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Febuxostat

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Contents

Abstract

▲ Febuxostat is an orally administered, non-purine, selective inhibitor of xanthine oxidase approved for the management of chronic hyperuricaemia in patients with gout.

▲ In a randomized, double-blind, dose-ranging study in patients with gout and hyperuricaemia, significantly more recipients of febuxostat 40–120 mg/day than placebo had serum urate levels of <6.0 mg/dL after 4 weeks of treatment.

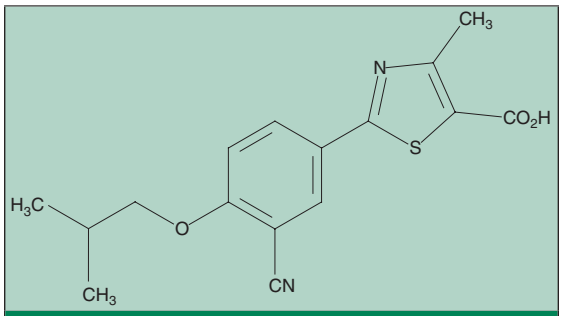
▲ Serum urate levels were reduced below 6.0 mg/dL at the last three monthly observations in a significantly greater proportion of patients with gout and hyperuricaemia receiving febuxostat 80 or 120 mg once daily than in those receiving allopurinol 300 mg once daily in a 52-week, randomized, double-blind trial (FACT).

▲ Similarly, febuxostat 80, 120 or 240 mg once daily showed significantly greater urate-lowering efficacy than allopurinol 100 or 300 mg once daily in a 28-week, randomized, double-blind, placebo-controlled trial (APEX) in patients with gout and hyperuricaemia.

▲ Long-term treatment with febuxostat for up to 4 years or more reduced the incidence of gout flares to (or close to) zero.

▲ Febuxostat was generally well tolerated in clinical trials, including extension studies lasting ≥4 years, with most treatment-related adverse events being mild to moderate in severity.

Features and properties of febuxostat (Adenuric®; TEI-6720; TMX-67)	
Indication	
Chronic hyperuricaemia in patients with gout (i.e. in conditions where urate deposition has already occurred)	
Mechanism of action	
Inhibition of xanthine oxidase	
Dose and administration	
Dose	80 or 120 mg
Route of administration	Oral
Frequency of administration	Once daily
Mean steady-state pharmacokinetic parameters in healthy volunteers (120 mg once daily for 13 days)	
Maximum plasma concentration (C_{max})	5.31 μg/mL
Area under the plasma concentration-time curve from time 0 to 24 h	11.96 μg • h/mL
Time to C_{max}	1.1 h
Elimination half-life	11.9 h
Adverse events	
Most frequently reported adverse events in phase III trials	Liver function test abnormalities, diarrhoea, headache, nausea, rash



Febuxostat

Gout is a common inflammatory joint disease worldwide,[1] and its incidence appears to be increasing in Western countries.[1,2] In the US, the prevalence of self-reported gout in the National Health Interview Survey in 1996 was 0.9%.[3] Men are at greater risk of gout than women, but this disparity lessens with increasing age.[4] The acute joint inflammation that is characteristic of gouty arthritis is caused by the deposition of monosodium urate crystals as a result of hyperuricaemia[5,6] (a serum uric acid [sUA] level >7 mg/dL in men and >6 mg/dL in premenopausal women). Uric acid is the end product of purine metabolism and exists predominantly as the urate anion at physiological pH.[5] At serum urate concentrations >6.8 mg/dL (360 μmol/L), body fluids become supersaturated and crystals can precipitate.[7]

Symptomatic treatment of acute gouty arthritis with agents such as colchicine and NSAIDs does not affect hyperuricaemia; in patients experiencing frequent attacks of gout, maintenance treatment with urate-lowering agents (such as xanthine oxidase inhibitors or uricosurics) is necessary for adequate prevention of further attacks.[8,9]

