1. Name of the medicinal product
ZURIG 40 & ZURIG 80

2. Qualitative and quantitative composition
Febuxostat Tablets 40 mg
Each film-coated tablet contains 40 mg of febuxostat
Colour: Titanium Dioxide

Febuxostat Tablets 80 mg
Each film-coated tablet contains 80 mg of febuxostat
Colour: Titanium Dioxide

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Film-coated tablet.

Febuxostat Tablets 40mg: White to off white bevelled edge, oval shaped tablets debossed with “401” on one side and plain on other side

Febuxostat Tablets 80mg: White to off white, round shaped, biconvex film-coated tablets, plain on both sides

The tablet can be divided into equal doses.

4. Clinical particulars
4.1 Therapeutic indications

Febuxostat is indicated 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).
Febuxostat is indicated in adults.

4.2 Posology and method of administration

Posology
Gout
The recommended oral dose of Febuxostat is 80 mg once daily without regard to food. If serum uric acid is > 6 mg/dl (357 µmol/L) after 2-4 weeks, Febuxostat 120 mg once daily may be considered.
Febuxostat works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks. The therapeutic target is to decrease and maintain serum uric acid below 6 mg/dl (357 µmol/L).
Gout flare prophylaxis of at least 6 months is recommended (see section 4.4).

Elderly
No dose adjustment is required in the elderly (see section 5.2).

Renal impairment
The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance < 30 ml/min, see section 5.2).

No dose adjustment is necessary in patients with mild or moderate renal impairment.

Hepatic impairment
The efficacy and safety of febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh Class C).
The recommended dose in patients with mild hepatic impairment is 80 mg. Limited information is available in patients with moderate hepatic impairment.

Paediatric population
The safety and the efficacy of febuxostat in children aged below the age of 18 years have not been established. No data are available.

Method of administration
Oral use
Febuxostat should be taken by mouth and can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see also section 4.8).

4.4 Special warnings and precautions for use

Cardiovascular disorders
Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended.

A numerical greater incidence of investigator-reported cardiovascular APTC events (defined endpoints from the Anti-Platelet Trialists' Collaboration (APTC) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was observed in the febuxostat total group compared to the allopurinol group in the APEX and FACT studies (1.3 vs. 0.3 events per 100 Patient Years (PYs)), but not in the CONFIRMS study (see section 5.1 for detailed characteristics of the studies). The incidence of investigator-reported cardiovascular APTC events in the combined Phase 3 studies (APEX, FACT and CONFIRMS studies) was 0.7 vs. 0.6 events per 100 PYs. In the long-term extension studies the incidences of investigator-reported APTC events were 1.2 and 0.6 events per 100 PYs for febuxostat and allopurinol, respectively. No statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure.

Medicinal product allergy/hypersensitivity
Rare reports of serious allergic/hypersensitivity reactions, including life-threatening Stevens-Johnson syndrome, toxic epidermal necrolysis and acute anaphylactic reaction/shock, have been collected in the post-marketing experience. In most cases, these reactions occurred during the first month of therapy with febuxostat. Some, but not all of these patients reported renal impairment and/or previous hypersensitivity to allopurinol. Severe hypersensitivity reactions, including drug reaction with eosinophilia and systemic symptoms (DRESS) were associated with fever, haematological, renal or hepatic involvement in some cases.

Patients should be advised of the signs and symptoms and monitored closely for symptoms of allergic/hypersensitivity reactions (see section 4.8). Febuxostat treatment should be immediately stopped if serious allergic/hypersensitivity reactions, including Stevens-Johnson syndrome, occur since early withdrawal is associated with a better prognosis. If patient has developed allergic/hypersensitivity reactions including Stevens-Johnson syndrome and acute anaphylactic reaction/shock, febuxostat must not be re-started in this patient at any time.

Acute gouty attacks (gout flare)
Febuxostat treatment should not be started until an acute attack of gout has completely subsided. Gout flares may occur during initiation of treatment due to changing serum uric acid levels resulting in mobilisation of urate from tissue deposits (see sections 4.8 and 5.1). At treatment initiation with febuxostat flare prophylaxis for at least 6 months with an NSAID or colchicine is recommended (see section 4.2).
If a gout flare occurs during febuxostat treatment, it should not be discontinued. The gout flare should be managed concurrently as appropriate for the individual patient. Continuous treatment with febuxostat decreases frequency and intensity of gout flares.

