

Febugout F.C. Tablets 80mg (Febuxostat)

1. NAME OF THE MEDICINAL PRODUCT

Febugout film coated tablets 80 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg of febuxostat.

Excipient(s) with known effects:

Each tablet contains 189 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

Off yellow capsule-shaped film coated tablet engraved with "980" on one side and "S D" on the other side having a splitting line between S and D.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of chronic hyperuricemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

Febugout is indicated for use in adults.

4.2 Posology and method of administration

Posology

The recommended oral dose of Febugout is 40 mg or 80 mg once daily without regard to food. The recommended starting dose of Febugout is 40 mg once daily.

If serum uric acid is > 6 mg/dL (357 µmol/L) after 2-4 weeks, Febugout 80 mg once daily is recommended.

The 80 mg tablet can be divided into equal halves. In order to provide a 40 mg dose, the tablet should be split just before use. Prescribers should advise patients on how to break the tablets in half and to keep the other half of the tablet for the next dose.

Febugout 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 6.0 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).

No dose adjustment is necessary in patients with mild hepatic impairment. Limited information is available in patients with moderate hepatic impairment.

Pediatric population

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

Method of administration

Oral use

Febugout 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 ischemic heart disease or congestive heart failure is not recommended.

Caution should be exercised for exacerbation and/or onset of cardiovascular disease when administering febuxostat.

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 incidence 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. In the post-approval CARES study (see section 5.1 for detailed characteristics of the

study), the rate of major adverse cardiovascular events (MACE) was similar in febuxostat versus allopurinol treated patients (hazard ratio [HR] 1.03; 95% CI 0.89-1.21), but a higher rate of cardiovascular deaths was observed (4.3% vs. 3.2% of patients; HR 1.34; 95% CI 1.03-1.73). In a subsequent post registrational FAST study (see section 5.1 for the detailed characteristics of the study), febuxostat was non-inferior to allopurinol in the incidence of the CV primary endpoint, with an adjusted HR 0.85 (95% CI: 0.70, 1.03). Overall, there were fewer CV deaths in the febuxostat group (62 CV deaths and 108 all-cause deaths) than in the allopurinol group (82 CV deaths and 174 all-cause deaths).

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, hematological, 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 a 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 flares)

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 mobilization 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 hematological effects (see section 4.5).

Organ transplant recipients

As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended (see section 5.1).

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 80 mg can be used in patients concomitantly treated with theophylline without risk of increasing theophylline plasma levels.

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 tests are recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment (see section 5.1).

Thyroid disorders

Increased TSH values ($> 5.5 \mu\text{IU/mL}$) 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 (see section 5.1).

Lactose

Febuxostat tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the 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 xanthine oxidase (XO) inhibition, concomitant use is not recommended. Inhibition of XO by febuxostat may cause increased plasma concentrations of these drugs leading to myelotoxicity (see section 4.4). A drug interaction study of febuxostat with drugs that are metabolized by XO has been performed in healthy volunteers.

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.

Naproxen and other inhibitors of glucuronidation

Febuxostat metabolism depends on Uridine Glucuronosyl Transferase (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 (C_{max} 28%, AUC 41% and t_{1/2} 26%). In clinical studies the use of naproxen or other NSAIDs/Cox-2 inhibitors were 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/indomethacin/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 C_{max}, 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 fetus/newborn child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development or parturition (see section 5.3). The potential risk for human is unknown. Febuxostat should not be used during pregnancy.

Breastfeeding

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 breastfeeding.

Fertility

In animals, reproduction studies up to 48 mg/kg/day showed no dose-dependent adverse effects on fertility (see section 5.3). The effect of febuxostat on human fertility is unknown.