Urate-lowering therapy is typically initiated 2–8 weeks after resolution of an acute gout attack.[8,9] Anti-inflammatory therapy with low-dose, oral colchicine or an NSAID is recommended during the first few months of maintenance treatment and may be required for 12 months or more, depending on the sUA level.[8,9] Urate-lowering maintenance treatment of gout is effective only if it is continuous (not intermittent) and life long;[9] an sUA level of <6 mg/dL is regarded as a suitable goal of urate-lowering therapy.[8,9] However, reduction of sUA levels below 5 mg/dL might be necessary to promote resorption of tophi (urate deposits).[9]

Xanthine oxidase inhibitors reduce sUA levels by impeding the transformation of hypoxanthine to xanthine and of xanthine to uric acid;[8] both conversions are catalyzed by the xanthine oxidoreductase enzymes xanthine oxidase and xanthine dehydrogenase.[10] The active sites of both enzymes are structurally equivalent; xanthine dehydrogenase readily converts to xanthine oxidase in mammals.[10] For decades, allopurinol (a hypoxanthine analogue) was the only available xanthine oxidase/xanthine dehydrogenase inhibitor; it is currently the most frequently prescribed urate-lowering therapy.[8,9] It functions as both a substrate and inhibitor of xanthine oxidase, and, in contrast to a uricosuric drug, such as probenecid, can be used (with dosage adjustment) in patients with renal impairment.[8] However, allopurinol inhibits other enzymes besides xanthine oxidase/xanthine dehydrogenase in the purine and pyrimidine pathway,[11] is not tolerated in up to 5% of patients[8] and has limited efficacy at a once-daily oral dose of 300 mg.[12]

Febuxostat (Adenuric®; TEI-6720; TMX-67)[1] is a non-purine, selective xanthine oxidase/xanthine dehydrogenase inhibitor[11] that was recently approved in the EU for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence, of tophus and/or gouty arthritis).[13] The clinical profile of febuxostat in this indication provides the focus of this review.

1. Pharmacodynamic Profile

In Vitro and Animal Studies

- Febuxostat inhibited xanthine oxidase potently and selectively in *in vitro* studies.[14,15] The drug completely inhibited human xanthine oxidase ac-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

tivity in the lung cancer cell line A549, whereas the activities of other enzymes involved in purine or pyrimidine metabolism (such as purine nucleoside phosphorylase, adenosine deaminase or pyrimidine nucleoside phosphorylase) were affected by <4%.[14]

- Febuxostat showed mixed-type inhibition of bovine milk xanthine oxidase (closely homologous to the human enzyme).[10] Unlike oxypurinol (the active metabolite of allopurinol), which binds tightly only to the reduced form of xanthine oxidase, febuxostat inhibited both the oxidized and reduced forms of the enzyme.[10,15]
- Febuxostat was bound in a long, narrow channel leading to the molybdenum-pterin active site of bovine milk xanthine dehydrogenase, as revealed by a crystal structure determination.[10] Enzyme activity was inhibited by febuxostat blocking substrate binding.[10]
- In preclinical studies, febuxostat was more potent than allopurinol in inhibiting xanthine oxidase and decreasing sUA levels.[16,17] *In vitro,* the drug concentrations resulting in 50% inhibition of the activity of xanthine oxidase/xanthine dehydrogenase derived from bovine milk, mouse liver or rat liver were 1.4, 1.8 and 2.2 nmol/L for febuxostat compared with 1700, 380 and 100 nmol/L for allopurinol.[16] *In vivo,* in chimpanzees (similar to humans in terms of purine metabolite levels and urate excretion), sUA levels were reduced after 24, 48 and 72 hours with febuxostat by 56%, 70% and 74%, and with allopurinol by 28%, 42% and 45% (each 5 mg/kg/day orally for 3 days).[17]

Studies in Humans

The pharmacodynamic effects of oral febuxostat have been examined in healthy volunteers (n = 130[18] and n = 48[19]) and in patients with renal (n = 31)[20] or hepatic impairment (n = 28)[21] in randomized, and placebo-controlled[18] or nonblind[19-21] studies. Subjects received oral febuxostat 10–240 mg once daily for 13 days[18] or 80 mg once daily for 1 week.[19-21] The effects of febuxostat on xanthine and hypoxanthine levels in patients with gout and hyperuricaemia[22] are also briefly mentioned in this section (see section 3 for study design details); the urate-lowering properties of febuxostat in this patient population are discussed in section 3.

