BUFEXO
(Febuxostat)

40 mg & 80 mg

Tablets

WARNING

CARDIOVASCULAR DEATH

Gout patients with established cardiovascular (CV) disease treated with Febuxostat had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study.

Consider the risks and benefits of Febuxostat when deciding to prescribe or continue patients on Febuxostat. Febuxostat should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.

COMPOSITION

Each film-coated tablet contains:
Febuxostat 40mg
(Product complies to Innovator's Specifications)
Each film-coated tablet contains:
Febuxostat 80mg
(Product complies to Innovator's Specifications)

THERAPEUTIC INDICATIONS

FEBUXOSTAT is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.

Limitations of Use: FEBUXOSTAT is not recommended for the treatment of asymptomatic hyperuricemia.

DOSAGE AND ADMINISTRATION

Recommended Dose

The recommended FEBUXOSTAT dosage is 40 mg or 80 mg once daily. The recommended starting dosage of FEBUXOSTAT is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg/dL after two weeks, the recommended FEBUXOSTAT dosage is 80 mg. FEBUXOSTAT can be taken without regard to food or antacid use.

Dosage Recommendations in Patients with Renal Impairment and Hepatic Impairment

No dose adjustment is necessary when administering FEBUXOSTAT in patients with mild or moderate renal impairment. The recommended dosage of FEBUXOSTAT is limited to 40 mg once daily in patients with severe renal impairment.

No dose adjustment is necessary in patients with mild to moderate hepatic impairment

Uric Acid Level

Testing for the target serum uric acid level of less than 6 mg/dL may be performed as early as two weeks after initiating FEBUXOSTAT therapy.

Recommended Prophylaxis for Gout Flares

Gout flares may occur after initiation of FEBUXOSTAT due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended upon initiation of FEBUXOSTAT. Prophylactic therapy may be beneficial for up to six months. If a gout flare occurs during FEBUXOSTAT treatment, FEBUXOSTAT need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient.

CONTRAINDICATIONS

FEBUXOSTAT is contraindicated in patients being treated with azathioprine or mercaptopurine.

WARNINGS AND PRECAUTIONS

Cardiovascular Death

In a cardiovascular (CV) outcome study, gout patients with established CV disease treated with FEBUXOSTAT had a higher rate of CV death compared to those treated with allopurinol.

Because of the increased risk of CV death, FEBUXOSTAT should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable. Consider the risks and benefits of FEBUXOSTAT when deciding to prescribe or continue patients on FEBUXOSTAT.

Consider use of prophylactic low-dose aspirin therapy in patients with a history of CV disease. Physicians and patients should remain alert for the development of adverse CV event signs and symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

Gout Flares

After initiation of FEBUXOSTAT, an increase in gout flares is frequently observed. This increase is due to reduction in serum uric acid levels, resulting in mobilization of urate from tissue deposits. In order to prevent gout flares when FEBUXOSTAT is initiated, concurrent prophylactic treatment with an NSAID or colchicine is recommended.

Hepatic Effects

There have been post marketing reports of fatal and nonfatal hepatic failure in patients taking FEBUXOSTAT, although the reports contain insufficient information necessary to establish the probable cause. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in FEBUXOSTAT and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted.

Obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) as a baseline before initiating FEBUXOSTAT. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), FEBUXOSTAT treatment should be interrupted and investigation done to establish the probable cause. FEBUXOSTAT should not be restarted in these patients without another explanation for the liver test abnormalities.

Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug induced liver injury and should not be restarted on FEBUXOSTAT. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with FEBUXOSTAT can be used with caution.

Serious Skin Reactions

Postmarketing reports of serious skin and hypersensitivity reactions, including Stevens - Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) have been reported in patients taking FEBUXOSTAT. Discontinue FEBUXOSTAT if serious skin reactions are suspected. Many of these patients had reported previous similar skin reactions to allopurinol. FEBUXOSTAT should be used with caution in these patients.