4.7 Effects on ability to drive and use machines

Somnolence, dizziness, paresthesia 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 Febugout 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, diarrhea, 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 ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) and rare ($\geq 1/10,000$ 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	<u>Rare</u> Pancytopenia, thrombocytopenia, agranulocytosis*, eosinophilia*
Immune system disorders	<u>Rare</u> Anaphylactic reaction*, drug hypersensitivity*
Endocrine disorders	<u>Uncommon</u> Blood thyroid stimulating hormone increased
Eye disorders	<u>Rare</u> Blurred vision

Metabolism and nutrition disorders	<u>Common***</u> Gout flares <u>Uncommon</u> Diabetes mellitus, hyperlipidemia, decrease appetite, weight increase <u>Rare</u> Weight decrease, increase appetite, anorexia
Psychiatric disorders	<u>Uncommon</u> Libido decreased, insomnia <u>Rare</u> Nervousness
Nervous system disorders	<u>Common</u> Headache <u>Uncommon</u> Dizziness, paresthesia, hemiparesis, somnolence, altered taste, hypoesthesia, hyposmia
Ear and labyrinth disorders	<u>Rare</u> Tinnitus
Cardiac disorders	<u>Uncommon</u> Atrial fibrillation, palpitations, ECG abnormal
Vascular disorders	<u>Uncommon</u> Hypertension, flushing, hot flush
Respiratory system disorders	<u>Uncommon</u> Dyspnoea, bronchitis, upper respiratory tract infection, cough
Gastrointestinal disorders	<u>Common</u> Diarrhoea**, nausea <u>Uncommon</u> Abdominal pain, abdominal distension, gastro-esophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort <u>Rare</u> Pancreatitis, mouth ulceration
Hepato-biliary disorders	<u>Common</u> Liver function abnormalities** <u>Uncommon</u> Cholelithiasis <u>Rare</u> Hepatitis, jaundice*, liver injury*

Skin and subcutaneous tissue disorders	<p><u>Common</u> Rash (including various types of rashes reported with lower frequencies, see below)</p> <p><u>Uncommon</u> Dermatitis, urticaria, pruritus, skin discoloration, skin lesion, petechiae, rash macular, rash maculopapular, rash papular</p> <p><u>Rare</u> Toxic epidermal necrolysis*, Stevens-Johnson Syndrome*, angioedema*, drug reaction with eosinophilia and systemic symptoms*, generalized rash (serious)*, erythema, erythema multiform*, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic*, rash erythematous, rash morbilliform, alopecia, hyperhidrosis</p>
Musculoskeletal and connective tissue disorders	<p><u>Uncommon</u> Arthralgia, arthritis, myalgia, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis</p> <p><u>Rare</u> Rhabdomyolysis*, joint stiffness, musculoskeletal stiffness</p>
Renal and urinary disorders	<p><u>Uncommon</u> Renal failure, nephrolithiasis, hematuria, pollakiuria, proteinuria</p> <p><u>Rare</u> Tubulointerstitial nephritis*, micturition urgency</p>
Reproductive system and breast disorder	<p><u>Uncommon</u> Erectile dysfunction</p>

General disorders and administration site conditions	<p><u>Common</u> Oedema</p> <p><u>Uncommon</u> Fatigue, chest pain, chest discomfort</p> <p><u>Rare</u> Thirst</p>
Investigations	<p><u>Uncommon</u> Blood amylase increase, platelet count decrease, WBC decrease, lymphocyte count decrease, blood creatine increase, blood creatinine increase, hemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, hematocrit decrease, blood lactate dehydrogenase increased, blood potassium increase</p>

	<p><u>Rare</u> Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase, blood creatine phosphokinase increase*</p>
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* Adverse reactions coming from post-marketing experience

** Treatment-emergent non-infective diarrhea 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 randomized 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 characterized by progressive skin rashes associated with blisters or mucosal lesions and eye irritation. Hypersensitivity reactions to febuxostat can be associated with the following symptoms: skin reactions characterized by infiltrated maculopapular eruption, generalised or exfoliative rashes, but also skin lesions, facial oedema, fever, hematologic abnormalities such as thrombocytopenia and eosinophilia, and single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis) (see section 4.4).

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 (see sections 4.2 and 4.4).

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 preparation, 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 catalyzed by 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 oxidized 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 4101 patients with hyperuricemia 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, 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 4.4).

CONFIRMS Study: The CONFIRMS study was a Phase 3, randomized, 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 hyperuricemia. Two thousand and two hundred-sixty nine (2269) patients were randomized: 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.

