Oxubat®

Febuxostat

FORMS AND PRESENTATION
Oxubat® 80: Film coated tablets: Box of 30.
Oxubat® 120: Film coated tablets: Box of 30.
COMPOSITION
Oxubat® 80: Each film coated tablet contains Febuxostat 80mg.
Oxubat® 120: Each film coated tablet contains Febuxostat 120mg.
Excipients: Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow.
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 of 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.
Pharmacokinetic properties
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, C_{max} is approximately 2.8-3.2 µg/mL, and 5.0-5.3 µg/mL, respectively. Febuxostat 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 the plasma of humans.
Elimination
Febuxostat is eliminated by both hepatic and renal pathways.
Renal impairment
No dose adjustment is necessary for 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 Cmax and AUC of febuxostat and its metabolites did not change significantly compared to subjects with normal hepatic function. No studies have been conducted on patients with severe hepatic impairment (Child-Pugh Class C).
INDICATIONS
Oxubat® is indicated for the treatment of chronic hyperuricemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).
Oxubat® 120 is indicated for the prevention and treatment of hyperuricemia in adult patients undergoing chemotherapy for hematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS).
Oxubat® is indicated in adults.
CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients of this drug.
PRECAUTIONS
Cardio-vascular disorders
In patients with pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke, or unstable angina), a higher number of fatal cardiovascular events were observed with febuxostat when compared to allopurinol.
Treatment of this patient group should be exercised cautiously, and they should be monitored regularly.
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 during the post-marketing experience. In most cases, these reactions occurred during the first month of therapy with febuxostat. Some, but not all these patients reported renal impairment and/or a 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.
Febuxostat treatment should be immediately stopped if serious allergic/hypersensitivity reactions occur since the early withdrawal is associated with a better prognosis. If the 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 the initiation of treatment due to changing serum uric acid levels resulting in the 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 the frequency and intensity of gout flares.
Xanthine deposition
In patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. As there has been no experience with febuxostat, its use in these populations is not recommended.
Mercaptopurine/azathioprine
Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine /azathioprine as inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of mercaptopurine/azathioprine that could result in severe toxicity.
Organ transplant recipients
As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended.
Theophylline
Febuxostat 80 mg can be used in patients concomitantly treated with theophylline without the risk of increasing theophylline plasma levels. No data is available for febuxostat 120 mg.
Liver disorders
A 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. Caution is required when febuxostat is used in patients with an alteration of thyroid function.
Lactose
Febuxostat tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.
Effects on ability to drive and use machines
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.
PREGNANCY AND LACTATION
Pregnancy
Data on a very limited number of exposed pregnancies have not indicated any adverse effects of febuxostat on pregnancy or on the health of the foetus/newborn child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, or parturition. The potential risk for humans 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 impaired development of suckling pups. A risk to a suckling infant cannot be excluded. Febuxostat should not be used while breastfeeding.
DRUG INTERACTIONS
Mercaptopurine/azathioprine
Based on the mechanism of action of febuxostat on XO inhibition concomitant use is not recommended. Inhibition of XO by febuxostat may cause increased plasma concentrations of these drugs leading to toxicity. Drug interaction studies of febuxostat with drugs (except theophylline) that are metabolized by XO have not been performed in humans.
Rosiglitazone/CYP2C8 substrates
Febuxostat was shown to be a weak inhibitor of CYP2C8 in vitro. In a study of healthy subjects, coadministration of 120 mg febuxostat with a single 4 mg oral dose of rosiglitazone had no effect on the pharmacokinetics of rosiglitazone and its metabolite N-desmethyl rosiglitazone, indicating that febuxostat is not a CYP2C8 enzyme inhibitor *in vivo*. Thus, co-administration of febuxostat with rosiglitazone or other CYP2C8 substrates is not expected to require any dose adjustment for those compounds.
Naproxen and other inhibitors of glucuronidation
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 the 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 or warfarin.
Desipramine/CYP2D6 substrates
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 aluminum hydroxide has been shown to delay the 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.