- Febuxostat 10–120 mg/day dose-dependently reduced mean sUA levels from baseline by 25–70% in healthy volunteers; 24-hour urinary uric acid excretion at day 8 was decreased by 46–66% relative to placebo.[18] Both effects seemed to plateau at dosages >120 mg/day.[18] Age and sex had no clinically significant effect on the urate-lowering properties of oral febuxostat 80 mg/day in healthy volunteers.[19]
- Febuxostat had similar urate-lowering effects in healthy and renally impaired adults.[20] After 1 week, febuxostat significantly (all $p \leq 0.05$) reduced mean 24-hour sUA levels from baseline by 58%, 64%, 57% and 55% in volunteers with normal renal function and mild, moderate or severe renal impairment, respectively.[20] Although there was a statistically significant ($p \leq 0.05$) quadratic relationship between the decrease in sUA levels and creatinine clearance, the differences in the percentage decrease in mean sUA levels between the healthy and renally impaired groups were <6%.[20]
- The reduction from baseline in mean 24-hour sUA levels was significantly ($p = 0.003$) smaller in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment than in volunteers with normal hepatic function following 1 week of febuxostat (49% and 48% vs 62%).[21] However, this between-group difference was not considered clinically significant.
- Although serum levels of xanthine and hypoxanthine increased in patients with gout and hyperuricaemia receiving febuxostat 40–120 mg/day for 28 days, they remained well below the solubility limits for these compounds (10 and 115 mg/dL) and xanthine crystals were not detected in urine.[22] Serum xanthine levels and urinary excretion of xanthine and hypoxanthine were increased in healthy volunteers receiving febuxostat, relative to those receiving placebo, but these effects seemed to plateau at dosages >120 mg/day.[18] In subjects with normal or impaired renal function, 24-hour mean serum levels of xanthine and hypoxanthine were ≤0.629 mg/dL and ≤0.154 mg/dL, respectively, after 1 week's treatment with febuxostat 80 mg/day.[20]

Mean 24-hour urinary concentrations of xanthine and hypoxanthine on day 7 in patients with normal renal function were 5.69 and 0.916 mg/dL, compared with 4.34 and 0.174 mg/dL in patients with severe renal impairment.[20]

2. Pharmacokinetic Profile

This section provides a brief overview of the pharmacokinetic properties of febuxostat in healthy volunteers,[18,19,23-28] or patients with hepatic[21] or renal[20] impairment. Several of the studies in this section are available only as abstracts/posters.[23,24,26,27]