Xanthine deposition
In patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. As there has been no experience with febuxostat, its use in these populations is not recommended.

Mercaptopurine/azathioprine
Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine. Where the combination cannot be avoided patients should be closely monitored. A reduction of dosage of mercaptopurine or azathioprine is recommended in order to avoid possible haematological effects.

Organ transplant recipients
As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended.

Theophylline
Co-administration of febuxostat 80 mg and theophylline 400 mg single dose in healthy subjects showed absence of any pharmacokinetic interaction (see section 4.5). Febuxostat 80mg can be used in patients concomitantly treated with theophylline without risk of increasing theophylline plasma levels. No data is available for febuxostat 120 mg.

Liver disorders
During the combined phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0 %). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment.

Thyroid disorders
Increased TSH values (> 5.5 µIU/ml) were observed in patients on long-term treatment with febuxostat (5.5 %) in the long-term open-label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function.

Lactose
Febuxostat tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Mercaptopurine/azathioprine
On the basis of the mechanism of action of febuxostat on XO inhibition concomitant use is not recommended. Inhibition of XO by febuxostat may cause increased plasma concentrations of these drugs leading to toxicity. Drug interaction studies of febuxostat with drugs that are metabolised by XO have not been performed.
Drug interaction studies of febuxostat with cytotoxic chemotherapy have not been conducted. No data is available regarding the safety of febuxostat during cytotoxic therapy.

Rosiglitazone/CYP2C8 substrates
Febuxostat was shown to be a weak inhibitor of CYP2C8 in vitro. In a study in healthy subjects, coadministration of 120 mg febuxostat QD with a single 4 mg oral dose of rosiglitazone had no effect on the pharmacokinetics of rosiglitazone and its metabolite N-desmethyl rosiglitazone, indicating that febuxostat is not a CYP2C8 enzyme inhibitor in vivo. Thus, co-administration of febuxostat with rosiglitazone or other CYP2C8 substrates is not expected to require any dose adjustment for those compounds.

Theophylline
An interaction study in healthy subjects has been performed with febuxostat to evaluate whether the inhibition of XO may cause an increase in the theophylline circulating levels as reported with other XO inhibitors. The results of the study showed that the co-administration of febuxostat 80 mg QD with theophylline 400 mg single dose has no effect on the pharmacokinetics or safety of theophylline. Therefore no special caution is advised when febuxostat 80 mg and theophylline are given concomitantly. No data is available for febuxostat 120 mg.

Naproxen and other inhibitors of glucuronidation
Febuxostat metabolism depends on uridine glucuronosyltransferase (UGT) enzymes. Medicinal products that inhibit glucuronidation, such as NSAIDs and probenecid, could in theory affect the elimination of febuxostat. In healthy subjects, concomitant use of febuxostat and naproxen 250 mg twice daily was associated with an increase in febuxostat exposure (Cmax 28 %, AUC 41 % and t1/2 26 %). In clinical studies, the use of naproxen or other NSAIDs/Cox-2 inhibitors was not related to any clinically significant increase in adverse events.
Febuxostat can be co-administered with naproxen with no dose adjustment of febuxostat or naproxen being necessary.

Inducers of glucuronidation
Potent inducers of UGT enzymes might possibly lead to increased metabolism and decreased efficacy of febuxostat. Monitoring of serum uric acid is therefore recommended 1-2 weeks after start of treatment with a potent inducer of glucuronidation. Conversely, cessation of treatment of an inducer might lead to increased plasma levels of febuxostat.

Colchicine/indometacin/hydrochlorothiazide/warfarin
Febuxostat can be co-administered with colchicine or indomethacin with no dose adjustment of febuxostat or the co-administered active substance being necessary.
No dose adjustment is necessary for febuxostat when administered with hydrochlorothiazide.
No dose adjustment is necessary for warfarin when administered with febuxostat. Administration of febuxostat (80 mg or 120 mg once daily) with warfarin had no effect on the pharmacokinetics of warfarin in healthy subjects. INR and Factor VII activity were also not affected by the co- administration of febuxostat.

