23-01-2020

Urigo® Tablets
(Febuxostat)

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

Urigo® 40mg Tablets:
Each film coated tablet contains:
Febuxostat MS…..40mg

Urigo® 80mg Tablets:
Each film coated tablet contains:
Febuxostat MS……80mg

DRUG DESCRIPTION

Urigo® (Febuxostat) is a xanthine oxidase inhibitor. The active ingredient in febuxostat is 2-[3-cyano4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, with a molecular weight of 316.38. The empirical formula is $C_{16}H_{16}N_2O_3S$.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS:
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. At therapeutic concentrations febuxostat does not inhibit other enzymes involved in purine or pyrimidine synthesis and metabolism.
Effect on Uric Acid and Xanthine Concentrations: In healthy patients, febuxostat resulted in a dose dependent decrease in 24 hour mean serum uric acid concentrations (40% and 55% at the exposure levels of 40mg and 80mg daily doses) and an increase in 24 hour mean serum xanthine concentrations. In addition, there was a decrease in the total daily urinary uric acid excretion & an increase in total daily urinary xanthine excretion.

PHARMACOKINETICS:
Absorption: • 49%, Distribution: Vss: ~50 L, Protein binding: ~99%, primarily to albumin, Time to peak, plasma: 1 to 1.5 hours, Metabolism: Extensive conjugation via uridine diphosphate glucuronosyltransferases (UGTs) 1A1, 1A3, 1A9, and 2B7 and oxidation via cytochrome P450 (CYP) 1A2, 2C8, and 2C9 as well as non-P450 enzymes. Oxidation leads to formation of active metabolites (67M-1, 67M-2, 67M-4). Half-life elimination: ~5 to 8 hours, Excretion: Urine (~49% mostly as metabolites, 3% as unchanged drug); feces (~45% mostly as metabolites, 12% as unchanged drug).
Gender: Following multiple oral doses, Cmax and AUC are 30% and 14% higher in women than men, respectively.

INDICATIONS AND DOSAGE

INDICATIONS AND USAGE:
Urigo® 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.
For the safe and effective use of allopurinol, see allopurinol prescribing information.
Limitations of Use: **Urigo®** is not recommended for the treatment of asymptomatic hyperuricemia.

DOSAGE AND ADMINISTRATION:
Method of Administration: It can be taken without regard to food or antacid use.
Dosage: The recommended dosage of **Urigo®** is 40mg or 80mg once daily.
The recommended starting dosage of febuxostat is 40mg 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 80mg once daily.
Dose Titration: If serum uric acid is > 6mg/dL (357 µmol/L) after 2-4 weeks, febuxostat 120mg once daily may be considered. It works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks. The therapeutic target is to decrease and maintain serum uric acid below 6 mg/dL (357 •mol/L).
Note: Testing for the target serum uric acid level of less than 6mg/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 for up to six months. If a gout flare occurs during its treatment, febuxostat need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient

SPECIAL POPULATIONS:
Paediatric population: Safety and effectiveness of febuxostat in pediatric patients under 18 years have not been established.
Geriatric population: No dose adjustment is necessary in elderly patients.
Renal impairment: Mild or moderate renal impairment: No dose adjustment. Severe renal impairment: 40mg once daily.
Hepatic Impairment: Mild to moderate hepatic impairment: No dose adjustment is necessary. Therapeutic impairment; Dosage adjustments has not been studied in severe use caution.

OVER DOSAGE:

Febuxostat was studied in healthy patients in doses up to 300mg 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.

CONTRAINDICATIONS

- Hypersensitivity to febuxostat or any component of the formulation.
- Febuxostat is contraindicated in patients being treated with azathioprine or mercaptopurine.

WARNINGS AND PRECAUTIONS

CONCERNS RELATED TO ADVERSE EFFECTS:
Hepatic failure: Postmarketing cases of hepatic failure (both fatal and nonfatal) have been reported (causal relationship has not been established). In controlled studies, significant hepatic transaminase elevations (>3 x ULN) have occurred. Liver function tests should be evaluated at baseline and periodically thereafter; also in patients experiencing signs and symptoms of hepatic injury (eg, fatigue, anorexia, right upper quadrant pain, dark urine, and jaundice). Interrupt therapy in patients who develop abnormal liver function tests (eg, ALT >3 x ULN); permanently discontinue use if no other explanation for the abnormalities is elucidated and in patients who develop ALT >3 x ULT and serum total bilirubin >2 x ULN. All other patients may be cautiously 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.
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 (up to 6 months).
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. Febuxostat should be used with caution in these patients.
Thromboembolic events: MI, stroke and cardiovascular deaths were reported at a slightly increased rate versus allopurinol in controlled studies (a causal relationship has not been established). Patients should be monitored for signs and symptoms of MI or stroke.

DISEASE-RELATED CONCERNS:
Cardiovascular Death: Gout patients with established CV disease treated with febuxostat showed a higher rate of CV death compared to those treated with allopurinol. The CV outcomes study in patients with gout (CARES) was a randomized, double-blinded, allopurinol-controlled, non-inferiority study conducted to evaluate the risk of major adverse cardiovascular events (MACE) in patients with gout who were treated with febuxostat. The study enrolled patients who had a history of major CV disease, cerebrovascular disease or diabetes mellitus with micro- and/or macrovascular disease. The primary endpoint was the time to first occurrence of MACE defined as the composite of CV death, nonfatal MI, nonfatal stroke, or unstable angina with urgent coronary revascularization. Results showed that febuxostat was non-inferior to allopurinol for the primary endpoint of MACE [Hazard Ratio: 1.03, 95% Confidence Interval (CI): 0.89, 1.21]. However, there was a significant increase in CV deaths in patients treated with febuxostat compared to patients treated with allopurinol [Hazard Ratio: 1.34, 95% CI: 1.03, 1.73]. Sudden cardiac death was the most common cause of adjudicated CV deaths in the febuxostat group (83 of 3,098; 2.7%) as compared to the allopurinol group (56 of 3,092; 1.8%). Febuxostat was similar to allopurinol for nonfatal MI, nonfatal stroke and unstable angina with urgent coronary revascularization. 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.
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.

CONCURRENT DRUG THERAPY ISSUES:
Please refer to drug interaction section for concurrent drug therapy issues.

210mm

120mm

SPECIAL POPULATIONS:
Pregnancy: Pregnancy Category C
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. The potential risk for human is unknown. Febuxostat should not be used during pregnancy.
Lactation: Animal studies have shown excretion of this active substance in breast milk. A risk to a suckling infant cannot be excluded. Febuxostat should not be used while breastfeeding.
Severe hepatic impairment: No clinical data, caution should be exercised.
Secondary Hyperuricemia: No clinical data (including patients being treated for Lesch-Nyhan syndrome or malignant disease, or in organ transplant recipients); therefore, febuxostat is not recommended for use in these patients.
Organ transplant recipients: Due to no experience in this subset of patient, febuxostat is not recommended

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.

ADVERSE REACTIONS

1% to 10%:
Dermatologic: Skin rash (1% to 2%)
Gastrointestinal: Nausea (1%)
Hepatic: Liver function abnormalities (5% to 7%)
Neuromuscular & skeletal: Arthralgia (1%)

<1%:
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, and 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: 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, angioedema, 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:
Agranulocytosis, eosinophilia; hepatic failure (some fatal), jaundice, serious cases of abnormal liver function test results, liver disorder; anaphylaxis, anaphylactic reaction; rhabdomyolysis; psychotic behavior including aggressive thoughts; tubulointerstitial nephritis; generalized rash, Stevens-Johnson Syndrome, hypersensitivity skin reactions, erythema multiforme, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
In male rats, a statistically significant increase in urinary bladder tumours (transitional cell papilloma and carcinoma) was found only at approximately 11 times human exposure. There was no significant increase in any other tumour type. It is considered a consequence of species specific purine metabolism and urine composition and of no relevance to clinical use. Test for genotoxicity did not reveal any biologically relevant genotoxic effects for febuxostat. There was no evidence of impaired fertility, teratogenic effects, or harm to the foetus due to febuxostat.

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 and patients/carers are asked to report any suspected adverse reactions at safety@samikhi.com or call on +92 (0) 21 34383400 (Office hours and out of office hours). Also, adverse event may be reported via website: www.samipharmapk.com

DRUG INTERACTIONS

INTERACTIONS RESULTING IN A CONTRAINDICATION:
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.

INTERACTIONS REQUIRING PRECAUTIONS:
Xanthine Oxidase Substrate Drugs: Febuxostat altered the metabolism of theophylline (a substrate of XO) in humans; use with caution is advised.

NO SIGNIFICANT INTERACTION:
Cytotoxic Chemotherapy Drugs: No data are available regarding the safety of febuxostat during cytotoxic chemotherapy.
In Vivo Drug Interaction Studies: Febuxostat does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine. Therefore, febuxostat may be used concomitantly with these medications.
P450 Substrate Drugs: In vitro studies have shown that febuxostat does not inhibit P450 enzymes CYP1A2, 2C9, 2C19, 2D6, or 3A4 and it also does not induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 at clinically relevant concentrations. As such, pharmacokinetic interactions between febuxostat and drugs metabolized by these CYP enzymes are unlikely.

STABILITY

See expiry on the pack.

AVAILABILITY

Urigo® 40mg tablets in a pack of 20's
Urigo® 80mg tablets in a pack of 20's

INSTRUCTIONS

Dosage as advised by physician. To be sold on the prescription of registered medical practitioner.
Keep out of reach of children.Avoid exposure to heat, light and humidity.
Store between 15 to 30°C. Improper storage may deteriorate the medicine.
Store in the original package in order to protect from moisture.

Please read the contents carefully before use.
This package insert is regularly reviewed and updated.

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

یوریگو® ٹیبلٹ

(فیبوکسوسٹیٹ)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔ دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔
دوا کو نمی سے محفوظ رکھنے کے لیے اسکی اصل پیکنگ میں رکھیں۔

R.N-06/HA/01/2020

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