DRUG INTERACTIONS

Xanthine Oxidase Substrate Drugs

FEBUXOSTAT is an XO inhibitor. Based on a drug interaction study in healthy patients, Febuxostat altered the metabolism of theophylline (a substrate of XO) in humans. Therefore, use with caution when coadministering FEBUXOSTAT with theophylline. Drug interaction studies of FEBUXOSTAT with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by FEBUXOSTAT may cause increased plasma concentrations of these drugs leading to toxicity. FEBUXOSTAT is contraindicated in patients being treated with azathioprine or mercaptopurine.

Cytotoxic Chemotherapy Drugs

Drug interaction studies of FEBUXOSTAT with cytotoxic chemotherapy have not been conducted. No data are available regarding the safety of FEBUXOSTAT during cytotoxic chemotherapy.

In Vivo Drug Interaction Studies

Based on drug interaction studies in healthy patients, FEBUXOSTAT does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine. Therefore, FEBUXOSTAT may be used concomitantly with these medications.

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

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.* 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

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

USE IN SPECIFIC POPULATIONS

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.

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.

Pediatric Use

Safety and effectiveness of FEBUXOSTAT in pediatric patients have not been established.

Geriatric Use

No dose adjustment is necessary in elderly patients

Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (ClCr 30 to 89 mL/min). For patients with severe renal impairment (ClCr 15 to 29 mL/min), the recommended dosage of FEBUXOSTAT is limited to 40 mg once daily.

Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (ChildPugh Class C); therefore, caution should be exercised in these patients

Secondary Hyperuricemia

No studies have been conducted in patients with secondary hyperuricemia (including organ transplant recipients); FEBUXOSTAT is not recommended for use in patients whom the rate of urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). The concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract.

ADVERSE DRUG REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

*Most common adverse drug reaction*s: Liver function abnormalities, Nausea, Arthralgia & Rash.

Less Common Adverse Reactions: In clinical studies the following adverse reactions occurred in less than 1% of patients and in more than one subject treated with doses ranging from 40 mg to 240 mg of FEBUXOSTAT. This list also includes adverse reactions (less than 1% of patients) associated with organ systems.

Blood and Lymphatic System Disorders: anemia, idiopathic thrombocytopenic purpura, leukocytosis/leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.

Cardiac Disorders: angina pectoris, atrial fibrillation/flutter, cardiac murmur, ECG abnormal, palpitations, sinus bradycardia, tachycardia.

Ear and Labyrinth Disorders: deafness, tinnitus, vertigo.

Eye Disorders: vision blurred.

Gastrointestinal Disorders: abdominal distention, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, frequent stools, gastritis, gastroesophageal reflux disease, gastrointestinal discomfort, gingival pain, haematemesis, hyperchlorhydria, hematochezia, mouth ulceration, pancreatitis, peptic ulcer, vomiting.

General Disorders and Administration Site Conditions: asthenia, chest pain/discomfort, edema, fatigue, feeling abnormal, gait disturbance, influenza-like symptoms, mass, pain, thirst.

Hepatobiliary Disorders: cholelithiasis/cholecystitis, hepatic steatosis, hepatitis, hepatomegaly.

Immune System Disorder: hypersensitivity.

Infections and Infestations: herpes zoster.

Procedural Complications: contusion.

Metabolism and Nutrition Disorders: anorexia, appetite decreased/increased, dehydration, diabetes mellitus, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypokalemia, weight decreased/increased.

Musculoskeletal and Connective Tissue Disorders: arthritis, joint stiffness, joint swelling, muscle spasms/twitching/tightness/weakness, musculoskeletal pain/stiffness, myalgia.

Nervous System Disorders: altered taste, balance disorder, cerebrovascular accident, Guillain-Barré syndrome, headache, hemiparesis, hypoesthesia, hyposmia, lacunar infarction, lethargy, mental impairment, migraine, paresthesia, somnolence, transient ischemic attack, tremor.

Psychiatric Disorders: agitation, anxiety, depression, insomnia, irritability, libido decreased,nervousness, panic attack, personality change.

Renal and Urinary Disorders: hematuria, nephrolithiasis, pollakiuria, proteinuria, renal failure, renal insufficiency, urgency, incontinence.

Reproductive System and Breast Changes: breast pain, erectile dysfunction, gynecomastia.

Respiratory, Thoracic and Mediastinal Disorders: bronchitis, cough, dyspnea, epistaxis, nasal dryness, paranasal sinus hypersecretion, pharyngeal edema, respiratory tract congestion, sneezing, throat irritation, upper respiratory tract infection.

Skin and Subcutaneous Tissue Disorders: alopecia, angio edema, dermatitis, dermographism, ecchymosis, eczema, hair color changes, hair growth abnormal, hyperhidrosis, peeling skin, petechiae, photosensitivity, pruritus, purpura, skin discoloration/altered pigmentation, skin lesion,skin odor abnormal, urticaria.

Vascular Disorders: flushing, hot flush, hypertension, hypotension.

Laboratory Parameters: activated partial thromboplastin time prolonged, creatine increased, bicarbonate decreased, sodium increased, EEG abnormal, glucose increased, cholesterol increased, triglycerides increased, amylase increased, potassium increased, TSH increased, platelet count decreased, hematocrit decreased, hemoglobin decreased, MCV increased, RBC decreased, creatinine increased, blood urea increased, BUN/creatinine ratio increased, creatine phosphokinase (CPK) increased, alkaline phosphatase increased, LDH increased, PSA increased, urine output increased/decreased, lymphocyte count decreased, neutrophil count decreased, WBC increased/decreased, coagulation test abnormal, low density lipoprotein (LDL) increased, prothrombin time prolonged, urinary casts, urine positive for white blood cells and protein.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of FEBUXOSTAT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: agranulocytosis, eosinophilia.

Hepatobiliary Disorders: hepatic failure (some fatal), jaundice, serious cases of abnormal liver function test results, liver disorder.

Immune System Disorders: anaphylaxis, anaphylactic reaction.

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis.

Psychiatric Disorders: psychotic behavior including aggressive thoughts.

Renal and Urinary Disorders: tubulointerstitial nephritis.

Skin and Subcutaneous Tissue Disorders: generalized rash, Stevens - Johnson syndrome, hypersensitivity skin reactions, erythema multiforme, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis.

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. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

Over dosage

FEBUXOSTAT was studied in healthy patients in doses up to 300 mg daily for seven days without evidence of dose-limiting toxicities. No overdose of FEBUXOSTAT was reported in clinical studies. Patients should be managed by symptomatic and supportive care should there be an overdose.

PHARMACOLOGICAL PROPERTIES

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 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 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)

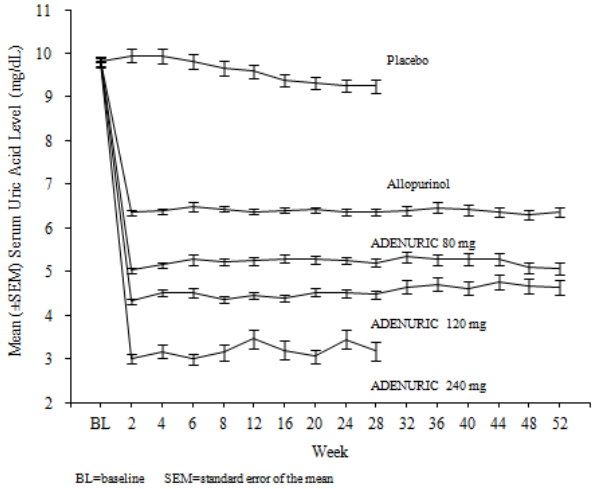
Last Three Monthly Visits

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 recommended highest dose.

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 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 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 randomized 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, 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.

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.

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.

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 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.

PRESENTATION

Bufexo 40mg Tablets are available in Alu-Alu blister pack of 20's.

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STORAGE INSTRUCTIONS

-To be sold on the prescription of a registered medical

practitioner only.

-Protect from sunlight, moisture and heat.

-Do not store above 30°C.

-Keep all medicines out of sight & reach of children.

-Product contains lactose

REGISTRATION NUMBER

Bufexo 40mg Tablets: 103251

Bufexo 80mg Tablets: 103252

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

The Searle Company Limited,

F-319, S.I.T.E., Karachi-Pakistan.

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