Healol

Urilog 40 Urilog 80

Febuxostat Film Coated Tablets 40 mg/ 80 mg

DESCRIPTION

Urilog Film-Coated Tablets 40mg
White coloured, round shaped, biconvex, film coated tablets plain on both sides.

Urilog Film-Coated Tablets 80mg
White coloured, round shaped, biconvex, film coated tablets with break line on one side and plain on other side.

The break line only meant for facilitating swallow of whole tablet in 2 smaller portions. The tablet is not to be broken into half for divided doses.

COMPOSITION

Urilog Film-Coated Tablets 40mg
Each tablet contains 40mg febuxostat.

Urilog Film-Coated Tablets 80mg
Each tablet contains 80mg febuxostat.

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 (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.

PHARMACOKINETICS

In healthy subjects, maximum plasma concentrations (Cmax) 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 (t1/2) 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 (tmax of 1.0-1.5 h) and well absorbed (at least 84%). After single or multiple oral 80 and 120 mg once daily doses, Cmax 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 Cmax 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 tablets may be taken without regard to food.

Distribution
The apparent steady state volume of distribution (Vss/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 14C-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
The mean total AUC of febuxostat increased by approximately 1.8-fold from 7.5µg·h/mL in the normal renal unction group to 13.2µg·h/mL in the severe renal dysfunction group. The Cmax and AUC of active metabolites increase up to 2- and 4-fold, respectively. However, no dose adjustment is necessary in patients with mold or moderate renal impairment.

Hepatic impairment
Following multiple doses of 80mg of febuxostat in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, the Cmax 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 Cmax and AUC were 24% and 12% higher in females than in males, respectively. However, weight-corrected Cmax and AUC were similar between the genders. No dose adjustment is needed based on gender.

INDICATION

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

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed at end of this insert.

WARNINGS AND PRECAUTIONS

Cardio-vascular disorders
Treatment with febuxostat in patients with pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke or unstable angina) should be avoided, unless no other therapy options are appropriate. Caution should be exercised for exacerbation and/or onset of cardiovascular disease when administering this drug.

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. 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. At treatment initiation with febuxostat flare prophylaxis for at least 6 months with an NSAID or colchicine is recommended. If a gout flare occurs during febuxostat treatment, it should not be discontinued. The gout flare should be managed concurrently as appropriate for the individual patient. Continuous treatment with febuxostat decreases frequency and intensity of gout flares.

Xanthine deposition
In patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. As there has been no experience with febuxostat, its use in these populations is not recommended.

Mercaptopurine/azathioprine
Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine. Where the combination cannot be avoided patients should be closely monitored. A reduction of dosage of mercaptopurine or azathioprine is recommended in order to avoid possible haematological effects.

Organ transplant recipients
As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended.

Theophylline
Co-administration of febuxostat 80 mg and theophylline 400mg single dose in healthy subjects showed absence of any pharmacokinetic interaction. Febuxostat 80 mg can be used in patients concomitantly treated with theophylline without risk of increasing theophylline plasma levels.

Liver disorders
During the combined phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0%). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment.

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.

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.

PREGNANCY AND LACTATION

Pregnancy
Data on a very limited number of exposed pregnancies have not indicated any adverse effects of febuxostat on pregnancy or on the health of the fetus/new born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal 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.

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Somnolence, dizziness, paraesthesia and blurred vision have been reported with the use of Urilog. Patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that Urilog does not adversely affect performance.

INTERACTIONS WITH OTHER MEDICAMENTS

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 4 concentrations of these drugs leading to toxicity. Drug interaction studies of febuxostat with drugs that are metabolized by XO have not been performed. Where the combination cannot be avoided patients should be closely monitored. A reduction of dosage of mercaptopurine or azathioprine is recommended in order to avoid possible haematological effects.

Drug interaction studies of febuxostat with cytotoxic chemotherapy have not been conducted. No data is available regarding the safety of febuxostat during cytotoxic therapy.

Rosiglitazone/CYP2C8 substrates
Febuxostat was shown to be a weak inhibitor of CYP2C8 in vitro. Co-administration of febuxostat with rosiglitazone or other CYP2C8 substrates is not expected to require any dose adjustment for those compounds.

Theophylline
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.

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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.

Inducers of glucuronidation
Potent inducers of UGT enzymes might possibly lead to increased metabolism and decreased efficacy of febuxostat. Monitoring of serum uric acid is therefore recommended 1-2 weeks after start of treatment with a potent inducer of glucuronidation. Conversely, cessation of treatment of an inducer might lead to increased plasma levels of febuxostat.

Colchicine/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. 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 Cmax, but no significant change in AUC was observed. Therefore, febuxostat may be taken without regard to antacid use.

MAIN SIDE/ ADVERSE EFFECTS

The most commonly reported adverse reactions 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
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness

Blood and lymphatic system disorders	Rare Pancytopenia, thrombocytopenia, agranulocytosis, eosinophilia
Immune system disorders	Rare Anaphylactic reaction, drug hypersensitivity
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
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 reflux disease, 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 lower frequencies) Uncommon Dermatitis, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash popular Rare Toxic epidermal necrolysis, Stevens- Johnson Syndrome, angioedema, drug reaction with eosinophilia and systemic symptoms, generalized rash (serious), erythema, erythema multiform, exfoliative rash, rash follicular, rash vesicular, rash pustula, rash pruritic, rash erythematous, rash morbilliform, alopecia, hyperhidrosis
Muscoloskeletal, connective tissue and bone disorders	Uncommon Arthralgia, arthritis, myalgia, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis Rare Rhamdomyolysis, joint stiffness, musculoskeletal stiffness
Renal and urinary disorders	Uncommon Renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria Rare Tubolointerstitial nephritis, micturition urgency
Reproductive system and breast disorder	Uncommon Erectile dysfuntion
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

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). Gout flares were commonly observed soon after the start of treatment and during the first months. Thereafter, the frequency of gout flare decreases in a time-dependent manner. Gout flare prophylaxis is recommended.

OVERDOSE

Patients with an overdose should be managed by symptomatic and supportive care.

DOSAGE AND ADMINISTRATION

Adult
The recommended oral dose of Urilog tablet is 40 mg or 80 mg once daily without regard to food. The recommended starting dose of Urilog tablet is 40 mg once daily. If serum uric acid is > 6.0 mg/dL (357 µmol/L) after 2-4 weeks, Urilog tablet 80 mg once daily may be considered.

Urilog tablet works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks. The therapeutic target is to decrease and maintain serum uric acid below 6.0 mg/dL (357 µmol/L).

Gout flare prophylaxis of at least 6 months is recommended.

Elderly
No dose adjustment is required in the elderly.

Renal impairment
The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 mL/min).
No dose adjustment is necessary in patients with mild or moderate renal impairment.

Hepatic impairment
The efficacy and safety of febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh Class C).

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

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

Method of administration
Oral use
Urilog tablet should be taken by mouth and can be taken with or without food.

STORAGE CONDITION

Store below 30°C. Protect from light and moisture.

Presentation/ packing:
3 x 10 tablets, packed in Aluminium-PVC blister

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