URIZAK®
(FEBUXOSTAT)
40mg, 80mg Tablets

DESCRIPTION:
Urizak (Febuxostat) is a non-purine selective inhibitor of xanthine oxidase (XO). Febuxostat is chemically described as 2-[3-cyano-4- (2-methylpropoxy) phenyl]-4-methylthiazole-5- carboxylic acid, with a molecular weight of 316.38. The empirical formula is $C_{16}H_{16}N_2O_3S$.

URIZAK TABLETS ARE AVAILABLE FOR ORAL ADMINISTRATION AS:
1. URIZAK Tablets 40mg
   Each Film coated Tablet contains:
   Febuxostat……40mg
2. URIZAK Tablets 80mg
   Each Film coated Tablet contains:
   Febuxostat……80mg

CLINICAL PHARMACOLOGY:
Mechanism of action:
Febuxostat is a potent, non-purine, selective inhibitor of xanthine oxidase (XO) that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting xanthine oxidase. Uric acid is the end product of purine metabolism and is generated in the cascade of hypoxanthine → xanthine → uric acid. Both steps in the transformation are catalyzed by xanthine oxidase. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of xanthine oxidase. 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:
Absorption:
Febuxostat is rapidly and extensively absorbed following oral dose administration, with a t_{max} at approximately 1.0 to 1.5 hours and 84% absorbed. There is no accumulation of febuxostat when therapeutic doses are administered every 24 hours. After single or multiple oral 80mg and 120mg once daily doses, C_{max} is approximately 2.8-3.2µg/mL, and 5.0-5.3µg/mL, respectively. Following multiple oral 80mg once daily doses or a single 120mg dose with a high fat meal, there was a 49% and 38% decrease in C_{max} and 18% and 16% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed.

Distribution:
The mean apparent steady state volume of distribution (Vss/F) of febuxostat was approximately 50L (CV~40%). The plasma proteins binding of Febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 40mg and 80mg doses.

Metabolism:
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. These 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 80mg 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 feces 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%). The apparent mean terminal half-life ($t_{1/2}$) of febuxostat was approximately 5 to 8 hours.

Special Population:
Renal Impairment

Following multiple doses of 80mg of febuxostat in patients with mild, moderate or severe renal insufficiency, the C_{max} of febuxostat did not change, relative to subjects with normal renal function.

Hepatic Impairment

Following multiple doses of 80mg of febuxostat in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic insufficiency, the C_{max} and AUC of febuxostat and its metabolites did not change significantly compared to subjects with normal hepatic function.

INDICATIONS:
Urizak (Febuxostat) is indicated for the chronic management of hyperuricemia in patients with gout.

DOSAGE AND ADMINISTRATION:
For treatment of hyperuricemia in patients with gout, Urizak (Febuxostat) is recommended at 40 mg or 80 mg once daily.

The recommended starting dose of Urizak (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 with 40 mg, Urizak (Febuxostat) 80 mg is recommended. Urizak (Febuxostat) can be taken without regard to food or antacid use.

Special Population:
Renal Impairment

No dose adjustment is necessary when administering febuxostat in patients with mild to moderate renal insufficiency.

Hepatic Impairment:

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

ADVERSE EFFECTS:
Common:
Headache, diarrhea, nausea, rash and LFT abnormalities.

Uncommon:

Blood amylase increase, platelet count decrease, blood creatinine increase, hemoglobin decrease, blood urea increase LDH increase, triglycerides increase, dizziness, paraesthesia, somnolence, altered taste, abdominal pain, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort, nephrolithiasis, hematuria, pollakiuria, dermatitis, urticaria, pruritus, arthralgia, arthritis, myalgia, muscle cramp, musculoskeletal pain, weight increase, increased appetite, hypertension, flushing, hot flush, fatigue, edema, influenza like symptoms and libido decreased.

Rare:
Palpitations, renal insufficiency, asthenia, thirst, nervousness and insomnia.

CONTRA-INDICATIONS:
Febuxostat is contraindicated in patients with:
- Hypersensitivity to the active substance or to any of the excipients of the product.
- Being treated with azathioprine, mercaptopurine or theophylline.
- Asymptomatic hyperuricemia.

Pregnancy:
Febuxostat should not be used during pregnancy.

Nursing Mother:
Febuxostat should not be used while breast-feeding.

PRECAUTIONS:
- Treatment with febuxostat in patients with ischemic heart disease o r congestive heart failure is not recommended.
- 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.
- As with other urate lowering medicinal products, 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.
- Laboratory assessment of liver function is recommended at, for example 2 and 4 months following initiation of febuxostat and periodically thereafter.

Drug Interactions:
- **Naproxen and other inhibitors of glucuronidation:**

Febuxostat metabolism depends on UGT enzymes. Medicinal products that inhibit glucuronidation, such as NSAIDs and probenecid, could in theory affect the elimination of febuxostat. In healthy subjects concomitant use of febuxostat and naproxen 250mg BID was associated with an increase in febuxostat exposure. 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.

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

STORAGE:
Store below 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED:
Urizak (Febuxostat) Tablets 40mg are available in Alu-Alu pack of 20's.
Urizak (Febuxostat) Tablets 80mg are available in Alu-Alu pack of 20's.

CAUTION:
Keep out of reach of children.
To be sold on prescription of a registered medical practitioner only

یوریزیک® ۴۰ ملی گرام، ۸۰ ملی گرام

فیبوکسوسٹیٹ

خوراک: یہ دوا ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

ہدایات: دوا کو گرمی، روشنی اور نمی سے محفوظ رکھیں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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Manufactured by:

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