Desipramine/CYP2D6 substrates
Febuxostat was shown to be a weak inhibitor of CYP2D6 in vitro. In a study in healthy subjects, 120 mg febuxostat QD resulted in a mean 22 % increase in AUC of desipramine, a CYP2D6 substrate indicating a potential weak inhibitory effect of febuxostat on the CYP2D6 enzyme in vivo. Thus, co-administration of febuxostat with other CYP2D6 substrates is not expected to require any dose adjustment for those compounds.

Antacids
Concomitant ingestion of an antacid containing magnesium hydroxide and aluminium hydroxide has been shown to delay absorption of febuxostat (approximately 1 hour) and to cause a 32 % decrease in Cmax, but no significant change in AUC was observed. Therefore, febuxostat may be taken without regard to antacid use.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data on a very limited number of exposed pregnancies have not indicated any adverse effects of febuxostat on pregnancy or on the health of the foetus/new born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition. The potential risk for human is unknown. Febuxostat should not be used during pregnancy.

Breast-feeding
It is unknown whether febuxostat is excreted in human breast milk. Animal studies have shown excretion of this active substance in breast milk and an impaired development of suckling pups. A risk to a suckling infant cannot be excluded. Febuxostat should not be used while breast-feeding.

Fertility
In animals, reproduction studies up to 48 mg/kg/day showed no dose-dependent adverse effects on fertility. The effect of febuxostat on human fertility is unknown.

4.7 Effects on ability to drive and use machines

Somnolence, dizziness, paraesthesia and blurred vision have been reported with the use of Febuxostat. Patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that febuxostat does not adversely affect performance.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in clinical trials (4,072 subjects treated at least with a dose from 10 mg to 300 mg) and post-marketing experience are gout flares, liver function abnormalities, diarrhoea, nausea, headache, rash and oedema. These adverse reactions were mostly mild or moderate in severity. Rare serious hypersensitivity reactions to febuxostat, some of which were associated to systemic symptoms, have occurred in the post-marketing experience.

Tabulated list of adverse reactions

Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000) adverse reactions occurring in patients treated with febuxostat are listed below.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions in combined phase 3, long-term extension studies and post-marketing experience

Blood and lymphatic system disorders	Rare Pancytopenia, thrombocytopenia
Immune system disorders	Rare Anaphylactic reaction*, drug hypersensitivity*
Endocrine disorders	Uncommon Blood thyroid stimulating hormone increased
Eye disorders	Rare Blurred vision
Metabolism and nutrition disorders	Common*** Gout flares Uncommon Diabetes mellitus, hyperlipidaemia, decreased appetite, weight increased Rare Weight decreased, increased appetite, anorexia
Psychiatric disorders	Uncommon Libido decreased, insomnia Rare Nervousness
Nervous system disorders	Common Headache Uncommon Dizziness, paraesthesia, hemiparesis, somnolence, dysgeusia, hypoaesthesia, hyposmia

Ear and labyrinth disorders	Rare Tinnitus
Cardiac disorders	Uncommon Atrial fibrillation, palpitations, ECG abnormal
Vascular disorders	Uncommon Hypertension, flushing, hot flush
Respiratory, thoracic and mediastinal disorders	Uncommon Dyspnoea, bronchitis, upper respiratory tract infection, cough
Gastrointestinal disorders	Common Diarrhoea**, nausea Uncommon: Abdominal pain, abdominal distension, gastrooesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort Rare Pancreatitis, mouth ulceration
Hepatobiliary disorders	Common Liver function abnormalities** Uncommon Cholelithiasis Rare Hepatitis, jaundice*, liver injury*
Skin and subcutaneous tissue disorders	Common Rash (including various types of rash reported with lower frequencies, see below) Uncommon Dermatitis, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash papular Rare Toxic epidermal necrolysis*, Stevens-Johnson syndrome*, angioedema*, drug reaction with eosinophilia and systemic symptoms*, generalised rash (serious)*, erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic*, rash erythematous, rash morbilliform, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders	Uncommon Arthralgia, arthritis, myalgia, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis Rare Rhabdomyolysis*, joint stiffness, musculoskeletal stiffness
Renal and urinary disorders	Uncommon Renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria Rare Tubulointerstitial nephritis*, micturition urgency
Reproductive system and breast disorders	Uncommon Erectile dysfunction
General disorders and administration site conditions	Common Oedema Uncommon Fatigue, chest pain, chest discomfort Rare

