ASPIN
An OBS Group Company

ZEROGOUT® (Febuxostat)
40 mg & 80 mg

زیروگاؤٹ

QUALITATIVE & QUANTITATIVE COMPOSITION
ZEROGOUT 40mg Tablets
Each film-coated tablet contains:
Febuxostat .....40 mg
ZEROGOUT 80mg Tablets
Each film-coated tablet contains:
Febuxostat.....80 mg

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

WARNING: CARDIOVASCULAR DEATH
Gout patients with established cardiovascular (CV) disease treated with Febuxostat may have a higher rate of CV death compared to those treated with allopurinol . 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.

CLINICAL INFORMATION
Indications
ZEROGOUT (Febuxostat) 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.

Dosage and administration
Adult dosage
The recommended ZEROGOUT (Febuxostat) dosage is 40 mg or 80 mg once daily.
The recommended starting dosage of ZEROGOUT (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, the recommended ZEROGOUT (Febuxostat) dosage is 80 mg once daily.
Uric Acid Level
Testing for the target serum uric acid level of less than 6 mg/dL may be performed as early as two weeks after initiating ZEROGOUT (Febuxostat) therapy.
Recommended Prophylaxis for Gout Flares
Gout flares may occur after initiation of ZEROGOUT (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 Zerogout. Prophylactic therapy may be beneficial for up to six months.
If a gout flare occurs during ZEROGOUT (Febuxostat) treatment, ZEROGOUT (Febuxostat) need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient.
Dosage adjustment
Renal Impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment. The recommended dosage is limited to 40 mg once daily in patients with severe renal impairment.
Hepatic Impairment
No dose adjustment is necessary in patients with mild to moderate hepatic impairment.
Administration requirements
ZEROGOUT (Febuxostat) can be taken without regard to food or antacid use.

Contraindications
Febuxostat is contraindicated in
- Patients being treated with azathioprine or mercaptopurine
- Hypersensitivity to the active substance

Warning and Precautions
Cardiovascular Death
Gout patients with established CV disease treated with Febuxostat may have a higher rate of CV death compared to those treated with allopurinol. Because of the increased risk of CV death, 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. Consider the risks and benefits of Febuxostat when deciding to prescribe or continue patients on Febuxostat. 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.
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.
Hepatic Effects
Transaminase levels may be elevated greater than three times the upper limit of normal (ULN). No dose-effect relationship for these transaminase elevations is there. Obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) as a baseline before initiating Febuxostat. Measure liver tests 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 (ALT greater than three times the upper limit of the reference range), 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 druginduced 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.
Serious Skin Reactions
Serious skin and hypersensitivity reactions, including Stevens - Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) may occur in patients taking Febuxostat. Discontinue Febuxostat if serious skin reactions are suspected. These reactions can also occur with allopurinol in such patients. Febuxostat should be used with caution in such patients.

Interactions
Xanthine Oxidase Substrate Drugs
Febuxostat is an XO inhibitor. Febuxostat may alter the metabolism of theophylline (a substrate of XO). Therefore, use with caution when coadministering Febuxostat with theophylline.
Data regarding the use of Febuxostat with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) is not available. 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.

Cytotoxic Chemotherapy Drugs
Data regarding the use of Febuxostat with cytotoxic chemotherapy is not available. No data are available regarding the safety of Febuxostat during cytotoxic chemotherapy.

Pregnancy and Breastfeeding

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. Febuxostat should not be used while breastfeeding.

Effects on ability to drive and use machines

Somnolence, dizziness, paraesthesia and blurred vision may occur 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

Blood and lymphatic system disorders	*Rare:* Pancytopenia, thrombocytopenia, agranulocytosis
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 *Rare:* Sudden cardiac death
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, flatulen ce, gastrointestinal discomfort *Rare:* Pancreatitis, mouth ulceration
Hepato-biliary disorders	*Common:* Liver function abnormalities *Uncommon:* Cholelithiasis *Rare:* Hepatitis, jaundice*, liver injury
Skin and subcutaneous tissu disorders	*Common:* Rash *Uncommon:* Dermatitis, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash papular *Rare:* Toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, drug reaction with eosinophilia and systemic symptoms, generalized rash (serious) erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic, rash erythematous, rash morbilliform, alopecia, hyperhidrosis
Musculoskeletal and connective tissue disorders	*Uncommon:* Arthralgia, arthritis, myalgia, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis *Rare:* Rhabdomyolysis, joint stiffness, musculoskeletal stiffness
Renal and urinary disorders	*Uncommon:* Renal failure, nephrolithiasis, haematuria pollakiuria, proteinuria *Rare:* Tubulointerstitial nephritis, micturition urgency
Reproductive system and breast disorder	*Uncommon:* Erectile dysfunction
General disorders and administration site conditions	*Common:* Oedema *Uncommon:* Fatigue, chest pain, chest discomfort *Rare:* Thirst

Overdose

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

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antigout preparation, preparations inhibiting uric acid production, ATC code: M04AA03

Mechanism of Action

Febuxostat, a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. Febuxostat is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.

Pharmacokinetic properties

Absorption

The absorption of radiolabeled Febuxostat following oral dose administration is estimated to be atleast 49% (based on total radioactivity recovered in urine). Maximum plasma concentrations of Febuxostat occur between 1 and 1.5 hours postdose. After multiple oral 40 mg and 80 mg once daily doses, C_{max} is approximately 1.6 ± 0.6 mcg/mL, and 2.6 ± 1.7 mcg/mL respectively. Absolute bioavailability of the Febuxostat tablet is not available. Following multiple 80 mg once daily doses with a high fat meal, there is a 49% decrease in C_{max} and an 18% decrease in AUC, respectively. Febuxostat may be taken without regard to food. Febuxostat may be taken without regard to antacid use.

Distribution

The mean apparent steady state volume of distribution (Vss/F) of Febuxostat is approximately 50 L (CV ~40%). 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**.**

Metabolism

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.

Elimination

Febuxostat is eliminated by both hepatic and renal pathways. The apparent mean terminal elimination half-life ($t_{1/2}$) of Febuxostat is approximately 5 to 8 hours.

PHARMACEUTICAL INFORMATION

Shelf life

2 years.

Special Precautions for Storage

- To be sold on the prescription of a registered medical practitioner only.
- Do not store above 30°C.
- Protect from light and moisture.
- Keep out of the reach of children.

ہدایات:

صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔

۳۰ ڈگری سینٹی گریڈ سے زیادہ درجۂ حرارت پر نہ رکھیں۔

دوا کو روشنی اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

Nature and contents of container

ZEROGOUT (Febuxostat) 40mg tablets are available in the pack of 20's (10's x 2).
ZEROGOUT (Febuxostat) 80mg tablets are available in the pack of 20's (10's x 2).

MANUFACTURED BY:

ASPIN
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