Febuxostat

Urinorm®
40 mg Film-Coated Tablet
80 mg Film-Coated Tablet
anti-gout

FORMULATION

Each film-coated tablet contains:
Febuxostat ……..……40 mg or 80 mg

PRODUCT DESCRIPTION

40 mg Film-Coated Tablet: White to off-white, approximately 6 mm, round, biconvex film-coated tablet with a break-line on one side and plain on the other side
80 mg Film-Coated Tablet: White to off-white, approximately 8 mm, round, biconvex film-coated tablet with a break-line on one side and plain on the other side.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Febuxostat inhibits xanthine oxidase, the enzyme that catalyzes the conversion of hypoxanthine to xanthine and xanthine to uric acid. By blocking uric acid production, febuxostat decreases serum concentrations of uric acid. Febuxostat is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.

In healthy subjects, febuxostat resulted in a dose dependent decrease in 24-hour mean serum uric acid concentrations and an increase in 24-hour mean serum xanthine concentrations. There was also a decrease in the total daily urinary uric acid excretion and an increase in total daily urinary xanthine excretion. Percent reduction in 24-hour mean serum uric acid concentrations was between 40 to 55% at the exposure levels of 40 mg and 80 mg daily doses.

Pharmacokinetics

Maximum plasma concentrations (C_{max}) and area under the curve (AUC) of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg in healthy subjects. There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours. The pharmacokinetic parameters of febuxostat for patients with hyperuricemia and gout were similar to those estimated in healthy subjects.

The absorption of radiolabeled febuxostat following oral dose administration was estimated to be at least 49% with maximum plasma concentrations occurring between 1 to 1.5 hours post-dose. After multiple oral 40 mg and 80 mg once daily doses, C_{max} is approximately 1.6 ± 0.6 mcg per mL, and 2.6 ± 1.7 mcg per mL, respectively. The absolute bioavailability of febuxostat tablet has not been studied.

Following multiple 80 mg once daily doses with a high fat meal, there was a 49% decrease in C_{max} and an 18% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed.

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminum hydroxide with an 80 mg single dose of febuxostat has been shown to delay absorption of febuxostat (approximately 1 hour) and to cause a 31% decrease in C_{max} and a 15% decrease in AUC_{∞}. As AUC rather than C_{max} was related to drug effect, change observed in AUC was not considered clinically significant.

The mean apparent steady state volume of distribution (V_{ss}/F) of febuxostat was approximately 50 L. The plasma protein binding of febuxostat is approximately 99.2%, primarily to albumin, and is constant over the concentration range achieved with 40 mg and 80 mg doses.

Febuxostat is extensively metabolized by both conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes including UGT1A1, UGT1A3, UGT1A9, and UGT2B7 and oxidation via cytochrome P450 (CYP) enzymes including CYP1A2, 2C8 and 2C9 and non-P450 enzymes. The oxidation of the isobutyl side chain leads to the formation of four pharmacologically active hydroxy metabolites, all of which occur in human plasma at a much lower extent than febuxostat.

The apparent mean terminal elimination half-life ($t_{1/2}$) of febuxostat is approximately 5 to 8 hours.

In urine and feces, acyl glucuronide metabolites of febuxostat and oxidative metabolites 67M-1, 67M-2, and 67M-4, a secondary metabolite from 67M-1, appeared to be the major metabolites of febuxostat *in vivo*.

Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of 14C-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the drug (30%), its known oxidative metabolites and their conjugates (13%), and other known metabolites (3%). Also, approximately 45% of the dose was recovered in feces as unchanged febuxostat (12%), the acyl glucuronide of the drug (1%), its known oxidative metabolites and their conjugates (25%), and other known metabolites (7%).

INDICATION

For the chronic management of hyperuricemia in patients with gout (including a history, or presence of, tophus and/or gouty arthritis).

Febuxostat is not recommended for the treatment of asymptomatic hyperuricemia.

DOSAGE AND ADMINISTRATION

May be taken without regard to food or antacid use.

Recommended Starting Dose: 40 mg once a day

The dosage may be increased to 80 mg in patients who do not achieve a serum uric acid (sUA) of less than 6 mg/dL after two weeks of therapy with febuxostat 40 mg.

Usual Adult Dose: 40 to 80 mg once a day, or, as prescribed by a physician.

Testing for the target sUA level of less than 6 mg/dL may be performed as early as two weeks after initiating febuxostat therapy.

Gout flare prophylaxis of at least 6 months is recommended (see **WARNINGS AND PRECAUTIONS**).

