxostat is a novel, nonpurine XO inhibitor.
- Selectively blocks XO resulting in decreased serum urate levels.
- Compared with allopurinol, it has more enzyme selectivity and can bind both to the oxidized and reduced form of XO.

Pharmacokinetics

- Rapid oral absorption, highly metabolized in the liver.
- Minimal renal excretion; no dose adjustments for mild-to-moderate renal insufficiency.

Choice of administration, dose & efficacy

- Febuxostat is administered orally, at a dose of 40 or 80 mg once daily.
- There have been four randomized controlled trials of febuxostat versus allopurinol or placebo for the primary end point of lowering serum urate level; secondary end points included reduction in gout flares and tophi.
- Febuxostat was effective in lowering serum urate levels, with higher doses being more efficacious.
- Long-term extension studies demonstrate a significant reduction in gout flares and some reduction in tophi with continued use.

Summary of adverse events & toxicity

- Generally well tolerated.
- Elevated liver enzymes occurred in approximately 3% of patients.
- Initial concern for a small increase in cardiovascular events was not reproduced in a subsequent, FDA-mandated safety evaluation.
- Insufficient data to report on safety in patients with a history of allopurinol hypersensitivity syndrome.

Potential interactions

- No significant drug–drug interactions have been reported, although caution should be used when febuxostat is used in conjunction with azathioprine and 6-mercaptopurine, based on data with allopurinol.

Questions being answered in ongoing studies

- Safety in patients with known cardiovascular disease and moderate-to-severe renal insufficiency.
- Efficacy in patients with hyperurcoisuria and calcium oxalate stones.
- Combination therapy with febuxostat and allopurinol.

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