- Following single- or multiple-dose administration of febuxostat, dose-proportional increases in the maximum plasma concentration (C_{max}) were seen over the 10–240 mg dose range, and in the area under the plasma concentration-time curve (AUC) over the 10–120 mg dose range.[18] The time to C_{max} (t_{max}) was ≈1 hour.[18] Multiple-dose administration of oral febuxostat 120 mg once daily for 13 days resulted in values for mean C_{max}, t_{max} and AUC from time 0 to 24 hours (AUC_{24}) of 5.31 μg/mL, 1.1 hours and 11.96 μg • h/mL, respectively.[18] Circulating febuxostat was substantially bound to albumin (≈99%), with an apparent volume of distribution at steady state of ≈0.7 L/kg.[20]
- The effects of food intake, antacid consumption, age and sex on the pharmacokinetics of oral, once-daily febuxostat 80 mg were not considered to be clinically significant in studies in healthy volunteers.[19,28]
- Febuxostat was metabolized mainly by conjugation via uridine diphosphate-glucuronosyltransferase (UGT) enzymes (mainly UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT1A10 and UGT2B7)[29] or to a smaller extent by oxidative metabolism via cytochrome P450 (CYP) enzymes (mainly CYP1A1, CYP1A2, CYP2C8 and CYP2C9) to form the active metabolites 67M-1, 67M-2 and 67M-4.[20,29] Oral administration of febuxostat 10–240 mg/day for 13 days in healthy volunteers resulted, at steady state, in urinary excretion of 25–45% of the drug dose as either intact febuxostat or its conjugate (1–6% as intact drug); an additional 2–8% of the dose was excreted in urine as oxidative metabolites.[18] The mean elimination half-life of febuxostat 120 mg once daily was 11.9 hours.[18]
- Dosage adjustment of febuxostat is not required in patients with mild or moderate renal impairment.[30] Plasma exposure to multiple-dose febuxostat and its oxidative metabolites tended to increase with decreasing renal function in adult subjects with mild, moderate or severe renal impairment (also see section 1).[20] There were no statistically significant effects of mild or moderate hepatic impairment on the pharmacokinetics of multiple-dose febuxostat and its oxidative metabolites (also see section 1).[21] The recommended daily dosage of febuxostat is 80 mg in patients with mild hepatic impairment.[30]
- CYP1A2, CYP2C9, CYP2C19 and CYP3A4 were not significantly affected by febuxostat *in vitro* (inhibition constant [K_i] >100 μmol/L), but the drug did have some inhibitory effect on CYP2D6 (K_i = 40 μmol/L).[27,29]
- The effect of febuxostat on the metabolism of a CYP2D6 substrate was not considered to be clinically significant in a double-blind, crossover study in 18 healthy volunteers who were CYP2D6 extensive metabolizers.[27] Subjects received multiple, once-daily oral doses of febuxostat 120 mg or placebo, followed by a single oral dose of desipramine 25 mg; the 2-hydroxydesipramine **:** desipramine AUC_∞ ratio was 0.88 with desipramine plus placebo and 0.74 with desipramine plus febuxostat.[27]
- Febuxostat had no clinically significant interactions with colchicine, indometacin, hydrochlorothiazide or warfarin in adults in randomized, crossover studies.[23-26] Although coadministration of naproxen 500 mg twice daily with febuxostat 80 mg once daily increased the C_{max} and AUC_{24} of febuxostat by 28% and 41%, this was not deemed clinically significant.[25]
- The metabolism of the purine antimetabolites azathioprine and mercaptopurine is known to be suppressed by allopurinol-induced xanthine oxidase inhibition, greatly increasing the risk of haematological toxicity with these agents.[31] No data are

available as yet concerning a possible interaction of febuxostat with azathioprine or mercaptopurine.

3. Therapeutic Efficacy

The antihyperuricaemic efficacy of oral, once-daily febuxostat has been evaluated in adult patients with gout and hyperuricaemia in randomized, multicentre trials consisting of a 4-week, double-blind, placebo-controlled, dose-response trial (n = 153)[22] and three trials with allopurinol as the comparator. The randomized, allopurinol comparisons consisted of: FACT (Febuxostat versus Allopurinol Controlled Trial), a phase III, 52-week, double-blind study (n = 760);[32] APEX (Allopurinol-Placebo-controlled Efficacy study of febuXostat), a phase III, 28-week, double-blind, placebo-controlled study (n = 1067);[33] and EXCEL (fEbuXostat Comparative Extension Long-term study), a long-term, nonblind extension study in patients completing FACT and APEX (n = 735).[34-36] Data for APEX and EXCEL are available only in abstracts.[33-36] In addition, the long-term efficacy and tolerability of febuxostat were assessed in the FOCUS (Febuxostat Open-label of Urate-lowering efficacy and Safety) study (n = 116), a long-term, noncomparative, extension of the dose-response trial (presented as abstracts).[37-39]

The dose-response[22] and FACT[32] trials excluded patients with a serum creatinine level of >1.5 mg/dL, while APEX[33] included patients with moderate renal impairment (serum creatinine level of 1.6–2.0 mg/dL).

In the three double-blind trials, patients who were already being treated with urate-lowering therapy underwent an initial 2-week washout period, during which colchicine 0.6 mg once[32,33] or twice[22] daily, or naproxen 250 mg twice daily[32,33] was administered. No between-group differences in patient characteristics at baseline were reported in the dose-response[22] and FACT[32] trials. In APEX, baseline characteristics were reported only for the total patient population.[33] In all trials, the majority of patients were male (>88%) and Caucasian (≥77%); mean patient age was 51.8–54.0 years.[22,32,33]