CONTRAINDICATIONS

- Hypersensitivity to febuxostat or to other ingredients in the product
- Patients on treatment with azathioprine, mercaptopurine or theophylline

WARNINGS AND PRECAUTIONS

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. Flare prophylaxis with a nonsteroidal anti-inflammatory drug (NSAID) or colchicine is

recommended upon initiation of febuxostat. Prophylactic therapy may be beneficial for up to 6 months. Febuxostat treatment should not be discontinued when gout flares occur. The gout flare should be managed concurrently, as appropriate for the individual patient.

Cardiovascular Events
Treatment with febuxostat in patients with ischemic heart disease or congestive heart failure is not recommended.

In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes) in patients treated with febuxostat than with allopurinol. A causal relationship with febuxostat has not been established. Signs and symptoms of myocardial infarction and stroke should be monitored.

Hepatic Effects
There have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking febuxostat, although the reports contain insufficient information necessary to establish the probable cause. Serum transaminase concentrations exceeding 3 times the upper limit of normal have been reported in patients receiving febuxostat. Laboratory assessment of liver function is recommended prior to initiation of febuxostat therapy and periodically thereafter.

A liver test panel [serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin] should be obtained as a baseline before initiating febuxostat.

Liver tests should be measured 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, 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.

Medicinal Product Allergy/Hypersensitivity
Rare reports of serious allergic/hypersensitivity reactions, including life-threatening Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and acute anaphylactic reaction/shock, have been reported in 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. Febuxostat treatment should be immediately stopped if serious allergic/hypersensitivity reactions, including SJS, occur since early withdrawal is associated with a better prognosis. If patient has developed allergic/hypersensitivity reactions and acute anaphylactic reaction/shock, febuxostat must not be re-started in this patient at any time.

Thyroid Disorders
Increased thyroid stimulating hormone values (>5.5 μIU/mL) were observed in patients on long-term treatment with febuxostat (5.5%). Caution is required when febuxostat is used in patients with alteration of thyroid function.

Effects on Ability to Drive and Use Machine
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 febuxostat does not adversely affect performance.

INTERACTIONS WITH OTHER MEDICAMENTS

CONCOMITANT DRUGS	EFFECTS
Cytotoxic Chemotherapy Drugs	No data are available on the safety of febuxostat during cytotoxic chemotherapy.
In vivo Drug Interactions	No clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine were seen. Dose adjustment of febuxostat is not needed.
Mercaptopurine, Azathioprine	Febuxostat may cause increased plasma concentrations of these drugs resulting in toxicity.
Xanthine Oxidase (XO) Substrate Drugs	Febuxostat was shown to alter the metabolism of XO substrate drugs (e.g., theophylline). A 400-fold increase in the amount of 1-methylxanthine, a major metabolite of theophylline, was excreted in the urine. Use with caution when co-administering febuxostat and theophylline.

STATEMENT ON USAGE FOR HIGH-RISK GROUPS
Pregnancy
Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Febuxostat should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effect of febuxostat in human fertility is unknown.

Lactation
It is not known if febuxostat is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when administering febuxostat to breastfeeding women.

Children (< 18 years old)
The safety and efficacy of febuxostat have not been established in pediatric patients.

Elderly (≥ 65 years old)
No dose adjustment is necessary in elderly patients. The C_{max} and AUC_{24} of febuxostat following multiple oral doses in geriatric subjects were similar to those in younger subjects (18 to 40 years old).

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

Renal Impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment. There are insufficient data in patients with severe renal impairment (creatinine clearance less than 30 mL/min); 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 whose rate of urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). In rare cases, the concentration of xanthine in urine could rise sufficiently to allow deposition in the urinary tract.

Other Diseases
Febuxostat is not recommended for use in patients with a greatly increased rate of urate formation (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). No studies have been conducted in these populations.

Febuxostat has not been studied in organ transplant patients.