APEX Study: The Allopurinol and Placebo-Controlled Efficacy Study of Febuxostat (APEX) was a Phase 3, randomized, double-blind, multicenter, 28-week study. One thousand and seventy-two (1072) patients were randomized: 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 the febuxostat 80 mg QD treatment arm versus the conventionally used doses of allopurinol 300 mg (n = 258) /100 mg (n = 10) treatment arm in reducing the sUA below 6.0 mg/dL (357 µmol/L) (see Table 2).

FACT Study: The Febuxostat Allopurinol Controlled Trial (FACT) Study was a Phase 3, randomized, double-blind, multicenter, 52-week study. Seven hundred and sixty (760) patients were randomized: 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 the febuxostat 80 mg QD treatment arm versus the conventionally used dose of allopurinol 300 mg treatment arm in reducing and maintaining sUA below 6.0 mg/dL (357 µmol/L).

Table 2 summarizes the efficacy endpoint results in all 3 studies:

Table 2: Proportion of Patients with Serum Uric Acid Levels < 6.0 mg/dL (357µmol/L) at Last Three-Monthly Visits and Final Visit						
STUDY	Treatment Group				Difference in Proportion (95% CI)	
	Febuxostat	Febuxostat	Allopurinol	Placebo		
	40mg QD	80 mg QD	300mg QD _{1,2}		Febuxostat 40 mg vs allopurinol	Febuxostat 80 mg vs allopurinol
LAST THREE MONTHLY VISITS						
APEX (6 months)		48%* (126/262)	22% (60/268)	0% (0/134)		26% (18%-34%)
FACT (12 months)		53%* (136/255)	21% (53/251)			32% (24%-40%)
FINAL VISIT						
CONFIRMS (6 months)	45% (342/757)	67%* (507/756)	42% (318/755)		3% (-2%, 8%)	25% (20%, 30%)
APEX (6 months)		72% (183/253)	39% (102/263)	1% (1/127)		33% (26%, 42%)
FACT (12 months)		74% (185/249)	36% (88/242)			38% (30%, 46%)
<p>¹ Allopurinol was administered at reduced doses of 200 mg (CONFIRMS study) and 100 mg (APEX / FACT studies) depending on renal function.</p> <p>² 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> <p>* p < 0.001 vs allopurinol</p>						

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.

Primary endpoint in the sub-group of patients with renal impairment

An analysis in patients with gout who had mild to moderate renal impairment (Cl_{cr} 30 to 89 mL/min, Stages 2-3 CKD) was prospectively defined in the CONFIRMS study. As shown in Table 3, febuxostat 80 mg was significantly more efficacious in lowering serum urate levels

to < 6.0 mg/dL (357 μmol/L) compared to allopurinol 300 mg/200 mg or febuxostat 40 mg.

Table 3: Proportion of subjects with Serum Urate Level < 6.0 mg/dL (357 μmol/L) at Final Visit by Renal Function in CONFIRMS Study

Renal Function	Number (%) Subjects			
	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Allopurinol 300 mg	Allopurinol 200 mg
Normal CL _{cr} > 90mL/min	104/278 (37%) ^a	147/253 (58%) ^b	106/254 (42%)	NA
Mildly impaired (Stage 2 CKD) CL _{cr} 60-89 mL/min	182/349 (52%) ^a	263/367 (72%) ^b	169/365 (46%)	NA
Moderately Impaired (Stage 3 CKD) CL _{cr} 30-59 mL/min	56/130 (43%) ^a	97/136 (71%) ^b	NA	43/136 (32%)

Note: Allopurinol dose was adjusted to renal function

a. p < 0.01 Febuxostat 40 mg vs febuxostat 80 mg

b. p < 0.001 Febuxostat 80 mg vs allopurinol 300/200 mg

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) 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, the proportion of subjects who required treatment for gout flare was 28% -febuxostat 80 mg, 23% -allopurinol 300 mg and 20% -placebo. 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 mg), 14% (allopurinol 300 mg) and 20% (placebo) of subjects.

FACT study: During the 8-week prophylaxis period, the proportion of subjects who required treatment for a gout flare was 22% and 21% for febuxostat 80 mg and allopurinol 300 mg treatment groups respectively. After the 8-week prophylaxis period, the incidence 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% (febuxostat 80 mg) and 11% (allopurinol 300 mg) of subjects.