All patients included in the double-blind trials had a baseline sUA level of ≥8.0 mg/dL[22,32,33] and fulfilled the American College of Rheumatology preliminary criteria for acute arthritis of gout.[22,32,40] Efficacy analyses were based on the intent-to-treat (ITT) population.[22,32,33]

Comparison with Placebo

In the dose-response study, once-daily doses of febuxostat (40, 80 or 120 mg) or placebo were administered to an ITT population of 140 patients (those with a valid baseline sUA value).[22] The primary endpoint was the proportion of patients in each treatment group with an sUA level <6.0 mg/dL at the completion of the 4-week, double-blind phase.[22] Secondary endpoints included the proportion of patients with an sUA level <6.0 mg/dL on days 7, 14 and 21, the percentage reduction from baseline in sUA level at each weekly visit and the percentage reduction from baseline to day 28 in daily urinary uric acid excretion.[22]

A total of 116 patients (including eight intolerant of allopurinol) continued therapy in the noncomparative FOCUS extension study in which febuxostat 80 mg/day was administered initially; three dose titrations were permitted to 40, 80 or 120 mg/day, but a stable dosage was maintained from week 28 onward.[37-39] Most patients (63%) remained on the 80 mg/day dosage.[37] The proportions of patients discontinuing treatment in years 1, 2, 3 and 4 were 36%, 4%, 3% and 4%, respectively.[39] Sixty nine patients completed 2 years of treatment,[37,38] while 61 patients (including six intolerant of allopurinol)[38] completed at least 4 years of treatment.[39] Colchicine 0.6 mg was administered twice daily for the first 2 weeks of the double-blind phase and for the first 4 weeks of the extension phase.[22,37]

- Febuxostat was significantly more effective than placebo at reducing sUA levels. After 4 weeks' treatment, a significantly greater proportion of patients receiving febuxostat 40, 80 or 120 mg/day than placebo had sUA levels <6.0 mg/dL (56%, 76%, 94% vs 0%; all $p < 0.001$).[22]
- In addition, significantly more febuxostat 40, 80 or 120 mg/day than placebo recipients had sUA

levels <6.0 mg/dL at weeks 1 (50%, 59%, 91% vs 3%), 2 (56%, 68%, 94% vs 0%) and 3 (59%, 76%, 97% vs 0%) [all $p < 0.001$].[22]

- Mean percentage changes from baseline in sUA levels at each weekly visit were significantly greater with febuxostat than placebo (−35% to −59% vs −2.2% to +1.6%; all $p < 0.001$), as were mean changes in daily urinary uric acid excretion (−44% to −47% vs +5.9%; all $p < 0.001$).[22]
- In FOCUS, the mean percentage reduction from baseline in sUA levels with febuxostat treatment for ≥2 years was 45–50%.[37] The proportions of patients who achieved an sUA level <6.0 mg/dL at years 1, 2, 3 and 4 were 78%, 76%, 84% and 90%, respectively.[39] An sUA level close to or <6.0 mg/dL was maintained in allopurinol-intolerant patients.[38] The incidence of gout flares requiring treatment declined over time, with the greatest reductions noted with the 80 mg/day dosage. The overall incidences of gout flares during years 1, 2, 3, 4 and 5 for febuxostat 80 mg/day were 1.67, 0.22, 0.02, 0.09 and 0.0 flares/subject-year.[39]

Comparisons with Allopurinol

The efficacy of febuxostat relative to allopurinol was assessed in patients with gout and hyperuricaemia in the pivotal phase III FACT[32] and APEX[33] trials. In FACT, febuxostat 80 or 120 mg/day or allopurinol 300 mg/day were administered for 52 weeks to 255, 250 and 251 patients.[32] Febuxostat 80, 120 or 240 mg/day, allopurinol 300 mg/day (or 100 mg/day in patients with moderate renal impairment) or placebo were administered for 28 weeks in APEX to 262, 269, 134, 268 and 134 patients, respectively; the group receiving febuxostat 240 mg/day was included primarily for safety evaluation.[33] Although allopurinol was administered in both the FACT and APEX trials at the most commonly used dosage of 300 mg once daily in patients without moderate renal impairment,[32,33] this dosage may not have been optimal; the prescribing information for allopurinol[41] recommends individualized dose titration (according to sUA level and renal function) within the dosage range 100–800 mg/day, with the proviso that a daily dose >300 mg should be administered as divided doses. Naproxen 250 mg twice daily or colchicine 0.6 mg once daily were administered during the initial 8 weeks of double-blind treatment in FACT.[32]

The primary efficacy endpoint was the proportion of patients with an sUA level <6.0 mg/dL at each of the final three monthly measurements.[32,33] Secondary efficacy endpoints in FACT included, at each patient visit (week 2, week 4 and then monthly), the percentage of patients with an sUA level <6.0 mg/dL and the percentage decline in sUA level from baseline.[32] Clinical endpoints included the percentage decrease in tophus size from baseline and the proportion of patients needing treatment for gout flare after cessation of prophylaxis with naproxen or colchicine.[32]

Patients completing FACT or APEX were eligible for enrolment in EXCEL, the long-term, extension study. Initially, all patients enrolled in EXCEL received febuxostat 80 mg/day (n = 351), but the protocol was amended to randomize patients (n = 735) 2 : 2 : 1 to open-label febuxostat 80 mg/day, febuxostat 120 mg/day or allopurinol 300 mg/day (or 100 mg/day in those with moderate renal impairment; n = 8), although regimens could be switched at the investigators' discretion in the first 6 months.[34] Approximately 20% of patients (214 of 1086) had tophi at baseline.[36] Patients with an sUA >6 mg/dL at 6 months were to be discontinued from the study.[34]

- Febuxostat had significantly greater urate-lowering efficacy than allopurinol in both the FACT[32] and APEX[33] trials. In FACT, the primary endpoint was achieved in a significantly (both $p < 0.001$) greater number of recipients of febuxostat 80 or 120 mg/day than allopurinol 300 mg/day (figure 1).[32] In APEX, significantly more patients receiving febuxostat 80, 120 or 240 mg/day than allopurinol or placebo achieved the primary endpoint (48%, 65% and 69% vs 22% and 0%; all $p < 0.05$).[33] There were also significant ($p < 0.05$) differences between allopurinol and placebo recipients for this parameter and between patients receiving febuxostat 120 or 240 mg/day and those receiving febuxostat 80 mg/day.[33]

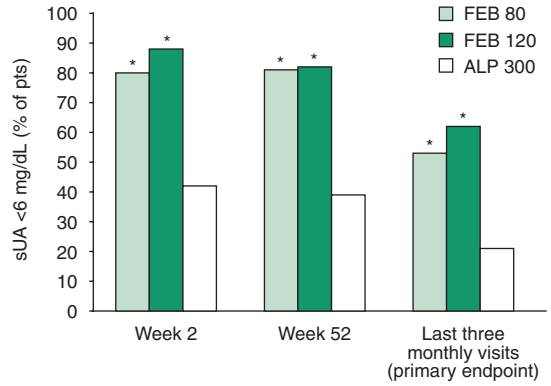


Fig. 1. Comparative efficacy of febuxostat (FEB) vs allopurinol (ALP). Proportion of patients (pts) with gout and hyperuricaemia achieving a serum uric acid (sUA) level <6.0 mg/dL after treatment with oral, once-daily FEB 80 (n = 255) or 120 (n = 250) mg/day, or ALP 300 mg/day (n = 251) at weeks 2 and 52, and at each of the last three monthly visits (primary endpoint) in the 1-year, randomized, double-blind, multicentre study FACT.[32] * $p < 0.001$ vs ALP.

- In patients with moderate renal impairment, the primary endpoint was attained in APEX in 44%, 45% and 60% of recipients of febuxostat 80 (n = 9), 120 (n = 11) or 240 (n = 5) mg/day, compared with 10% of allopurinol 100 mg/day (n = 10) and none of placebo (n = 5) recipients (no statistical analysis reported).[33]

- Significantly more febuxostat than allopurinol recipients ($p < 0.001$) achieved an sUA level of <6.0 mg/dL at all patient visits in FACT (see figure 1 for data at weeks 2 and 52).[32] In addition, the mean percentage reductions from baseline in sUA level at the last visit were 45% and 52% in patients receiving febuxostat 80 and 120 mg/day compared with 33% in recipients of allopurinol 300 mg/day (both $p < 0.001$ vs allopurinol).[32]

- There were no significant differences between febuxostat and allopurinol in FACT for reduction of tophus size or the proportion of patients treated for post-prophylaxis gout flare.[32] The median reductions in tophus area from baseline at week 52 were 83%, 66% and 50% in recipients of febuxostat 80 or 120 mg/day, or allopurinol 300 mg/day.[32] The proportions of patients receiving treatment for gout flare during weeks 9–52 were 64%, 70% and 64% in the respective treatment groups; the corresponding proportions for weeks 49–52 were 8%, 6% and 11%.[32]

- At the interim analysis of EXCEL, 75% of patients (815 of 1086) continued treatment with >16 months of exposure.[34] The proportions of patients switching treatment owing to failure to achieve or maintain an sUA <6.0 mg/dL were 22% with febuxostat 80 mg/day, 8% with febuxostat 120 mg/day and 57% with allopurinol.[34] Of those switched from allopurinol (n = 82), 67% were subsequently successfully treated with febuxostat.[35] The incidences of gout flares during years 1, 2 and 3 were 1.40, 0.27 and 0.19 flares/subject-year with febuxostat 80 mg/day, 1.72, 0.44 and 0.0 flares/subject-year with febuxostat 120 mg/day, and 1.49, 0.37 and 0.11 flares/subject-year with allopurinol.[34,36] Of those with tophi at baseline, complete resolution of tophi was observed in 38% (44 of 115) and 36% (16 of 44) of febuxostat 80 and 120 mg/day recipients, and 17% (4 of 23) of allopurinol recipients at the final visit of initial treatment.[34] At 18 months, 52% of febuxostat 80 (30 of 58) and 120 (11 of 21) mg/day recipients, and 40% (2 of 5) of allopurinol recipients had achieved complete resolution of tophi.[36]

4. Tolerability

Tolerability data were obtained from the clinical trials discussed in section 3,[22,32-38] supplemented with information from the manufacturer's prescribing information.[30] Where defined,[32] treatment-related adverse events included only events that were possibly, probably or definitely related to the study drug.

- Febuxostat was generally well tolerated in patients with gout and hyperuricaemia; most treatment-related adverse events were of mild to moderate severity.[22,32,33,37]

- In the 4-week dose-response trial, the incidences of treatment-related adverse events were similar in the placebo (n = 38) and febuxostat (n = 115) groups; the most frequent events were diarrhoea (0–10% of febuxostat 40–120 mg/day recipients vs 8% of placebo recipients), abdominal pain (3% vs 5%) and liver function test (LFT) abnormalities

(3–5% vs 0%).[22] The most common events with febuxostat in the noncomparative 2-year extension phase were diarrhoea (9% of patients), headache (4%) and LFT abnormalities (4%).[37] In both the double-blind and extension phases, LFT abnormalities were associated with colchicine administration.[22,37] The eight allopurinol-intolerant patients (section 3) experienced a total of eight treatment-related adverse events during the extension phase; all of the events, except for one case of LFT abnormalities (possibly caused by alcohol abuse), resolved while febuxostat therapy continued.[38]

- Febuxostat 80 or 120 mg/day showed similar tolerability to allopurinol in FACT; the overall incidence of treatment-related adverse events in the corresponding treatment groups was 25%, 24% and 23%.[32] The most common treatment-related adverse events in FACT are presented in figure 2.[32]

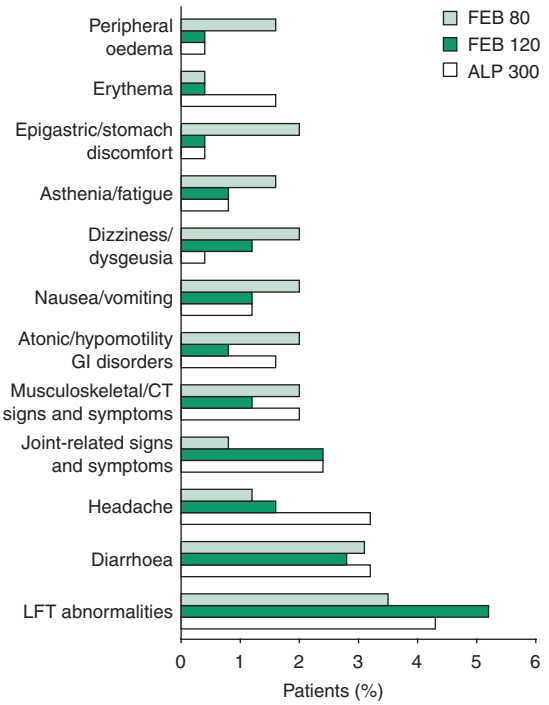


Fig. 2. Comparative tolerability of febuxostat (FEB) vs allopurinol (ALP). Incidence of the most frequent treatment-related adverse events in patients with gout and hyperuricaemia receiving oral, once-daily FEB 80 (n = 256) or 120 (n = 251) mg/day, or ALP 300 mg/day (n = 253) for 52 weeks in the randomized, double-blind, multicentre study FACT.[32] The most frequent treatment-related adverse events were defined as those occurring in ≥2% (when rounded to whole percentages) of patients in at least one treatment group. **CT** = connective tissue; **GI** = gastrointestinal; **LFT** = liver function test.

- In APEX, there was no increased incidence of adverse events in patients with moderate renal impairment (n = 40) compared with that in patients with normal renal function.[33]
- In a pooled analysis of the phase III FACT and APEX trials (n = 1043), the most commonly reported adverse events according to the investigators' assessment were LFT abnormalities (3.5%), diarrhoea (2.7%), headache (1.8%), nausea (1.7%) and rash (1.5%).[30] Diarrhoea, nausea and vomiting were more frequent in patients treated concomitantly with colchicine.[30]
- Discontinuation of treatment in FACT because of an adverse event occurred in 6.3% and 9.2% of patients receiving febuxostat 80 or 120 mg/day and in 3.2% of allopurinol 300 mg/day recipients.[32] The most common event causing withdrawal was LFT abnormalities (2.0%, 2.8% and 0.4% in the respective treatment groups; p = 0.04 for febuxostat 120 mg/day vs allopurinol 300 mg/day), followed by rash (1.6%, 1.6% and 0.4%).[32]
- Serious adverse events occurred in 3% and 10% of febuxostat recipients in the double-blind[22] and extension[37] phases of the dose-response trial, and 4%, 8% and 8% of febuxostat 80 or 120 mg/day and allopurinol 300 mg/day recipients in FACT.[32] In APEX, 34 of 1067 patients (3.2%) experienced serious adverse events with no difference across treatment groups.[33] All of these serious adverse events were considered to be either unrelated to treatment or unlikely to be related to treatment, except for Guillain-Barré syndrome in a recipient of febuxostat 80 mg/day in the dose-response trial (deemed possibly related).[22]
- The most frequent adverse events (≥5 events/100 patient-years) in EXCEL were upper respiratory tract infections, musculoskeletal, connective tissue or joint signs and symptoms, headache and diarrhoea; the incidences of events were similar in febuxostat and allopurinol recipients.[35] The incidences of serious adverse events were also similar between febuxostat (10 events/100 patient-years)

and allopurinol (11 events/100 patient-years) recipients.[35] In each group, cardiac disorders (3 events/100 patient-years) were the most common serious adverse events.[35]

5. Dosage and Administration

The recommended dosage of febuxostat in the EU is 80 mg orally once daily without regard to food, and the therapeutic target is to reduce and maintain sUA levels below 6.0 mg/dL (357 μmol/L).[30] If sUA is >6.0 mg/dL after 2–4 weeks of treatment with febuxostat 80 mg/day, a dosage of 120 mg once daily may be considered. At the initiation of therapy with febuxostat, prophylaxis for gout flare is recommended for at least 6 months.[30]

Local prescribing information should be consulted for detailed administration information, including contraindications, warnings, precautions, drug interactions and use in special patient populations.

6. Febuxostat: Current Status

Febuxostat has been approved for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence, of tophus and/or gouty arthritis).[30]

In well controlled clinical trials in patients with hyperuricaemia and gout, febuxostat reduced sUA levels with significantly greater efficacy than allopurinol, and was generally well tolerated.

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