ADVERSE EFFECTS

Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), and rare (≥1/10,000 to <1/1,000).
Blood and lymphatic system disorders: Pancytopenia, thrombocytopenia, agranulocytosis, anemia (rare)
Immune system disorders: Anaphylactic reaction, drug hypersensitivity (rare)
Endocrine disorders: Blood thyroid stimulating hormone increased, hypothyroidism (uncommon)
Eye disorders: Blurred vision (uncommon); Retinal artery occlusion (rare)
Metabolism and nutrition disorders: Gout flares (common); Diabetes mellitus, hyperlipidemia, decreased appetite, weight increase (uncommon); Weight decrease, increase appetite, anorexia (rare)
Psychiatric disorders: Libido decreased, insomnia (uncommon); Nervousness, depressed mood, sleep disorder (rare)
Nervous system disorders: Headache, dizziness (common); Paraesthesia, hemiparesis, somnolence, lethargy altered taste, hypoaesthesia, hyposmia (uncommon); Ageusia, burning sensation (rare)
Ear and labyrinth disorders: Tinnitus (uncommon); vertigo (rare)
Cardiac disorders: Atrial fibrillation, palpitations, ECG abnormal, left bundle branch block, sinus tachycardia, arrhythmia (uncommon); Sudden cardiac death (rare)
Vascular disorders: Hypertension, flushing, hot flush, hemorrhage (uncommon); Circulatory collapse (rare)
Respiratory system disorders: Dyspnea (common); Bronchitis, upper respiratory tract infection, lower respiratory tract infection, cough, rhinorrhea (uncommon); Pneumonia (rare)
Gastrointestinal disorders: Diarrhea, nausea (common); Abdominal pain, abdominal pain upper, abdominal distension, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort, mouth ulceration, lip swelling, pancreatitis (uncommon); Gastrointestinal perforation, stomatitis (rare)
Hepato-biliary disorders: Liver function abnormalities (common); Cholelithiasis (uncommon); Hepatitis, jaundice, liver injury, cholecystitis (rare)
Skin and subcutaneous tissue disorders: Rash, pruritus (common); Dermatitis, urticaria, skin discoloration, skin lesion, petechiae, rash macular, rash maculopapular, rash papular, hyperhidrosis, alopecia, eczema, erythema, night sweats, psoriasis, rash pruritic (uncommon); Toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, drug reaction with eosinophilia and systemic symptoms, generalized rash (serious), exfoliative rash, rash follicular, rash vesicular, rash pustular, rash erythematous, rash morbilliform (rare)
Musculoskeletal and connective tissue disorders: Arthralgia, myalgia, pain in extremity (common); Arthritis, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis, joint swelling, back pain, musculoskeletal stiffness, joint stiffness (uncommon); Rhabdomyolysis, rotator cuff syndrome, polymyalgia rheumatica (rare)
Renal and urinary disorders: Renal failure, nephrolithiasis, hematuria, pollakiuria, proteinuria, micturition urgency, urinary tract infection (uncommon); Tubulointerstitial nephritis (rare)
Reproductive system and breast disorder: Erectile dysfunction (uncommon)
General disorders and administration site conditions: Oedema, Fatigue (common); Chest pain, chest discomfort, pain, malaise (uncommon); Thirst, feeling hot (rare)
Investigations: Blood amylase increase, platelet count decrease, WBC decrease, lymphocyte count decrease, blood creatine increase, blood creatinine increase, hemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, hematocritic decrease, blood lactate dehydrogenase increased, blood potassium increase, INR increased (uncommon); Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase, blood creatine phosphokinase increase (rare)
Injury, poisoning, and procedural complications: Contusion (uncommon)

DOSAGE AND ADMINISTRATION

Posology
Gout: The recommended oral dose of Oxubat® is 80 mg once daily without regard to food. If serum uric acid is > 6 mg/dL (357 µmol/L) after 2-4 weeks, Oxubat® 120 mg once daily may be considered.
Oxubat® 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 µmol/L).
Gout flare prophylaxis of at least 6 months is recommended.
Tumor Lysis Syndrome: The recommended oral dose of Oxubat® is 120 mg once daily without regard to food.
Oxubat® should be started two days before the beginning of cytotoxic therapy and continued for a minimum of 7 days; however, treatment may be prolonged up to 9 days according to chemotherapy duration as per clinical judgment.
Elderly
No dose adjustment is required in the elderly.
Renal impairment
No dose adjustment is necessary for patients with mild or moderate renal impairment.
The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 mL/min).
Hepatic impairment
The recommended dose in patients with mild hepatic impairment is 80 mg. Limited information is available on patients with moderate hepatic impairment.
The efficacy and safety of febuxostat have not been studied in patients with severe hepatic impairment (Child Pugh Class C).
Pediatric population
The safety and efficacy of Oxubat® in children aged below the age of 18 years have not been established. No data are available.
Method of administration
Oral use
Oxubat® should be taken by mouth and can be taken with or without food.

OVERDOSAGE

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

STORAGE CONDITIONS

Store below 30°C
Keep in original pack in intact condition.

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MARKETING AUTHORIZATION HOLDER:
Benta SAL – Lebanon

MANUFACTURER:
Manufactured by MSN Laboratories Private Limited, India
For Benta SAL – Lebanon