	Thirst
Investigations	Uncommon Blood amylase increased, platelet count decreased, white blood cell count decreased, lymphocyte count decreased, blood creatine increased, blood creatinine increased, haemoglobin decreased, blood urea increased, blood triglycerides increased, blood cholesterol increased, haematocrit decreased, blood lactate dehydrogenase increased, blood potassium increased Rare Blood glucose increased, activated partial thromboplastin time prolonged, red blood cell count decreased, blood alkaline phosphatase increased, blood creatine phosphokinase increased*
* Adverse reactions coming from post-marketing experience ** Treatment-emergent non-infective diarrhoea and abnormal liver function tests in the combined Phase 3 studies are more frequent in patients concomitantly treated with colchicine. *** See section 5.1 for incidences of gout flares in the individual Phase 3 randomised controlled studies.	

Description of selected adverse reactions
Rare serious hypersensitivity reactions to febuxostat, including Stevens-Johnson syndrome, toxic epidermal necrolysis and anaphylactic reaction/shock, have occurred in the post-marketing experience. Stevens-Johnson syndrome and toxic epidermal necrolysis are characterised by progressive skin rashes associated with blisters or mucosal lesions and eye irritation. Hypersensitivity reactions to febuxostat can be associated to the following symptoms: skin reactions characterised by infiltrated maculopapular eruption, generalised or exfoliative rashes, but also skin lesions, facial oedema, fever, haematologic abnormalities such as thrombocytopenia and eosinophilia, and single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis).
Gout flares were commonly observed soon after the start of treatment and during the first months. Thereafter, the frequency of gout flare decreases in a time-dependent manner. Gout flare prophylaxis is recommended.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorization holder, or, if available, via the national reporting system (see details below);

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions.*

4.9 Overdose

Patients with an overdose should be managed by symptomatic and supportive care.

5. Pharmacological properties
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antigout preparations, preparations inhibiting uric acid production.
ATC code: M04AA03

Mechanism of action
Uric acid is the end product of purine metabolism in humans and is generated in the cascade of hypoxanthine → xanthine → uric acid. Both steps in the above transformations are catalysed by xanthine oxidase (XO). Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting XO. Febuxostat is a potent, non-purine selective inhibitor of XO (NP-SIXO) with an in vitro inhibition Ki value less than one nanomolar. Febuxostat has been shown to potently inhibit both the oxidised and reduced forms of XO. At therapeutic concentrations febuxostat does not inhibit other enzymes involved in purine or pyrimidine metabolism, namely, guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase or purine nucleoside phosphorylase.

Clinical efficacy and safety
The efficacy of febuxostat was demonstrated in three Phase 3 pivotal studies (the two pivotal APEX and FACT studies, and the additional CONFIRMS study described below) that were conducted in 4,101 patients with hyperuricaemia and gout. In each phase 3 pivotal study, febuxostat demonstrated superior ability to lower and maintain serum uric acid levels compared to allopurinol. The primary efficacy endpoint in the APEX and FACT studies was the proportion of patients whose last 3 monthly serum uric acid levels were < 6.0 mg/dl (357 µmol/l). In the additional phase 3 CONFIRMS study, for which results became available after the marketing authorisation for febuxostat was first issued, the primary efficacy endpoint was the proportion of patients whose serum urate level was < 6.0 mg/dl at the final visit. No patients with organ transplant have been included in these studies (see section 4.2).
APEX Study: The Allopurinol and Placebo-Controlled Efficacy Study of Febuxostat (APEX) was a Phase 3, randomised, double-blind, multicentre, 28-week study. One thousand and seventy-two (1,072) patients were randomised: placebo (n=134), febuxostat 80 mg QD (n=267), febuxostat 120 mg QD (n=269), febuxostat 240 mg QD (n=134) or allopurinol (300 mg QD [n=258] for patients with a baseline serum creatinine ≤ 1.5 mg/dl or 100 mg QD [n=10] for patients with a baseline serum creatinine > 1.5 mg/dl and ≤ 2.0 mg/dl). Two hundred and forty mg febuxostat (2 times the recommended highest dose) was used as a safety evaluation dose.
The APEX study showed statistically significant superiority of both the febuxostat 80 mg QD and the febuxostat 120 mg QD treatment arms versus the conventionally used doses of allopurinol 300 mg (n=258)/100 mg (n=10) treatment arm in reducing the sUA below 6 mg/dl (357 µmol/l) (see Table 2 and Figure 1).
FACT Study: The Febuxostat Allopurinol Controlled Trial (FACT) Study was a Phase 3, randomised, double-blind, multicentre, 52-week study. Seven hundred sixty (760) patients were randomised: Febuxostat 80 mg QD (n=256), febuxostat 120 mg QD (n=251), or allopurinol 300 mg QD (n=253).
The FACT study showed the statistically significant superiority of both febuxostat 80 mg and febuxostat 120 mg QD treatment arms versus the conventionally used dose

of allopurinol 300 mg treatment arm in reducing and maintaining sUA below 6 mg/dl (357 µmol/L).
Table 2 summarises the primary efficacy endpoint results:

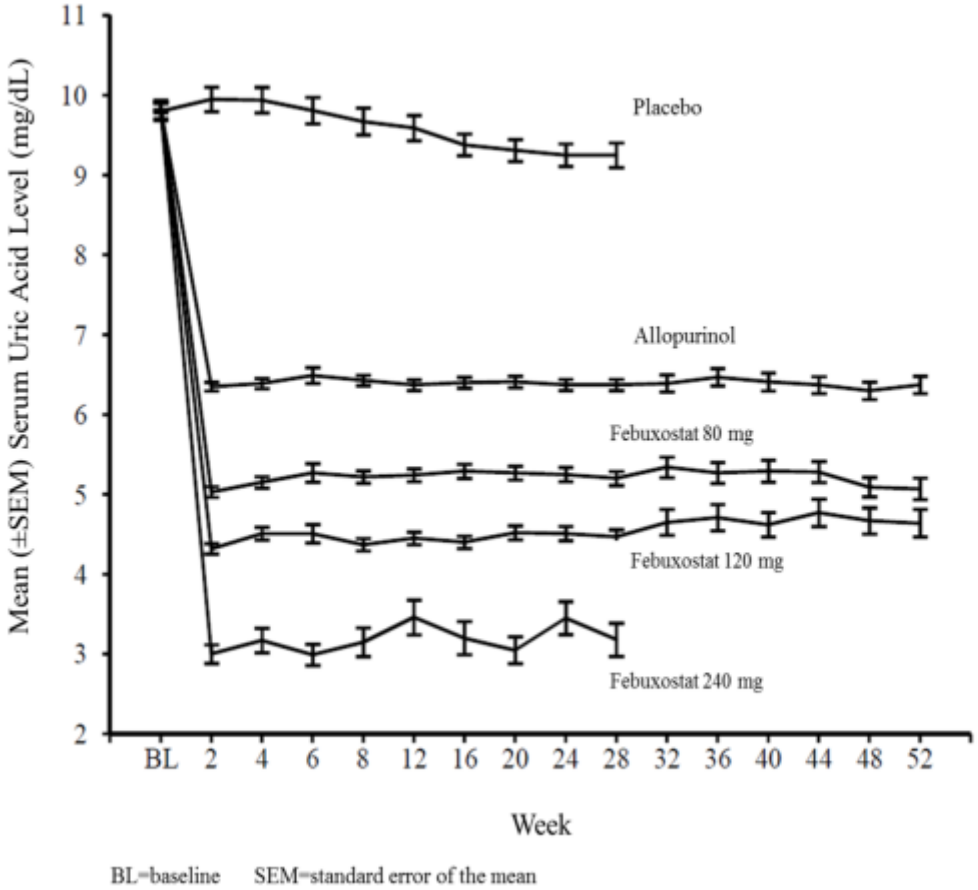
Table 2: Proportion of patients with serum uric acid levels < 6.0 mg/dl (357 µmol/L)
Last three monthly visits

Study	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Allopurinol 300/100 mg QD[1]
APEX (28 weeks)	48%* (n=262)	65%*,# (n=269)	22% (n=268)
FACT (52 weeks)	53%* (n=255)	62%* (n=250)	21% (n=251)
Combined Results	51%* (n=517)	63%*,# (n=519)	22% (n=519)

[1] results from subjects receiving either 100 mg QD (n=10: patients with serum creatinine > 1.5 and ≤ 2.0 mg/dl) or 300 mg QD (n=509) were pooled for analyses.
* $p < 0.001$ vs allopurinol, # $p < 0.001$ vs 80 mg

The ability of febuxostat to lower serum uric acid levels was prompt and persistent. Reduction in serum uric acid level to < 6.0 mg/dl (357 µmol/L) was noted by the Week 2 visit and was maintained throughout treatment. The mean serum uric acid levels over time for each treatment group from the two pivotal Phase 3 studies are shown in Figure 1.

Figure 1: Mean serum uric acid levels in combined pivotal phase 3 studies



Note: 509 patients received allopurinol 300 mg QD; 10 patients with serum creatinine > 1.5 and < 2.0 mg/dl were dosed with 100 mg QD. (10 patients out of 268 in APEX study). 240 mg febuxostat was used to evaluate the safety of febuxostat at twice the recommended highest dose.
CONFIRMS Study: The CONFIRMS study was a Phase 3, randomised, controlled, 26-week study to evaluate the safety and efficacy of febuxostat 40 mg and 80 mg, in comparison with allopurinol 300 mg or 200 mg, in patients with gout and hyperuricaemia. Two thousand and two hundred-sixty nine (2,269) patients were randomised: Febuxostat 40 mg QD (n=757), febuxostat 80 mg QD (n=756), or allopurinol 300/200 mg QD (n=756). At least 65 % of the patients had mild-moderate renal impairment (with creatinine clearance of 30-89 ml/min). Prophylaxis against gout flares was obligatory over the 26-week period.
The proportion of patients with serum urate levels of < 6.0 mg/dl (357 µmol/l) at the final visit, was 45 % for 40 mg febuxostat, 67 % for febuxostat 80 mg and 42 % for allopurinol 300/200 mg, respectively.
Primary endpoint in the sub-group of patients with renal impairment
The APEX Study evaluated efficacy in 40 patients with renal impairment (i.e., baseline serum creatinine > 1.5 mg/dl and ≤ 2.0 mg/dl). For renally impaired subjects who were randomised to allopurinol, the dose was capped at 100 mg QD. Febuxostat achieved the primary efficacy endpoint in 44 % (80 mg QD), 45 % (120 mg QD), and 60 % (240 mg QD) of patients compared to 0 % in the allopurinol 100 mg QD and placebo groups. There were no clinically significant differences in the percent decrease in serum uric acid concentration in healthy subjects irrespective of their renal function (58 % in the normal renal function group and 55 % in the severe renal dysfunction group).
An analysis in patients with gout and renal impairment was prospectively defined in the CONFIRMS study, and showed that febuxostat was significantly more efficacious in lowering serum urate levels to < 6 mg/dl compared to allopurinol 300 mg/200 mg in patients who had gout with mild to moderate renal impairment (65 % of patients studied).
Primary endpoint in the sub group of patients with sUA ≥ 10 mg/dl
Approximately 40 % of patients (combined APEX and FACT) had a baseline sUA of ≥ 10 mg/dl. In this subgroup febuxostat achieved the primary efficacy endpoint (sUA < 6.0 mg/dl at the last 3 visits) in 41 % (80 mg QD), 48 % (120 mg QD), and 66 % (240 mg QD) of patients compared to 9 % in the allopurinol 300 mg/100 mg QD and 0 % in the placebo groups.
In the CONFIRMS study, the proportion of patients achieving the primary efficacy endpoint (sUA < 6.0 mg/dl at the final visit) for patients with a baseline serum urate level of ≥ 10 mg/dl treated with febuxostat 40 mg QD was 27 % (66/249), with febuxostat 80 mg QD 49 % (125/254) and with allopurinol 300 mg/200 mg QD 31 % (72/230), respectively.
Clinical outcomes: proportion of patients requiring treatment for a gout flare
APEX study: During the 8-week prophylaxis period, a greater proportion of subjects in the febuxostat 120 mg (36 %) treatment group required treatment for gout flare compared to febuxostat 80 mg (28 %), allopurinol 300 mg (23 %) and placebo (20 %). Flares increased following the prophylaxis period and gradually decreased over time. Between 46 % and 55 % of subjects received treatment for gout flares from Week 8 and Week 28. Gout flares during the last 4 weeks of the study (Weeks 24-28) were observed in 15 % (febuxostat 80, 120 mg), 14 % (allopurinol 300 mg) and 20 % (placebo) of subjects.

FACT study: During the 8-week prophylaxis period, a greater proportion of subjects in the febuxostat 120 mg (36 %) treatment group required treatment for a gout flare compared to both the febuxostat 80 mg (22 %) and allopurinol 300 mg (21 %) treatment groups. After the 8-week prophylaxis period, the incidences of flares increased and gradually decreased over time (64 % and 70 % of subjects received treatment for gout flares from week 8-52). Gout flares during the last 4 weeks of the study (Weeks 49-52) were observed in 6-8 % (febuxostat 80 mg, 120 mg) and 11 % (allopurinol 300 mg) of subjects.
The proportion of subjects requiring treatment for a gout flare (APEX and FACT Study) was numerically lower in the groups that achieved an average post-baseline serum urate level < 6.0 mg/dl, < 5.0 mg/dl, or < 4.0 mg/dl compared to the group that achieved an average post-baseline serum urate level ≥ 6.0 mg/dl during the last 32 weeks of the treatment period (Week 20-Week 24 to Week 49 - 52 intervals).
During the CONFIRMS study, the percentages of patients who required treatment for gout flares (Day 1 through Month 6) were 31 % and 25 % for the febuxostat 80 mg and allopurinol groups, respectively. No difference in the proportion of patients requiring treatment for gout flares was observed between the febuxostat 80 mg and 40 mg groups.
Long-term, open label extension Studies
EXCEL Study (C02-021): The Excel study was a three years Phase 3, open label, multicentre, randomised, allopurinol-controlled, safety extension study for patients who had completed the pivotal Phase 3 studies (APEX or FACT). A total of 1,086 patients were enrolled: Febuxostat 80 mg QD (n=649), febuxostat 120 mg QD (n=292) and allopurinol 300/100 mg QD (n=145). About 69 % of patients required no treatment change to achieve a final stable treatment. Patients who had 3 consecutive sUA levels > 6.0 mg/dl were withdrawn.
Serum urate levels were maintained over time (i.e. 91 % and 93 % of patients on initial treatment with febuxostat 80 mg and 120 mg, respectively, had sUA < 6 mg/dl at Month 36).
Three years data showed a decrease in the incidence of gout flares with less than 4 % of patients requiring treatment for a flare (i.e. more than 96 % of patients did not require treatment for a flare) at Month 16-24 and at Month 30-36.
46 % and 38 %, of patients on final stable treatment of febuxostat 80 or 120 mg QD, respectively, had complete resolution of the primary palpable tophus from baseline to the Final Visit.
FOCUS Study (TMX-01-005) was a 5 years Phase 2, open-label, multicentre, safety extension study for patients who had completed the febuxostat 4 weeks of double blind dosing in study TMX-00-004.
116 patients were enrolled and received initially febuxostat 80 mg QD. 62 % of patients required no dose adjustment to maintain sUA < 6 mg/dl and 38 % of patients required a dose adjustment to achieve a final stable dose.
The proportion of patients with serum urate levels of < 6.0 mg/dl (357 µmol/l) at the final visit was greater than 80 % (81-100 %) at each febuxostat dose.
During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0 %). These rates were similar to the rates reported on allopurinol (4.2 %) (see section 4.4). Increased TSH values (> 5.5 µIU/ml) were observed in patients on long-term treatment with febuxostat (5.5 %) and patients with allopurinol (5.8 %) in the long term open label extension studies (see section 4.4).

5.2 Pharmacokinetic properties

In healthy subjects, maximum plasma concentrations (C_{max}) and area under the plasma concentration time curve (AUC) of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed for febuxostat. There is no appreciable accumulation when doses of 10 mg to 240 mg are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours.
Population pharmacokinetic/pharmacodynamic analyses were conducted in 211 patients with hyperuricaemia and gout, treated with febuxostat 40-240 mg QD. In general, febuxostat pharmacokinetic parameters estimated by these analyses are consistent with those obtained from healthy subjects, indicating that healthy subjects are representative for pharmacokinetic/pharmacodynamic assessment in the patient population with gout.

Absorption
Febuxostat is rapidly (t_{max} of 1.0-1.5 h) and well absorbed (at least 84 %). After single or multiple oral 80 and 120 mg once daily doses, C_{max} is approximately 2.8-3.2 µg/ml, and 5.0-5.3 µg/ml, respectively. Absolute bioavailability of the febuxostat tablet formulation has not been studied.
Following multiple oral 80 mg once daily doses or a single 120 mg dose with a high fat meal, there was a 49 % and 38 % decrease in C_{max} and a 18 % and 16 % decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed where tested (80 mg multiple dose). Thus, febuxostat may be taken without regard to food.

Distribution
The apparent steady state volume of distribution (Vss/F) of febuxostat ranges from 29 to 75 l after oral doses of 10-300 mg. The plasma protein binding of febuxostat is approximately 99.2 %, (primarily to albumin), and is constant over the concentration range achieved with 80 and 120 mg doses. Plasma protein binding of the active metabolites ranges from about 82 % to 91 %.

Biotransformation
Febuxostat is extensively metabolised by conjugation via uridine diphosphate glucuronosyltransferase (UDPGT) enzyme system and oxidation via the cytochrome P450 (CYP) system. Four pharmacologically active hydroxyl metabolites have been identified, of which three occur in plasma of humans. *In vitro* studies with human liver microsomes showed that those oxidative metabolites were formed primarily by CYP1A1, CYP1A2, CYP2C8 or CYP2C9 and febuxostat glucuronide was formed mainly by UGT 1A1, 1A8, and 1A9.

Elimination
Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of ^{14}C-labelled febuxostat, approximately 49 % of the dose was recovered in the urine as unchanged febuxostat (3 %), the acyl glucuronide of the active substance (30 %), its known oxidative metabolites and their conjugates (13 %), and other unknown metabolites (3 %). In addition to the urinary excretion, approximately 45 % of the dose was recovered in the faeces as the unchanged febuxostat (12 %), the acyl glucuronide

of the active substance (1 %), its known oxidative metabolites and their conjugates (25 %), and other unknown metabolites (7 %).

Renal impairment
Following multiple doses of 80 mg of febuxostat in patients with mild, moderate or severe renal impairment, the C_{max} of febuxostat did not change, relative to subjects with normal renal function. The mean total AUC of febuxostat increased by approximately 1.8-fold from 7.5 µg.h/ml in the normal renal function group to 13.2 µg.h/ml in the severe renal dysfunction group. The C_{max} and AUC of active metabolites increased up to 2- and 4-fold, respectively. However, no dose adjustment is necessary in patients with mild or moderate renal impairment.

Hepatic impairment
Following multiple doses of 80 mg of febuxostat in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, the C_{max} and AUC of febuxostat and its metabolites did not change significantly compared to subjects with normal hepatic function. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

Age
There were no significant changes observed in AUC of febuxostat or its metabolites following multiple oral doses of febuxostat in elderly as compared to younger healthy subjects.

Gender
Following multiple oral doses of febuxostat, the C_{max} and AUC were 24 % and 12 % higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. No dose adjustment is needed based on gender.

5.3 Preclinical safety data

Effects in non-clinical studies were generally observed at exposures in excess of the maximum human exposure.

Carcinogenesis, mutagenesis, impairment of fertility
In male rats, a statistically significant increase in urinary bladder tumours (transitional cell papilloma and carcinoma) was found only in association with xanthine calculi in the high dose group, at approximately 11 times human exposure. There was no significant increase in any other tumour type in either male or female mice or rats. These findings are considered a consequence of species-specific purine metabolism and urine composition and of no relevance to clinical use.
A standard battery of test for genotoxicity did not reveal any biologically relevant genotoxic effects for febuxostat.
Febuxostat at oral doses up to 48 mg/kg/day was found to have no effect on fertility and reproductive performance of male and female rats.
There was no evidence of impaired fertility, teratogenic effects, or harm to the foetus due to febuxostat. There was high dose maternal toxicity accompanied by a reduction in weaning index and reduced development of offspring in rats at approximately 4.3 times human exposure. Teratology studies, performed in pregnant rats at

approximately 4.3 times and pregnant rabbits at approximately 13 times human exposure did not reveal any teratogenic effects.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core
Microcrystalline cellulose 101
Lactose monohydrate
Croscarmellose sodium
Povidone K-30
Purified water
Colloidal anhydrous silica
Talc
Sodium stearyl fumarate
Opadry white 03F58750

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 30^0C.
Keep out of reach of children.

6.5 Nature and contents of container

Alu-PVC blisters of 3 x 10 Tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Cadila Healthcare Limited,
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Ahmedabad 380015,
India.
Email: Rajeev.nanda@zyduscadila.com

8. Date of revision of the text

October 2023