The proportion of subjects requiring treatment for a gout flare (APEX and FACT Studies) 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 \geq 6.0 mg/dL during the last 32 weeks of the treatment period (Week 20-Week 24 to Week 49-52 intervals).

CONFIRMS study: The percentage 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, multicenter, randomized, 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% of patients on initial treatment with febuxostat 80 mg 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% of patients on final stable treatment of febuxostat 80 mg QD, had complete resolution of the primary palpable tophus from baseline to the Final Visit.

FOCUS Study (TMX-01-005) was a five years Phase 2, open-label, multicenter, 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 μ mol/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 μ IU/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).

Post Marketing Long Term Studies

CARES Study (TMX-67 301) was a multicenter, randomized, double-blind, non-inferiority trial comparing CV outcomes with febuxostat versus allopurinol in patients with gout and a history of major CV disease including MI, hospitalization for unstable angina, coronary or cerebral revascularization procedure, stroke, hospitalized transient ischemic attack, peripheral

vascular disease, or diabetes mellitus with evidence of microvascular or macrovascular disease. To achieve sUA less than 6 mg/dL, the dose of febuxostat was titrated from 40 mg up to 80 mg (regardless of renal function) and the dose of allopurinol was titrated in 100 mg increments from 300 to 600 mg in patients with normal renal function and mild renal impairment and from 200 to 400 mg in patients with moderate renal impairment.

The primary endpoint in CARES was the time to first occurrence of MACE, a composite of non-fatal MI, non-fatal stroke, CV death and unstable angina with urgent coronary revascularization.

The endpoints (primary and secondary) were analyzed according to the intention-to-treat (ITT) analysis including all subjects who were randomized and received at least 1 dose of double-blind study medication.

Overall 56.6% of patients discontinued trial treatment prematurely and 45% of patients did not complete all trial visits.

In total, 6,190 patients were followed for a median of 32 months and the median duration of exposure was 728 days for patients in febuxostat group (n=3098) and 719 days in allopurinol group (n=3092).

The primary MACE endpoint occurred at similar rates in the febuxostat and allopurinol treatment groups (10.8% vs. 10.4% of patients, respectively; hazard ratio [HR] 1.03; two sided repeated 95% confidence interval [CI] 0.89-1.21)

In the analysis of the individual components of MACE, the rate of CV deaths was higher with febuxostat than allopurinol (4.3% vs. 3.2% of patients; HR 1.34; 95% CI 1.03-1.73). Sudden cardiac death was the most common cause of adjudicated CV deaths in the febuxostat group (83 of 3,098; 2.7%) as compared to the allopurinol group (56 of 3,092; 1.8%).

The biological plausibility of CV death associated with febuxostat is unclear. The rates of the other MACE events were similar in the febuxostat and allopurinol groups, i.e. non fatal MI (3.6% vs. 3.8% of patients; HR 0.93; 95% CI 0.72-1.21), non-fatal stroke (2.3% vs. 2.3% of patients; HR 1.01; 95% CI 0.73-1.41) and urgent revascularization due to unstable angina (1.6% vs. 1.8% of patients; HR 0.86; 95% CI 0.59-1.26). The rate of all-cause mortality was also higher with febuxostat than allopurinol (7.8% vs. 6.4% of patients; HR 1.22; 95% CI 1.01-1.47), which was mainly driven by the higher rate of CV deaths in that group (see section 4.4).

Rates of adjudicated hospitalization for heart failure, hospital admissions for arrhythmias not associated with ischemia, venous thromboembolic events and hospitalization for transient ischemic attacks were comparable for febuxostat and allopurinol.

FAST study was a prospective, randomized, open-label, blinded-endpoint study comparing the CV safety profile of febuxostat versus allopurinol in patients with chronic hyperuricaemia (in conditions where urate deposition had already occurred) and CV risk factors (i.e. patients 60 years or older and with at least one other CV risk factor). Eligible patients received allopurinol treatment prior to randomization, and dose adjustments were required when needed, according to clinical judgement, EULAR recommendations and the approved posology. At the end of the allopurinol lead-in phase, patients with a sUA level of < 0.36 mmol/L (< 6 mg/dL) or receiving the maximum tolerated dose or the maximum licensed dose of allopurinol were randomized in a 1:1 ratio to receive either febuxostat or allopurinol treatment. The primary endpoint of the study FAST was the time to the first occurrence of any event included in the

Antiplatelet Trialists' Collaborative (APTC) composite endpoint, which included: i) hospitalization for non-fatal MI/biomarker positive acute coronary syndrome (ACS); ii) non-fatal stroke; iii) death due to a CV event. The primary analysis was based on the on-treatment (OT) approach.