UNDESIRABLE EFFECTS
Infections and infestations: Cellulitis, herpes zoster
Neoplasms benign, malignant and unspecified (incl cysts and poplyps): Malignant melanoma, myelodysplastic syndrome
Blood and lymphatic system disorders: Anemia, idiopathic thrombocytopenic purpura, leukocytosis/leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia
Immune system disorders: Anaphylaxis, hypersensitivity, rare serious reactions including anaphylactic reaction/shock
Metabolism and nutrition disorders: Anorexia, decreased/increased appetite, cow's milk intolerance, decreased/increased weight, dehydration, diabetes mellitus, dyslipidemia, gout, gout flares, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypokalemia
Psychiatric disorders: Agitation, anxiety, decreased libido, depression, insomnia, irritability, nervousness, panic attack, psychotic behavior including aggressive thoughts
Nervous system disorders: Altered taste, amnesia, balance disorder, burning sensation, cerebrovascular accident, dizziness, Guillain-Barré syndrome, headache, hemiparesis, hypoesthesia, hyposmia, lacunar infarction, lethargy, mental impairment, migraine, paresthesia, peripheral neuropathy, somnolence, transient ischemic attack, tremor
Eye disorders: Blurred vision, cataract
Ear and labyrinth disorders: Deafness, tinnitus, vertigo
Cardiac disorders: Abnormal electrocardiogram (ECG), angina pectoris, atrial fibrillation/flutter, cardiac murmur, cardiovascular thromboembolic events [e.g., cardiovascular death, myocardial infarction (some fatal) and non-fatal stroke], palpitations, sinus bradycardia, tachycardia
Vascular disorders: flushing, hot flush, hypertension, hypotension
Respiratory, thoracic and mediastinal disorders: Bronchitis, cough, dyspnea, epistaxis, nasal dryness, paranasal sinus hypersecretion, pharyngeal edema, respiratory tract congestion, sinusitis, sneezing, throat irritation, upper respiratory tract infection, wheezing
Gastrointestinal disorders: Abdominal distention, abdominal pain, colitis, constipation, dry mouth, dyspepsia, esophageal stenosis, flatulence, frequent stools, gastritis, gastroenteritis, gastroesophageal reflux disease, gastrointestinal discomfort, gingival pain, hematemesis, hematochezia, hyperchlorhydria, mouth ulceration, nausea, pancreatitis, peptic ulcer, rectal hemorrhage, vomiting
Hepatobiliary disorders: Cholelithiasis/cholecystitis, hepatic failure (some fatal), hepatic steatosis, hepatitis, hepatomegaly, jaundice, liver disorder/injury, serious cases of abnormal liver function test results
Skin and subcutaneous tissue disorders: Abnormal hair growth, abnormal skin odor, alopecia, angioedema, dermatitis, dermographism, drug reaction with eosinophilia and systemic symptoms

(DRESS), ecchymosis, eczema, erythema, exfoliative rash, hair color changes, hyperhidrosis, peeling skin, petechiae, photosensitivity, pruritus, purpura, rash follicular, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash papular, rash pustular, rash vesicular, skin discoloration/altered pigmentation, skin hypersensitivity reactions, skin lesion, tinea pedis, toxic epidermal necrolysis (TEN), urticaria

Musculoskeletal and connective tissue disorders: Arthralgia, arthritis, bunion, bursitis, costochondritis, gouty tophus, joint stiffness, joint swelling, muscle spasms/twitching/tightness/weakness, musculoskeletal pain/stiffness, myalgia, rhabdomyolysis

Renal and urinary disorders: Hematuria, incontinence, kidney infection, micturition urgency, nephrolithiasis, pollakiuria, proteinuria, renal failure, renal insufficiency, tubulointerstitial nephritis, urgency, urinary tract infection

Reproductive system and breast disorders: Breast pain, erectile dysfunction, gynecomastia, mastitis

General disorders and administration site conditions: Asthenia, chest pain/discomfort, edema, fatigue, feeling abnormal, gait disturbance, influenza-like symptoms, mass, pain, thirst

Investigations: Activated partial thromboplastin time prolonged, abnormal electroencephalogram (EEG), abnormal coagulation test, alkaline phosphatase increased, amylase increased, bicarbonate decreased, blood urea nitrogen/creatinine ratio increased, blood urea increased, cholesterol increased, creatine phosphokinase (CPK) increased, creatine increased, glucose increased, hematocrit decreased, hemoglobin decreased, lactate dehydrogenase increased, low density lipoprotein increased, lymphocyte count decreased, mean corpuscular volume increased, neutrophil count decreased, platelet count decreased, potassium increased, prothrombin time prolonged, prostate specific antigen increased, red blood cell count decreased, sodium increased, thyroid stimulating hormone increased, triglycerides increased, urinary casts, urine output decreased/increased, urine positive for white blood cells and protein, white blood cell count decreased/increased

Injury, poisoning and procedural complications: Contusion

OVERDOSE AND TREATMENT

Febuxostat was studied in healthy subjects 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 when an overdose occurs.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY

Febuxostat (Urinorm®) 40 mg Film-Coated Tablet, in alu-alu blister pack x 10s (box of 30s)
Febuxostat (Urinorm®) 80 mg Film-Coated Tablet, in alu-alu blister pack x 10s (box of 30s)

STORE AT TEMPERATURES NOT EXCEEDING 30°C
PROTECT FROM LIGHT
KEEP THE PRODUCT OUT OF SIGHT AND REACH OF CHILDREN

Manufactured for Anvaxx Laboratories Pvt. Ltd.
21, Satyam, 318, Linking Road, Khar (W), Mumbai 400 052, India
By Ajanta Pharma Limited
Plot No. B-4/5/6, MIDC, Paithan, Aurangabad 431138, Maharashtra State, India
Imported and distributed by **UNILAB, Inc**.
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines