FEBUTON F.C. TABLETS 80mg (FEBUXOSTAT)
(Febuxostat 80mg)

1. Name of Medicinal Product

FEBUTON F.C. TABLETS 80mg (FEBUXOSTAT) film-coated tablet

2. Qualitative and Quantitative Composition

Each tablet contains Febuxostat 80mg

3. Pharmaceutical dosage form

Film-coated tablet (tablet).

A off-yellow to yellow, capsule shaped film-coated tablet, engraved with “980” on one surface 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 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

<u>Posology</u>

The recommended oral dose of FEBUXOSTAT is 80 mg once daily without regard to food. If serum uricacid 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. Thetherapeutic 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 isavailable 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 beenestablished. 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 alsosection 4.8).

4.4 Special warnings and precautions for use

Cardio-vascular disorders

Treatment with febuxostat in patients with pre-existing major cardiovascular diseases (e.g. myocardialinfarction, stroke or unstable angina) should be avoided, unless no other therapy options are appropriate.

A numerical greater incidence of investigator-reported cardiovascular APTC events (defined endpointsfrom 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. In the post registrational CARES trial (see section 5.1 for detailed characteristics of the study) the rate of MACE events was similar in febuxostat versus allopurinol treated patients (HR 1.03; 95% CI 0.87- 1.23), 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).

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 mobilization of urate from tissue deposits (see section 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 as inhibition of xanthine oxidase by febuxostat may cause increasedplasma concentrations of mercaptopurine/azathioprine that could result in severe toxicity. No interaction studies have been performed in humans.

Where the combination cannot be avoided, a reduction of the dose of mercaptopurine/azathioprine is recommended. Based on modelling and simulation analysis of data from a pre-clinical study in rats, when coadministered with febuxostat, the dose of mercaptopurine/azathioprine should be reduced to the 20% or less of the previously prescribed dose in order to avoid possible haematological effects (seesection 4.5 and 5.3).

The patients should be closely monitored and the dose of mercaptopurine/azathioprine should be subsequently adjusted based on the evaluation of the therapeutic response and the onset of eventualtoxic effects.

Organ transplant recipients

As there has been no experience in organ transplant recipients, the use of febuxostat in such patients isnot recommended (see section 5.1).

Theophylline

Co-administration of febuxostat 80 mg and theophylline 400mg single dose in healthy subjects showed absence of any pharmacokinetic interaction (see section 4.5). Febuxostat 80 mg can be used inpatients 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 inpatients 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 (see section 5.1).

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 (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 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 (except theophylline) that are metabolized by XO have not been performed in humans.

Modelling and simulation analysis of data from a pre-clinical study in rats indicates that, in case of concomitant administration with febuxostat, the dose of mercaptopurine/azathioprine should be reduced to 20% or less of the previously prescribed dose (see section 4.4 and 5.3)

Drug interaction studies of febuxostat with other cytotoxic chemotherapy have not been conducted. No data is available regarding the safety of febuxostat during other 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 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 was not related to anyclinically significant increase in adverse events.

Febuxostat can be co-administered with naproxen with no dose adjustment of febuxostat or naproxenbeing necessary.

Inducers of glucuronidation

Potent inducers of UGT enzymes might possibly lead to increased metabolism and decreased efficacyof 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 offebuxostat 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 offebuxostat (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 anydose adjustment for those compounds.

Antacids

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminium hydroxide hasbeen 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 foetus/new born child. Animal studies do not indicatedirect or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition (see section 5.3). The potential risk for human is unknown. Febuxostat should not be usedduring 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 riskto 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 onfertility (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, 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 adose 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, and rare events of sudden cardiac death, 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-marketingexperience

Blood and lymphatic system disorders	Rare Pancytopenia, thrombocytopenia, agranulocytosis*
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, hyperlipidemia, decrease appetite, weight increase Rare Weight decrease, increase appetite, anorexia

Psychiatric disorders	Uncommon Libido decreased, insomnia Rare Nervousness
Nervous system disorders	Common Headache Uncommon Dizziness, paraesthesia, hemiparesis, somnolence, altered taste, hypoaesthesia, hyposmia
Ear and labyrinth disorders	Rare Tinnitus
Cardiac disorders	Uncommon Atrial fibrillation, palpitations, ECG abnormal Rare Sudden cardiac death*
Vascular disorders	Uncommon Hypertension, flushing, hot flush
Respiratory system disorders	Uncommon Dyspnoea, bronchitis, upper respiratory tract infection, cough
Gastrointestinal disorders	Common Diarrhoea**, nausea Uncommon: Abdominal pain, abdominal distension, gastro-oesophageal refluxdisease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort Rare Pancreatitis, mouth ulceration
Hepato-biliary 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 lowerfrequencies, 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*, generalized rash (serious)*, erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic*,rash erythematous, rash morbillifom, alopecia, hyperhidrosis
Musculoskeletal and connectivetissue 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 disorder	Uncommon Erectile dysfunction

General disorders and administration site conditions	Common Oedema Uncommon Fatigue, chest pain, chest discomfort Rare Thirst
Investigations	Uncommon Blood amylase increase, platelet count decrease, WBC decrease, lymphocyte count decrease, blood creatine increase, blood creatinine increase, haemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, haematocritic decrease, blood lactate dehydrogenase increased, blood potassium increase Rare Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase, blood creatine phosphokinase increase*

* 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 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 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) (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 prophylaxisis recommended (see section 4.2 and 4.4).

