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ADIS DRUG EVALUATION

Febuxostat: A Review of Its Use in the Treatment of Hyperuricaemia in Patients with Gout

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Abstract Febuxostat (Adenuric®, Uloric®, Feburic®) is an orally-active, potent, non-purine, selective xanthine oxidase inhibitor. In the EU, it is indicated in adults for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred. Unlike allopurinol, the prototypical xanthine oxidase inhibitor that is the cornerstone therapy for chronic gout, febuxostat does not require dosage adjustment in patients with mild or moderate renal impairment. In randomized, double-blind studies, 6–12 months' treatment with febuxostat at dosages approved for use in the EU (80 and 120 mg/day) was significantly more effective in lowering serum uric acid (sUA) levels in patients with hyperuricaemia and gout than allopurinol at dosages commonly prescribed in practice (100–300 mg/day); febuxostat demonstrated greater urate-lowering efficacy than allopurinol in patients with renal impairment. In open-label extension studies, 3–5 years' treatment with febuxostat maintained a target sUA level of <6.0 mg/dL in most patients; sustained reduction in sUA level was associated with near elimination of gout flares and improved tophus status. Febuxostat therapy was generally well tolerated during clinical development; frequently reported adverse events included liver function abnormalities, diarrhoea and rash. Cardiovascular (CV) events were the most common serious adverse events; the comparative safety of febuxostat and allopurinol is being examined further in large, ongoing trials in patients with gout who already have, or are at risk of developing, CV disease. In conclusion, febuxostat is a well established antihyperuricaemic agent that provides an effective alternative to allopurinol for the management of chronic gout.

Febuxostat in patients with gout: a summary

Recommended starting dosage in EU is 80 mg/day; can increase to 120 mg/day if serum uric acid (sUA) level is >6 mg/dL (300 μmol/L) after 2–4 weeks
Febuxostat 80 or 120 mg/day more effective in lowering sUA level than allopurinol 100–300 mg/day
Gout flare prophylaxis is recommended for ≥6 months after initiating febuxostat therapy
Dosage adjustment not necessary in the elderly or patients with mild or moderate renal impairment
Monitoring of liver function prior to initiating febuxostat therapy (and periodically during treatment, based on clinical judgement) is recommended
Not recommended for use in patients with ischaemic heart disease or congestive heart failure

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1 Introduction

Gout, the most common form of inflammatory arthritis, affects 1–2 % of the general population, predominantly middle-aged to elderly men [1]. It is characterized biochemically as a disorder of uric acid metabolism and clinically by painful and potentially debilitating acute/episodic flares caused by the deposition of monosodium urate crystals in peripheral joints—especially the first metatarsophalangeal joint—as a result of hyperuricaemia [2, 3]. Although these flares are usually self-limiting, untreated gout may progress, with attacks becoming more frequent and, eventually, the formation of tophi and associated deforming arthritis [4]. Moreover, patients with hyperuricaemia, including those with gout, often have comorbidities, such as chronic kidney disease, insulin resistance, diabetes mellitus, obesity, hyperlipidaemia and hypertension, and therefore are at increased risk of cardiovascular (CV) disease [1, 5, 6].

In terms of the pharmacological management of gout, acute attacks are symptomatically treated with anti-inflammatory agents, such as colchicine, NSAIDs and systemic corticosteroids, which are intended to provide rapid relief of joint pain and swelling [1, 7–9]. Colchicine and NSAIDs are also used prophylactically to prevent acute flares, including 'mobilization' flares that can occur during the initiation of long-term urate-lowering therapy in patients with evidence of disease progression, such as those experiencing recurrent flares [7, 8]. Life-long reduction and maintenance of serum uric acid (sUA) levels below the physiological saturation threshold ($\approx$6.8 mg/dL) suppresses the formation and deposition of monosodium urate crystals (reducing the risk of future flares) and promotes resolution of existing tophi (thereby preventing further joint damage); it is considered to be the optimal treatment strategy with the potential to 'cure' chronic gout [1, 7, 10]. Achieving and sustaining an sUA level of <6 mg/dL (<360 μmol/L) [or <5 mg/dL (<300 μmol/L) in patients with persistent or severe gout] are goals of urate-lowering therapy, as set out in, for example, guidelines issued by the European League Against Rheumatism (EULAR) [11] and the American College of Rheumatology (ACR) [12].

Currently, there are three commercially available classes of drugs for lowering sUA levels: xanthine oxidase inhibitors (which block the synthesis of uric acid); uricosuric agents (which block the renal tubular reabsorption of uric acid); and uricase agents (which convert uric acid into soluble allantoin) [7, 8]. Xanthine oxidase inhibitors are the usual first-choice antihyperuricaemic drugs; the prototypical agent allopurinol continues to be the cornerstone therapy for chronic gout around half a century after its clinical introduction. However, aspects of allopurinol, such as its association with a rare, but potentially fatal hypersensitivity reaction, and the need (at least initially) for dose reductions in patients with renal impairment, have adversely affected its use in clinical practice; the drug is commonly prescribed at lower dosages ($\leq$300 mg/day) that are often suboptimal [5–7, 12, 13]. These limitations have prompted the development of an alternative xanthine oxidase inhibitor, namely febuxostat (Adenuric®, Uloric®, Feburic®). Among other countries, febuxostat has been 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) [14], in the USA for the chronic management of hyperuricemia in patients with gout [15], and in Japan for the treatment of hyperuricaemia in patients with or without gout [16]. This article briefly summarizes the pharmacological properties of febuxostat and reviews, primarily from an EU perspective, its therapeutic efficacy and tolerability in the treatment of patients with hyperuricaemia and gout.

2 Pharmacological Properties

The pharmacological properties of febuxostat have been reviewed previously [3, 6, 17, 18]; therefore, this section only provides an updated overview.