Overall, 6,128 patients were randomized, 3,063 to febuxostat and 3,065 to allopurinol.

In the primary OT analysis, febuxostat was non-inferior to allopurinol in the incidence of the primary endpoint, which occurred in 172 patients (1.72/100 patient years) on febuxostat compared to 241 patients (2.05/100 patient years) on allopurinol, with an adjusted HR 0.85 (95% CI: 0.70, 1.03), $p < 0.001$. The OT analysis for the primary endpoint in the subgroup of patients with a history of MI, stroke or ACS showed no significant difference between treatment groups: there were 65 (9.5%) patients with events in the febuxostat group and 83 (11.8%) patients with events in the allopurinol group; adjusted HR 1.02 (95% CI: 0.74-1.42); $p = 0.202$.

Treatment with febuxostat was not associated with an increase in CV death or all-cause death, overall or in the subgroup of patients with a baseline history of MI, stroke or ACS. Overall, there were fewer deaths in the febuxostat group (62 CV deaths and 108 all-cause deaths), than in the allopurinol group (82 CV deaths and 174 all-cause deaths).

There was a greater reduction in uric acid levels on febuxostat treatment compared to allopurinol treatment.

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 hyperuricemia 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 40 mg, 80 mg and 120 mg once daily doses, C_{max} is approximately 1.5-1.6 $\mu\text{g/mL}$, 2.8-3.2 $\mu\text{g/mL}$, and 5.0-5.3 $\mu\text{g/mL}$, 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, Febugout may be taken without regard to food.

Distribution

The apparent steady state volume of distribution (V_{ss}/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 40 and 80 mg doses. Plasma protein binding of the active metabolites ranges from about 82% to 91%.

Biotransformation

Febuxostat is extensively metabolized 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 - labeled 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 feces as 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

In a dedicated phase I pharmacokinetics study, 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 $\mu\text{g}\cdot\text{h}/\text{mL}$ in the normal renal function group to 13.2 $\mu\text{g}\cdot\text{h}/\text{mL}$ 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.

Based on population pharmacokinetic analysis, following multiple 40 mg or 80 mg doses of febuxostat, the mean oral clearance (CL/F) values of febuxostat in patients with gout and mild ($n=334$), moderate ($n=232$) or severe ($n=34$) renal impairment were decreased by 14%, 34%, and 48%, respectively, compared to patients with normal ($n=89$) renal function. The corresponding median AUC values of febuxostat at steady-state in patients with renal impairment were increased by 18%, 49%, and 96% after 40 mg dose, and 7%, 45% and 98% after 80 mg dose, respectively, compared to patients with normal renal function.

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

Two-year carcinogenicity studies were conducted in F344 rats and B6C3F1 mice. Increased transitional cell papilloma and carcinoma of urinary bladder was observed at 24 mg/kg (25 times the human plasma exposure at maximum recommended human dose of 80 mg/day) and 18.75 mg/kg (12.5 times the human plasma exposure at 80 mg/day) in male rats and female mice, respectively. The urinary bladder neoplasms were secondary to calculus formation in the kidney and urinary bladder.

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 fetus 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

Lactose monohydrate
Microcrystalline cellulose
Hydroxypropyl cellulose
Croscarmellose sodium
Magnesium stearate

Tablet coating

Opadry 03B82459 containing:

HPMC 2910/Hypromellose
Titanium dioxide
Macrogol/PEG
Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

PVC/PVDC-Aluminium Blister of 14 tablets.
Box of 2 blisters x 14 tablets

6.6 Special precautions for disposal

No special requirements.

Manufactured by
STANDARD CHEM. & PHARM. CO. LTD. No. 6-20,
Tuku, Tuku Village, Sinying District, Tainan City 73055, Taiwan