<u>**Reporting of suspected adverse reactions**</u>

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Health Product Vigilance Center; HPVC.

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, ATCcode: M04AA03

<u>**Mechanism of action**</u>

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 xanthine oxidase (XO). Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect ofdecreasing 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 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, 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 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, randomized, double-blind, multicenter, 52-week study. Seven hundred 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 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

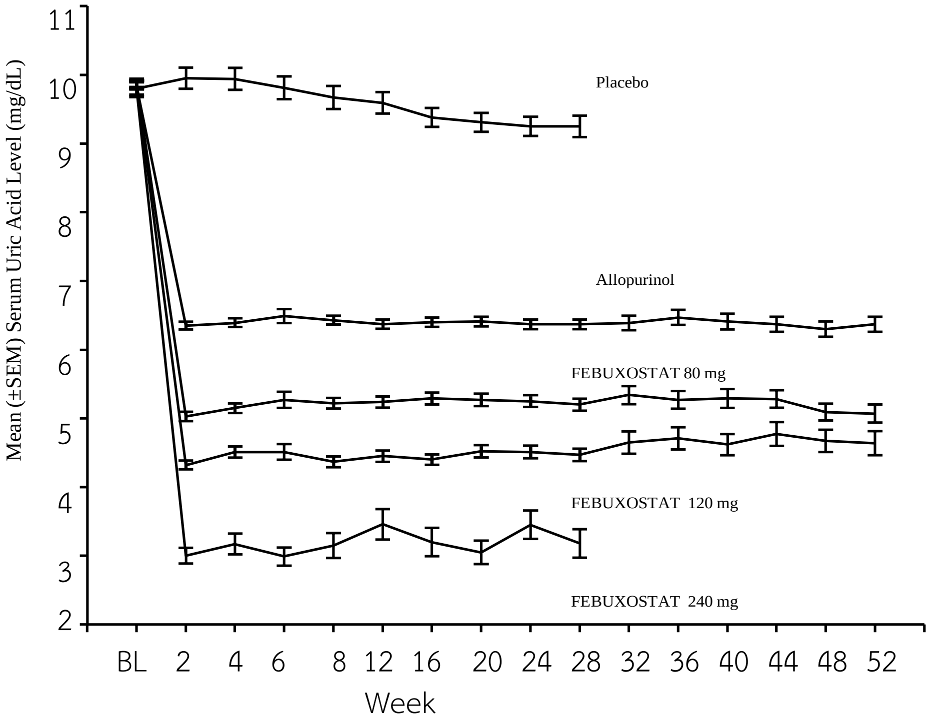
Study	FEBUXOSTAT 80 mg QD	FEBUXOSTAT 120 mg QD	Allopurinol 300/100 mg QD[1]
APEX (28 weeks)	48% * (n=262)	65% *,# (n=269)	22% (n=268)
FACT (52 weeks)	53%* (n=255)	62%* (n=250)	21% (n=251)
Combined Results	51%* (n=517)	63%*,# (n=519)	22% (n=519)

[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



BL=baseline SEM=standard error of the mean

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 recommendedhighest dose.

CONFIRMS Study: The CONFIRMS study was a Phase 3, randomized, controlled, 26-week study toevaluate 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 (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 renalimpairment (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, was45% 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 randomized to allopurinol, the dose was capped at 100 mg QD. FEBUXOSTAT achieved the primary efficacy endpointin 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 functiongroup 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 moderaterenal 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% inthe 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 withfebuxostat 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 febuxostat120 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, multicenter, 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, 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 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).

Post Marketing long term studies

CARES Study 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 analysed according to the intention-to-treat (ITT) analysis including all subjects who were randomized and received at least one 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] 0.87-1.23).

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). 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.

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 (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 80 and 120 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 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.

Pharmacokinetic modelling and simulation of rat data suggests that, when co-administered with febuxostat, the clinical dose of mercaptopurine/azathioprine should be reduced to 20% or less of the previously prescribed dose in order to avoid possible haematological effects (see section 4.4 and 4.5).

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

Lactose monohydrate, Microcrystalline Cellulose, Hydroxypropyl Cellulose, Croscarmellose Sodium, Magnesium stearate

Tablet coating

Opadry 03B82459

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium) blister of 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7. Name and address of Manufacturer/Marketing authorization Holder

Manufacturer by

STANDARD CHEM. & PHARM. CO. LTD.

Sinying, Tainan, Taiwan.

Imported and Distributed by

UNION MEDICAL (THAILAND) CO., LTD.

Bangkok, Thailand.

8. Marketing Authorization Numbers

รอใส่เลขทะเบียนยา

9. Date of first authorization

รอใส่วันที่อนุมัติ

10. Date of Revision of the text

March 2022