Xanthine oxidase inhibitors, such as febuxostat and allopurinol, reduce sUA levels by impeding the transformation of hypoxanthine to xanthine and of xanthine to uric acid; both conversions are catalysed by xanthine oxidoreductase, an enzyme complex that exists in two separate, but interconvertible, forms that have structurally equivalent molybdenum-pterin active sites—xanthine dehydrogenase and xanthine oxidase. Xanthine oxidoreductase is synthesized (and normally present in vivo) as the dehydrogenase form, but can be readily converted to the oxidase form by oxidation of sulfhydryl residues or by proteolysis [3, 19].

Febuxostat is a potent and selective inhibitor of xanthine oxidase/xanthine dehydrogenase; it acts by noncompetitively blocking substrate binding to the active site. Febuxostat, a 2-arylthiazole derivative, differs structurally from allopurinol in that it lacks a modified purine ring; whereas febuxostat inhibits both the oxidized and reduced forms of xanthine oxidase, oxypurinol, the active metabolite of allopurinol, only inhibits the reduced form of xanthine oxidase. In preclinical studies, febuxostat was more potent than allopurinol in inhibiting XO and decreasing sUA levels. Febuxostat has minimal effects on other enzymes involved in purine or pyrimidine metabolism [3, 6, 17, 18].

The key pharmacodynamic properties of orally administered febuxostat are summarized in Table 1; the effects of

Table 1 Key pharmacodynamic properties of oral febuxostat

Dose-dependently decreased sUA levels in HVs [55] and pts with HU and gout [24–26]
sUA-lowering effect unaltered in pts with renal impairment [20]
sUA-lowering effect not reduced to a clinically significant extent in pts with mild or moderate hepatic impairment [56]
Decreased daily uUA excretion in HVs [55] and pts with HU and gout [24]
Increased serum levels of hypoxanthine and/or xanthine in HVs [55] and pts with HU and gout [24][a]
Increased urinary excretion of hypoxanthine and xanthine in HVs [55]
No effect on corrected QT interval in HVs and pts with HU and gout at dosages ≤300 mg/day [15]

FEB febuxostat, *HU* hyperuricaemia, *HVs* healthy volunteers, *pts* patients, *sUA* serum uric acid, *uUA* urinary uric acid

[a] FEB 40–120 mg/day dose-dependently increased serum hypoxanthine and xanthine levels in pts with HU and gout; however, levels remained substantially below solubility limits for these compounds [24]

Table 2 Key pharmacokinetic properties of oral febuxostat. Data are in healthy volunteers, except where indicated [3, 14]

Absorption and distribution
Systemic exposure is dose proportional over the range 10–120 mg and greater than dose-proportional over the range 120–300 mg
No appreciable accumulation following multiple (once daily) doses of 10–240 mg
Time to peak plasma concentration: 1–1.5 h
Can be taken without regard to food and antacid use
Plasma protein binding: ≈99 % (primarily to albumin)
Volume of distribution at steady state: 29–75 L
Metabolism and elimination
Extensively metabolized by conjugation (via UGT enzymes) and, to a lesser extent, by oxidation (primarily via CYP1A1, 1A2, 2C8 and 2C9)
Three pharmacologically active hydroxyl metabolites identified in human plasma: 67 M-1, -2 and -4
≈49 % of administered dose recovered in urine (30 % as acyl glucuronide of FEB); ≈45 % recovered in faeces (25 % as active metabolites of FEB and their conjugates)
Terminal elimination half-life: ≈5–8 h
Special populations
Exposure to FEB not affected to clinically significant extent by age; dosage adjustment not necessary in the elderly
Exposure to FEB (and its active metabolites) generally higher in pts with increasing degrees of renal impairment; however, dosage adjustment not necessary in pts with mild or moderate renal impairment. Efficacy and safety of FEB in pts with severe renal impairment not fully evaluated
Exposure to FEB (and its active metabolites) not altered to clinically significant extent in pts with mild or moderate hepatic impairment
Drug interactions
No clinically significant interactions demonstrated (or expected) with colchicine, naproxen, indomethacin, hydrochlorothiazide, theophylline, warfarin, rosiglitazone (or other CYP2C8 substrates) or desipramine (or other CYP2D6 substrates)

CYP cytochrome P450, *FEB* febuxostat, *pts* patients, *UGT* uridine diphosphate glucuronosyltransferase

febuxostat on sUA levels in patients with hyperuricaemia and gout are discussed in detail in Sect. 3. Of note, the urate-lowering effect of febuxostat 80 mg/day was unaltered in healthy volunteers with mild [creatinine clearance (CL_{CR}) of 50–80 mL/min/1.73 m^2), moderate (CL_{CR} of 30–49 mL/min/1.73 m^2) or severe (CL_{CR} of 10–29 mL/min/1.73 m^2) renal impairment relative to that in healthy volunteers with normal renal function (CL_{CR} of >80 mL/min/1.73 m^2) [20]; febuxostat 40–80 mg/day was effective in lowering sUA levels in pts with hyperuricaemia and gout who had mild to moderate renal impairment (in a large phase III study [21]; see Sect. 3) or moderate to severe renal impairment (in a small phase II study; $n = 96$ [22]).

The key pharmacokinetic properties of oral febuxostat are summarized in Table 2. Population pharmacokinetic analyses in patients with hyperuricaemia and gout indicate the pharmacokinetics of febuxostat in healthy volunteers are representative of those in the target population [14].

Regarding drugs that are metabolized by xanthine oxidase, febuxostat can be used in patients concomitantly treated with theophylline (albeit only the 80 mg dose has been studied in a drug-drug interaction study [23]). However, a possible interaction of febuxostat with azathioprine or mercaptopurine has not been formally evaluated; concomitant use of febuxostat with these immunosuppressants is not recommended [14].

3 Therapeutic Efficacy

The antihyperuricaemic efficacy of oral febuxostat at dosages ranging from 20 to 240 mg once daily has been evaluated in several randomized, double-blind, placebo and/or allopurinol-controlled, multicentre, phase II or III studies of 4–52 weeks' duration, which were conducted in the USA, Canada, China or Japan (n = 102–2,269) [21, 24–30]. This section focuses on findings from the five North American and Chinese studies, which exclusively enrolled adult patients with hyperuricaemia (sUA level ≥8.0 mg/dL) and gout (ACR preliminary criteria), and examined at least one of the two febuxostat dosages approved for use in the EU (80 and 120 mg once daily) [21, 24–26, 30].

Patients who completed a phase II dose-response study of febuxostat 40, 80 or 120 mg/day [24] were eligible to enter an open-label, multicentre, 5-year, extension study (FOCUS) [31]. In addition, patients who completed either a 28-week comparison with placebo and allopurinol (APEX)

[25] or a 52-week comparison with allopurinol (FACT) [26] were eligible to enter an open-label, multicentre, extension study of ≤40 months' duration that included an allopurinol treatment arm (EXCEL) [13]. Patients who successfully completed either of these extension studies were among those eligible to enter a third (26-week) comparison with allopurinol (CONFIRMS) [21].

Patients with renal impairment, those with a serum creatinine level >1.5 mg/dL or creatinine clearance (CL_{CR}) of <50 mL/min were excluded from the dose-response [24], Chinese [30] and FACT [26] trials, whereas those with a serum creatinine level >1.5 to ≤2.0 mg/dL were included in the APEX trial [25] and those with a CL_{CR} of 30–89 mL/min were included in the CONFIRMS trial [21]. Accordingly, a renally-adjusted dosage of allopurinol was administered to patients in the active-comparator arms of the APEX [25] and CONFIRMS [21] trials, but not the Chinese [30] and FACT [26] trials (Table 3).

All patients entering phase III double-blind studies were either treatment naïve or had washout of prior ULT; they received prophylaxis for gout flares (e.g. colchicine 0.5 or 0.6 mg/day, naproxen 500 mg/day or meloxicam 7.5 mg/day) during the washout period (all patients receiving prior urate-lowering therapy) and the first 8 [25, 26, 30] weeks of, or the entire 26 weeks of [21], double-blind treatment (all patients). Prophylaxis was also administered for the first 4 weeks and 2 months of open-label treatment in the FOCUS [31] and EXCEL [13] extension trials, respectively.

3.1 Urate-Lowering Efficacy

Febuxostat 80 and 120 mg/day were significantly more effective than allopurinol 100–300 mg/day in lowering sUA levels in patients with hyperuricaemia and gout, based on multiple assessments of urate-lowering efficacy from across four phase III studies (Table 3). Moreover, for both dosages, a significant ($p < 0.001$) treatment effect versus allopurinol was rapidly apparent (i.e. seen at the first post-baseline assessment after 2 weeks) and persistent (i.e. observed at all study visits through 52 weeks) [26]. Febuxostat 40 mg/day was noninferior to allopurinol 200 or 300 mg/day [21, 30].

The antihyperuricaemic activity of febuxostat was largely dose-dependent (Table 3). In particular, febuxostat 80 mg/day was significantly more effective than febuxostat 40 mg/day in the two phase III trials that simultaneously evaluated these dosages (the CONFIRMS and Chinese studies) (Table 3). In addition, febuxostat 120 mg/day generally demonstrated greater urate-lowering efficacy than febuxostat 80 mg/day in the two phase III trials that simultaneously evaluated these dosages (the APEX and FACT studies) (Table 3).

A target sUA level of <6.0 mg/dL at the final study visit (the primary efficacy outcome measure in the CONFIRMS study) was achieved in just over two-thirds of patients who received febuxostat 80 mg/day, compared with less than one-half of those who received allopurinol (Table 3). Similarly, almost three-quarters of the patients with moderate renal impairment who received febuxostat 80 mg/day in the CONFIRMS study reached this endpoint, compared with less than one-half of those who received allopurinol 200 or 300 mg/day (Table 3). Of note, significantly ($p < 0.001$) more febuxostat 80 mg/day recipients than allopurinol recipients reached the more stringent target sUA levels of <5.0 and <4.0 mg/dL at the final visit in the CONFIRMS and FACT studies, while significantly ($p < 0.001$) more febuxostat 120 mg/day than febuxostat 80 mg/day or allopurinol recipients reached these stricter targets at the final study visit in the FACT study [26].

A target sUA level of <6.0 mg/dL at the last 3 monthly visits (the primary efficacy outcome measure in the APEX [25], FACT [26] and Chinese [30] studies), was achieved in 45–53 and 62–65 % of all patients receiving febuxostat 80 and 120 mg/day, compared with 21–24 % of all patients receiving allopurinol (Table 3). Just under one-half of the patients with renal impairment who received febuxostat 80 or 120 mg/day reached this endpoint in the APEX study, compared with none of those who received allopurinol 100 mg/day (Table 3).

Post hoc subgroup analyses of the CONFIRMS trial [32–35] and the pooled APEX, CONFIRMS and FACT trials [36] confirmed the greater ($p < 0.05$) efficacy of febuxostat 80 mg/day compared with allopurinol 100–300 mg/day in female patients [36], elderly patients (aged ≥65 years) [33], younger patients (aged <65 years) [33], patients with or without concomitant diabetes mellitus [34], African–American patients [35] and Caucasian patients [35]. The efficacy of febuxostat 80 mg/day was significantly greater in elderly than younger patients ($p < 0.001$) [33], although it did not differ significantly between African-American and Caucasian patients [35]. These results were based on all patients in the afore-mentioned subgroups; the same pattern was seen in the further subsets of patients with either mild or moderate renal impairment [33–35]. Comparisons between febuxostat 120 mg/day and allopurinol 100–300 mg/day have not reported, except in female patients; this significantly ($p = 0.006$) favoured febuxostat over allopurinol [36].

In addition, subgroup analyses of the APEX [37], CONFIRMS [21] and FACT [26] studies suggested that febuxostat at dosages of 80 and 120 mg/day was significantly ($p < 0.05$) more effective than allopurinol 100–300 mg/day, irrespective of baseline sUA level (<9, 9 to <10 or ≥10 mg/dL). Higher baseline sUA levels were,

Table 3 Antihyperuricaemic efficacy of oral febuxostat in adult patients with gout and hyperuricaemia: results from phase III trials

Study	Duration (weeks)	Regimen[a] [mg/day] (no. of pts[b])	% pts with sUA <6.0 mg/dL		% change from BL in sUA at final visit
			At final visit	At last 3 monthly visits	
Becker et al. [21, 57] (CONFIRMS)	26	FEB 40 (757)	45.2[c] [49.7[†]][d]	–	−33.1[†]
		FEB 80 (756)	67.1[†††‡c] [71.6[†††‡]][d]	–	−40.6[†††‡]
		ALP 200 or 300[e] (755)	42.1[c] [42.3][d]	–	−31.3
Becker et al. [26] (FACT)	52	FEB 80 (255)	74[††]	53[††c]	−44.7[††]
		FEB 120 (250)	80[††]	62[††c]	−51.5[†††‡]
		ALP 300 (251)	36	21[c]	−33.0
Huang et al. [30] (Chinese Study)	28	FEB 40 (172)	–	27.3[c]	−32.9[f]
		FEB 80 (172)	–	44.8[†††‡c]	−41.8[†††‡f]
		ALP 300 (172)	–	23.8[c]	−32.7[f]
Schumacher et al. [25, 39] (APEX)	28	FEB 80 (262)	72*[††]	48*[††c] [44[†]][g]	−45.2*[††]
		FEB 120 (269)	79*[††]	65*[†††‡c] [45[†]][g]	−51.9*[†††‡]
		FEB 240 (134)	92*[†††‡§]	69*[†††‡c] [60[†]][g]	−66.3*[†††‡§]
		ALP 100 or 300[h] (268)	39*	22*[c] [0][g]	−33.7*
		PL (134)	1	0[c] [0][g]	−3.0

ALP allopurinol, *BL* baseline, CL_{CR} creatinine clearance, *FAS* full analysis set, *FEB* febuxostat, *ITT* intent to treat, *PL* placebo, *pts* patients, *RI* renal impairment, *sUA* serum urate concentration

* $p < 0.001$ vs. PL, [†] $p \leq 0.05$, [††] $p \leq 0.001$ vs. ALP, [‡] $p \leq 0.001$ vs. FEB 40 or 80, [§] $p < 0.001$ vs. FEB 120

[a] FEB, PL and ALP were all administered once daily

[b] Included in the analysis of the primary endpoint (FAS or ITT/modified ITT cohort). All pts had a sUA level ≥8.0 mg/dL at enrollment [30] or at BL [21, 25, 26]. Where known, the same number or fewer pts were included in analyses of other (secondary) endpoints

[c] Primary endpoint

[d] Pts with RI ($n = 479$, 503 and 501 in the FEB 40, FEB 80 and ALP 200 or 300 groups, respectively)

[e] Pts with normal renal function or mild RI (CL_{CR} 60–89 mL/min) received ALP 300; those with moderate RI (CL_{CR} 30–59 mL/min) received ALP 200

[f] Based on BL sUA of 9.89, 9.98 and 9.95 mg/dL in the FEB 80, FEB 120 and ALP 300 groups, respectively

[g] Pts with RI ($n = 9$, 11, 5, 10 and 5 in the FEB 80, FEB 120, FEB 240, ALP 100 and PL groups, respectively)

[h] Pts with normal renal function received ALP 300; those with RI (serum creatinine level >1.5 to ≤2.0 mg/dL) received ALP 100

however, significantly ($p < 0.001$) associated with lower rates of endpoint attainment [21].

In a further subgroup analysis of the CONFIRMS study, the proportion of febuxostat 80 mg/day recipients achieving an sUA level <6.0 mg/dL at the final visit was reportedly significantly higher among 88 patients who had previously maintained goal range sUA over 3–5 years in the EXCEL and FOCUS extension studies (see Sect. 3.3), as compared with 668 patients who had not previously participated in one or other of these extension trials (77.3 vs. 65.7 %) [21].

3.2 Clinical Efficacy

3.2.1 Gout Flares

A similar pattern with respect to the rate of gout flares requiring treatment was seen throughout the course of the APEX [25] and FACT [26] studies, in which prophylaxis was administered for the first 8 weeks only. During the period of prophylaxis, significantly more febuxostat 120 mg/day recipients than febuxostat 80 mg/day or allopurinol 100 or 300 mg/day recipients required treatment for gout flares [APEX: 36 vs. 28 and 23 % ($p \leq 0.05$ for both comparisons); FACT: 36 vs. 22 and 21 % ($p < 0.001$ for both comparisons)]. After withdrawal of prophylaxis, an initial marked increase in the rate of gout flares requiring treatment (up to 40 %) was followed by a gradual decrease over time [38]; flares requiring treatment were observed in 15, 15 and 14 % of febuxostat 80 mg/day, febuxostat 120 mg/day and allopurinol recipients, respectively, during the last 4 weeks of the APEX study [25], and 8, 6 and 11 % of febuxostat 80 mg/day, febuxostat 120 mg/day and allopurinol 300 mg/day recipients, respectively, during the last 4 weeks of the FACT study [26]. There were no significant differences between these treatment groups in the rates of gout flares requiring treatment during weeks 9 through 28 in the APEX study (55 and

54 % of febuxostat 80 and 120 mg/day recipients vs. 46 % of allopurinol recipients) [39] and weeks 9 through 52 in the FACT study (64 and 70 vs. 64 %) [26].

A different pattern was observed in the 6-month CONFIRMS study, in which prophylaxis was administered throughout. Among febuxostat 80 mg/day recipients who had not previously successfully completed either the FOCUS or EXCEL extension studies, the rate of flare requiring treatment declined steadily from ≈13 % during the first 2 months of treatment to ≈6 % during the last month of treatment; similar results were seen among allopurinol 200 or 300 mg/day recipients who had not previously taken part in one or other of these extension trials [21]. Furthermore, febuxostat 80 mg/day and allopurinol recipients with prior participation in an extension study had significantly ($p < 0.001$) lower rates of flare requiring treatment compared with the corresponding febuxostat 80 mg/day and allopurinol recipients without prior participation [21].

3.2.2 *Tophi*

There were no significant differences between the febuxostat 80 mg/day, febuxostat 120 mg/day and allopurinol 100–300 mg/day groups in the percentage reduction in tophus area or in the reduction in the number of tophi by the end of the APEX [25] and FACT [26] studies. In a post hoc analysis of the FACT study [26], the median reduction from baseline in tophus area at week 52 was 75 % among patients with a mean post-baseline sUA level of <6.0 mg/dL, as compared with 50 % among those with a mean post-baseline sUA level of ≥6.0 mg/dL ($p = 0.06$).

3.3 Extension Studies

Long-term treatment with febuxostat maintained a target sUA level of <6.0 mg/dL in most patients in the FOCUS and EXCEL extension trials [13, 31]. Moreover, sustained reduction in sUA level was associated with near elimination of gout flares [13, 31], improved tophus status [13, 31] and preservation of renal function [40, 41].

The EXCEL extension trial enrolled 1,086 patients who previously completed either the APEX or FACT study. They were initially assigned to treatment with either febuxostat (at a dosage of 80 or 120 mg/day; $n = 941$) or allopurinol (at a dosage of 100 or 300 mg/day, depending on renal function; $n = 145$), but were permitted to switch between either dosage of febuxostat and/or allopurinol during the first 6 months of treatment either to achieve and maintain an sUA level ≥3 to < 6.0 mg/dL, or due to any adverse event, or at the investigator's discretion. By the end of month 6, patients were required to be on a final, stable (maintenance) dosage of febuxostat or allopurinol [13].

At all assessments during a 3-year treatment period, >80 % of patients initially assigned to receive febuxostat 80 or 120 mg/day had an sUA level of <6.0 mg/dL (primary efficacy outcome measure); results at 1, 6, 12, 24 and 36 months are shown in Fig. 1. Although fewer than one-half of patients initially assigned to receive allopurinol achieved the target sUA level at 1 month, this figure gradually increased during the drug/dosage reassignment period (as patients failing to meet the goal sUA range were shifted to febuxostat therapy); it was ≥75 % at all assessments from month 12 through 36 [13] (see Fig. 1).

Regarding clinical outcomes, the incidence of gout flares requiring treatment increased immediately after prophylaxis withdrawal (end of month 2), but thereafter decreased over time in each treatment group (see Fig. 2). At each of the 2-monthly assessments from month 16 onwards, flares requiring treatment occurred in ≤4 % of patients receiving a maintenance dosage of febuxostat 80 or 120 mg/day [13].

Among patients with tophi, there were mean reductions from baseline to the final visit of 67 and 48 % in the size of index tophi and 60 and 57 % in the total number of tophi in those who received a febuxostat maintenance dosage of 80 and 120 mg/day, respectively. Additionally, 46 and 38 % of patients receiving a stable dosage of febuxostat 80 and 120 mg/day had complete resolution of the index tophus from baseline to the final visit [13].

Similar results were seen in the smaller FOCUS extension trial in which 116 patients who previously completed the 4-week dose-response study were enrolled and initially assigned to receive febuxostat 80 mg/day for 4 weeks. Between weeks 5 and 24, patients were titrated to one of three permitted maintenance dosages (40, 80 or 120 mg/day); by week 28, patients were required to have been receiving a stable dosage for ≥4 weeks [31].

At the final visit, 82, 81 and 100 % of patients receiving febuxostat 40, 80 and 120 mg/day ($n = 79$, 27 and 8) had an sUA level of <6.0 mg/dL (primary efficacy outcome measure) [31]. Among patients receiving maintenance dosages of febuxostat 80 and 120 mg/day who remained in the study at the time of the following annual assessments, the proportions achieving the target sUA level were 85 and 67 % at 1 year, 76 and 92 % at 2 years, 84 and 92 % at 3 years, 92 and 85 % at 4 years, and 82 and 81 % at 5 years [31]. The percentage of patients receiving a stable dose of febuxostat who remained in the study and required treatment for gout flares declined to zero during the fifth year of follow-up. In addition, the majority (69 %) of patients with a palpable tophus at baseline ($n = 29$) had complete resolution of the index tophus by the final visit. Results for these clinical endpoints in the three maintenance dosage groups were not reported separately [31].

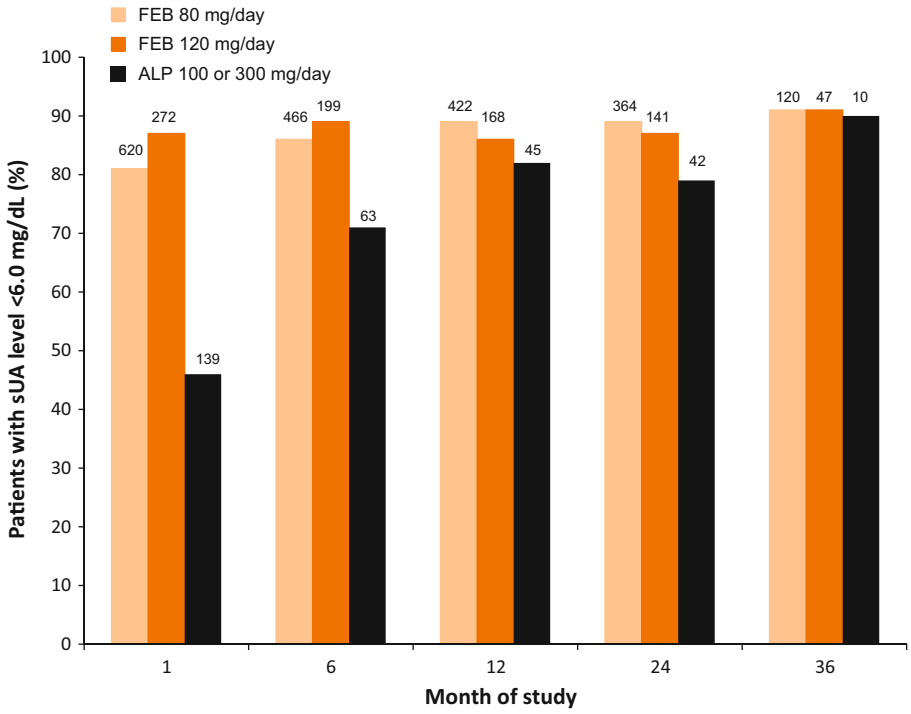

Fig. 1 Effects of febuxostat and allopurinol on serum uric acid levels in the EXCEL study [13]. Above each bar is the number of patients still in the study at the timepoint specified. *ALP* allopurinol, *FEB* febuxostat, *sUA* serum uric acid

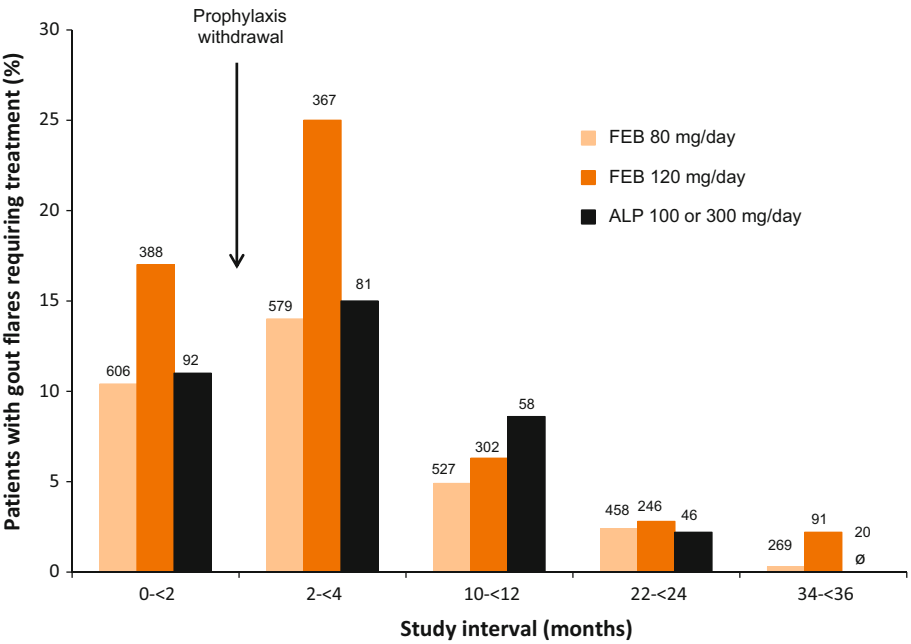

Fig. 2 Effects of febuxostat and allopurinol on gout flares in the EXCEL study [13]. Above each bar is the number of patients who received maintenance treatment during the time period specified. *ALP* allopurinol, *FEB* febuxostat, $\phi = 0$ %

Interestingly, post hoc analyses of the EXCEL [40] and FOCUS [41] studies suggested that greater sustained reductions in sUA levels (in patients treated with febuxostat) were associated with less decline in renal function. Specifically, these analyses predicted that for every long-term decrease of 1 mg/dL in sUA level, there would be a preservation of $\approx$1 mL/min of estimated glomerular filtration rate.

4 Tolerability

Short- (1–12 months) and longer-term (3–5 years) treatment with febuxostat was generally well tolerated in patients with gout and hyperuricaemia in the seven clinical trials discussed in Sect. 3, with most adverse events being of mild to moderate severity [13, 21, 24–26, 30, 31]. Excluding gout flares, the most frequently reported adverse

events in febuxostat recipients include abnormal liver function tests (LFTs), diarrhoea, nausea, headache, rash and oedema [14].

Abnormal LFTs (designated as adverse events by investigators) were reported by ≈3–7 % of febuxostat 80 or 120 mg/day recipients in North American studies, with no apparent dose dependence [21, 24–26]. However, febuxostat therapy was not associated with combined serum transaminase and bilirubin increases in CONFIRMS or any of the other short- or long-term studies that comprised the clinical development programme [13, 24–26, 31], except when explained by cholecystitis or by bile duct obstruction due to stones or malignancy [21]. Rash-related adverse events were reported by 5.6 % of febuxostat 80 mg/day recipients in CONFIRMS [21].

The 28-week APEX trial was the only phase III study to include a placebo arm; more than two-thirds of patients in each arm reported adverse events (68, 68 and 72 % in the febuxostat 80 mg/day, febuxostat 120 mg/day and placebo groups, respectively) [25]. In general, the incidences of commonly reported adverse events were similar across these three treatment groups, although (investigator-defined) LFT abnormalities were reported more frequently by febuxostat 80 and 120 mg/day recipients than placebo recipients (6 and 4 vs. 2 %) [25].

Just over one-half (54.2 %) of the 756 febuxostat 80 mg/day recipients in CONFIRMS, the largest study conducted to date, reported at least one adverse event; the adverse event rate in the large subgroup of 503 febuxostat 80 mg/day recipients with mild or moderate renal impairment was very similar (53.7 %) [21].

CV events were the most common serious adverse events during treatment with febuxostat [13, 25]. In the APEX study [25], for example, CV disorders were reported by 2 and 2 % of febuxostat 80 and 120 mg/day recipients (vs. <1 % of placebo recipients), while in the EXCEL extension study [13], cardiac disorders were reported by 4 and 2 % of febuxostat 80 and 120 mg/day recipients. All patients affected had a history of underlying CV disease and/or risk factors [13, 25]. No severe rashes or hypersensitivity reactions were seen during treatment with febuxostat in CONFIRMS or any of the other studies that comprised the clinical development programme [21]. Post-marketing surveillance, however, has revealed rare reports of serious hypersensitivity reactions to febuxostat [14] (see Sect. 6 for further discussion).

The rate of premature treatment discontinuation due to adverse events was ≈6–9 % among patients receiving febuxostat 80 or 120 mg/day in studies of 6–12 months' [21, 25, 26, 30] or up to 3 years' [13] duration. Investigator-defined LFT abnormalities were the most common adverse event leading to early cessation of febuxostat therapy (in 2 % of febuxostat 80 mg/day recipients [21, 25, 26] and 1 % [25] or ≈3 % [26] of febuxostat 120 mg/day recipients).

4.1 Comparisons with Allopurinol

In general, the adverse event profile of febuxostat was qualitatively and quantitatively similar to that of allopurinol in clinical trials [5, 13, 21, 25, 26, 30]. The rate of discontinuation for adverse events ranged from ≈2–9 % in patients receiving allopurinol 100–300 mg/day (vs. ≈6–9 % in patients receiving febuxostat 80 or 120 mg/day)] [13, 21, 25, 26, 30]. In the FACT study, significantly more febuxostat 120 mg/day recipients than allopurinol 300 mg/day recipients discontinued treatment early due to LFT abnormalities (2.8 vs. 0.4 %; $p = 0.04$) [26].

The overall incidence of primary Antiplatelet Trialists Collaboration (APTC) events was numerically, but not significantly, higher among febuxostat 80 and 120 mg/day recipients, as compared with allopurinol 200 or 300 mg/day recipients, according to data pooled from the APEX and FACT trials [0.8 and 1.0 vs. 0.2 % (1.3 and 1.6 vs. 0.3 events per 100 patient-years of exposure); $n = 523$ and 520 vs. 521] and the longer-term FOCUS and EXCEL extension studies [2.2 and 1.72 vs. 0.56 % (1.4 and 1.3 vs. 0.7 events per 100 patient-years of exposure); $n = 910$ and 522 vs. 178] [37]. Primary APTC events included CV death, non-fatal myocardial infarction (MI), non-fatal stroke and—only in the pooled analysis of APEX and FACT—non-fatal cardiac arrest [37]. Against this background, one of the objectives of the CONFIRMS study was to provide prospective, uniformly reviewed information regarding the comparative CV safety of febuxostat and allopurinol [21]. CV adverse events were reported by 5 and 6 % of febuxostat 80 mg/day and allopurinol 100–300 mg/day recipients, respectively ($n = 756$ and 756); there were no significant differences between these two treatment groups with respect to specific CV adverse events [21]. Adjudicated APTC events (CV death, non-fatal MI or non-fatal stroke) occurred in three (0.4 %) febuxostat 80 mg/day recipients and, likewise, three (0.4 %) allopurinol 100–300 mg/day recipients. All patients experiencing adjudicated APTC events had a history of underlying CV disease and/or risk factors [21].

5 Dosage and Administration

In the EU, the recommended dosage of febuxostat is 80 mg once daily [14]. The therapeutic target is to decrease and maintain the sUA level <6 mg/dL (<360 μmol/L); increasing the febuxostat dosage to 120 mg once daily may be considered if the sUA level is >6 mg/dL after

2–4 weeks of treatment with febuxostat 80 mg/day. Febuxostat treatment should not be started until an acute attack of gout has completely subsided; gout flare prophylaxis is recommended for ≥6 months after initiating febuxostat therapy [14].

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

6 Place of Febuxostat in the Management of Gout

Febuxostat is an established, effective and generally well tolerated alternative xanthine oxidase inhibitor to allopurinol, the long-standing gold standard and still most widely prescribed urate-lowering therapy for gout, and offers the potential advantage of not requiring dose adjustment in patients with mild to moderate renal impairment [42] (Sect. 2). Consistent with the goals of managing chronic gout (Sect. 1), clinical trial data demonstrate that long-term (3–5 years') treatment with EU-approved dosages of febuxostat (80 or 120 mg/day) maintains target sUA levels in most patients, and is associated with near elimination of gout flares and improved tophus status (Sect. 3.3).

In comparative trials, 6 to 12 months' treatment with febuxostat 80 or 120 mg/day was significantly more effective than allopurinol at dosages of 100–300 mg/day in achieving sUA target levels in patients with hyperuricaemia and gout, including those with renal impairment (Sect. 3.1). Of note, these studies were primarily designed to evaluate urate-lowering efficacy rather than clinical manifestations of gout (e.g. flare rate and tophus size); there were no significant differences between the two xanthine oxidase inhibitors with respect to the latter (Sect. 3.2). Concerning the real-world relevance of these comparisons, allopurinol dosages of 100–300 mg/day correspond to those commonly prescribed (Sect. 1); although these lower dosages are often suboptimal, and up-titration of the dosage (to a maximum of 800 or 900 mg/day as per UK- and US-approved drug labelling) in patients who can tolerate the drug is the established best clinical practice [7], allopurinol is rarely administered at dosages >300 mg/day (in <5 % of patients) [21, 43]. Studies comparing febuxostat 80 or 120 mg with higher maintenance dosages of allopurinol (e.g. 400–600 mg/day) are nonetheless desirable; ideally, these trials would adequately address clinical outcomes.

Data are available regarding the relative efficacy of febuxostat and allopurinol in clinical practice; according to this real-world comparison, significantly ($p < 0.0001$) more febuxostat- than allopurinol-treated patients reached the target sUA level of <6 mg/dL, as assessed within 6 months of, as well as 2 years after, initiating urate-lowering therapy [44]. Additionally, almost half of the allopurinol-treated patients who switched to febuxostat after failing to reach the sUA goal level subsequently achieved the target on febuxostat [44]. The authors of another real world study compared utilization patterns of these xanthine oxidase inhibitors and concluded that while allopurinol is still the most frequently prescribed urate-lowering therapy in patients with gout, febuxostat is being used in more difficult to treat patients, including those with higher baseline sUA levels and with commonly associated comorbidities [45].

Abnormal LFTs are among the adverse events most commonly reported in febuxostat-treated patients (Sect. 4); it is recommended that LFTs be performed prior to the initiation of febuxostat therapy and periodically thereafter based on clinical judgment [14]. In this context, it is interesting to note the results of a prospective cohort study suggested that patients with severe gout and altered LFTs at baseline, including those with chronic liver disease, showed no signs of worsening LFTs during febuxostat therapy, as compared with patients with normal LFTs at baseline [46].

Febuxostat differs structurally from allopurinol and provides a potential alternative urate-lowering therapy in patients with allopurinol hypersensitivity syndrome [47]. There have, however, been rare post-marketing reports of serious allergic/hypersensitivity reactions to the drug, including life-threatening Stevens–Johnson Syndrome, toxic epidermal necrolysis and acute anaphylactic reaction/shock; some, but not all, of these patients reported renal impairment and/or previous hypersensitivity to allopurinol [14, 47]. It is therefore recommended that patients be closely monitored for symptoms of allergic/hypersensitivity reactions, especially during the early stages of treatment, as most of the reported reactions have occurred within 1 month of initiating febuxostat therapy [14, 47].

The CV tolerability of febuxostat is potentially of concern, based on data from early phase III clinical trials and post-marketing experience [47]. However, the observation of a numerically, but not significantly, higher incidence of APTC events in febuxostat recipients compared with allopurinol recipients in the pooled APEX and FACT studies was not substantiated in a greater number of patients in the subsequent CONFIRMS study (Sect. 4.1). The long-term comparative CV safety of these agents in patients with gout is currently being examined in two large, ongoing, multicentre studies [48, 49]. The 3-year FAST study is a prospective, randomized, open-label, blinded endpoint trial evaluating the risk of the APTC composite endpoint of non-fatal MI, non-fatal stroke or CV death in patients receiving febuxostat 80 or 120 mg/day and those receiving

Table 4 Febuxostat for the management of hyperuricaemia in patients with gout: summary of guideline recommendations

Authority (countries represented)	Recommendation
ACR (USA) [12]	Alternative to ALP[a,b]
EULAR (EU) [11]	Alternative if ALP not tolerated[c]
3e Initiative (Europe, South America, Australasia) [58]	Alternative if ALP is inadequate or not tolerated[b,c]
NICE (England and Wales) [59]	Appropriate if ALP is not tolerated or contraindicated
SER (Spain) [54]	Alternative to ALP[d]
SIR (Italy) [53]	Alternative to ALP[e]
SMC (Scotland) [60]	Appropriate if ALP is inadequate, not tolerated or contraindicated

ACR American College of Rheumatology, *ALP* allopurinol, *EULAR* European League Against Rheumatism, *FEB* febuxostat, *NICE* National Institute for Health and Clinical Excellence, *pts* patients, *SER* Spanish Society of Rheumatology, *SIR* Italian Society of Rheumatology, *SMC* Scottish Medicines Authority, *XOI* xanthine oxidase inhibitor

[a] For first-line therapy. FEB can also be substituted for ALP when (first-line therapy with) the latter is not tolerated. Combination of a uricosuric agent and XOI can be considered in pts refractory to XOI therapy

[b] Uricase therapy (pegloticase) is recommended for pts with severe gout without, or refractory to, other therapeutic options

[c] Uricosuric agents are alternatives to FEB

[d] For initial therapy. The uricosuric agent benzbromarone is restricted to use in pts refractory to XOI therapy

[e] Uricosuric agents or other XOIs (e.g. FEB) are options if ALP not tolerated

optimal dosages of allopurinol in the UK and Denmark; all of the ≈5700 participants are aged >60 years and have at least one additional CV risk factor [48]. The 5-year CARES study is a randomized, double-blind trial evaluating the risk of the composite endpoint of non-fatal MI, non-fatal stroke, unstable angina with urgent revascularization or CV death in patients receiving febuxostat 40 or 80 mg/day and those receiving allopurinol 200–600 mg/day in North America; all of the ≈7500 participants have well-defined CV disease [49]. In the EU, use of febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended [14].

In support of the clinical data, the results of pharmacoeconomic analyses (Markov models) from Scotland [50] and Spain [51] suggest that febuxostat, either as first-line therapy (with or without allopurinol as second-line therapy) or as second-line therapy (after allopurinol), is cost-effective compared with a strategy of allopurinol alone (i.e. allopurinol as first-line therapy with no second line therapy).

Febuxostat is 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) [14] (Sect. 1). According to current EULAR guidelines [11], allopurinol is an appropriate long-term urate-lowering therapy; another xanthine oxidase inhibitor (e.g. febuxostat) is an option in patients in whom allopurinol is not tolerated (Table 4). These guidelines are in the process of being updated [52]. Italian Society of Rheumatology guidelines [53], while also acknowledging the appropriateness of allopurinol, indicate that febuxostat is an effective alternative to allopurinol that shows greater efficacy and minor adverse effects as a urate-lowering agent. According to Spanish Rheumatology Society guidelines [54], the choice of initial therapy for all patients with gout is effectively between allopurinol and febuxostat; however, neither one of these xanthine oxidase inhibitors is preferentially recommended over the other. Likewise, recently updated ACR guidelines [12] recommend either allopurinol or febuxostat as a first-line urate-lowering therapy, albeit with no preference expressed for one agent over the other. Febuxostat is also recommended if first-line allopurinol is not tolerated (and vice-versa) [12] (Table 4). Thus, febuxostat is a well established antihyperuricaemic agent that provides an effective alternative to allopurinol for the management of chronic gout.

Data selection sources:

Relevant medical literature (including published and unpublished data) on febuxostat was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 16 February 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Hyperuricaemia, gout, febuxostat.
Study selection: Studies in patients with hyperuricaemia and gout who received febuxostat. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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