GOURIC®
(Febuxostat)

گیوریک

COMPOSITION
Gouric® 40mg Tablet
Each film-coated tablet contains:
Febuxostat……..40mg
Gouric® 80mg Tablet
Each film-coated tablet contains:
Febuxostat……..80mg
(Pharmevo Specs.)

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.

DESCRIPTION
GOURIC tablets contain Febuxostat, a xanthine oxidase inhibitor used as an anti-hyperuricemic agent. The chemical name of Febuxostat is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4- methylthiazole-5- carboxylic acid, with a molecular weight of 316.38. The empirical formula is $C_{16}H_{16}N_2O_3S$.

CLINICAL PHARMACOLOGY

Mechanism of Action
Febuxostat, a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. 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). 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.

Pharmacodynamics

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 and an increase in 24 hour mean serum xanthine concentrations. In addition, there was a decrease in the total daily urinary uric acid excretion. Also, there was an increase in total daily urinary xanthine excretion. Percent reduction in 24 hour mean serum uric acid concentrations was between 40% and 55% at the exposure levels of 40 mg and 80 mg daily doses.
Effect on Cardiac Repolarization
The effect of Gouric on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy patients and in patients with gout. Febuxostat in doses up to 300 mg daily (3.75 times the maximum recommended daily dosage), at steady-state, did not demonstrate an effect on the QTc interval.

Pharmacokinetics
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 is a 49% and 38% decrease in Cmax and an 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 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%.

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. 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%). Febuxostat has an apparent mean terminal elimination half-life (t1/2) of approximately 5 to 8 hours.

INDICATIONS

Gouric 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.

Limitations of Use:
Gouric is not recommended for the treatment of asymptomatic hyperuricemia.

DOSAGE AND ADMINISTRATION
Adult dosage
Recommended Dose
The recommended Gouric dosage is 40 mg or 80 mg once daily.
The recommended starting dosage of Gouric 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 Gouric dosage is 80 mg once daily.
Gouric can be taken without regard to food or antacid use

Dosage Recommendations in Patients with Renal Impairment and Hepatic Impairment
No dose adjustment is necessary when administering Gouric in patients with mild or moderate renal impairment.
The recommended dosage of Gouric is limited to 40 mg once daily in patients with severe renal impairment.
No dose adjustment is necessary in patients with mild to moderate hepatic impairment.

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 Gouric therapy.

Recommended Prophylaxis for Gout Flares
Gout flares may occur after initiation of Gouric 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 Gouric. Prophylactic therapy may be beneficial for up to six months.
If a gout flare occurs during Gouric treatment, Gouric need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient.

Pediatric dosage
Safety and effectiveness not established in pediatric patients

Dosage adjustment in Special Populations

Renal impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment. Insufficient data is available regarding Febuxostat dosing in patients with severe renal impairment (CrCl less than 30ml/min).

Hepatic impairment
No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No data is available regarding Febuxostat dosing in patients with severe liver impairment. (Child Pugh Class C).

Administration requirements
GOURIC should be taken by mouth and can be taken with or without food.

CONTRAINDICATIONS
• Hypersensitivity condition
• Febuxostat is contraindicated in patients being treated with azathioprine or mercaptopurine. (See DRUG INTERACTIONS)

WARNING AND PRECAUTIONS
Cardiovascular Death
In a CV outcomes study, there was a higher rate of CV death in patients treated with Febuxostat compared to allopurinol; in the same study Febuxostat was non-inferior to allopurinol for the primary endpoint of major adverse cardiovascular events (MACE). Consider the risks and benefits of Febuxostat, when deciding to prescribe or continue patients on Febuxostat.

Prevention and treatment of hyperuricaemia in patients at risk of TLS
Patients undergoing chemotherapy for hematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS) treated with febuxostat should be under cardiac monitoring as clinically appropriate.

Hypersensitivity Reactions
Rare reports of serious allergic/hypersensitivity reactions, including life-threatening Stevens - Johnson syndrome, Toxic epidermal necrolysis and acute anaphylactic reaction/shock, have been reported in the post-marketing experience. Mostly, 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 cautioned 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.

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.

Mercaptopurine/azathioprine
Febuxostat use is contraindicated in patients concomitantly treated with mercaptopurine/azathioprine. Where the combination cannot be avoided patients must be closely monitored. A reduction in dosage of mercaptopurine or azathioprine is recommended in order to avoid possible haematological effects. (See DRUG INTERACTIONS)

Urate Formation / 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. This has not been observed in the pivotal clinical study with Febuxostat in the Tumor Lysis Syndrome. In the randomized, double-blind, Phase 3 pivotal FLORENCE (FLO-01) study comparing febuxostat with allopurinol (346 patients undergoing chemotherapy for haematologic malignancies and at intermediate-to-high risk of TLS), no urinary tract problems or additional adverse effects were observed as compared to the previous clinical studies' experience with Febuxostat in gout.
As there has been no experience with febuxostat, its use in patients with Lesch-Nyhan Syndrome is not recommended.

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

Cardiac monitoring in TLS patients
Patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome treated with Febuxostat should be under cardiac monitoring as clinically appropriate.

Liver disorders
During randomized controlled studies, transaminase elevations were observed with Febuxostat. Liver function tests including alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin are recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment. These tests are also advised promptly in patients who report symptoms of potential liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If the ALT is greater than 3 times the upper limit of the normal range, treatment should be interrupted and investigation done to establish the probable cause. Febuxostat should not be restarted in these patients without another explanation for liver test abnormalities. Patients having serum ALT greater than 3 times the normal range with serum total bilirubin greater than 2 times the normal range without alternative etiologies

are at risk for severe drug-induced 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.

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 altered of thyroid function.

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
Blood and lymphatic system disorders
Rare: Pancytopenia, thrombocytopenia
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, left bundle branch block, sinus tachycardia
Vascular disorders
Uncommon: Hypertension, flushing, hot flush, hemorrhage
Respiratory system disorders
Uncommon: Dyspnea, bronchitis, upper respiratory tract infection, cough
Gastrointestinal disorders
Common: Diarrhea**, 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
Uncommon: Dermatitis, urticarial, pruritus, skin discoloration, 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 morbillifom, 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, hematuria, 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
Investigations
Uncommon: 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, haematocritic decrease, blood lactate dehydrogenase increased, blood potassium increase.
Rare: Blood glucose increased, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase.
* Adverse reactions coming from post-marketing experience
** Treatment-emergent non-infective diarrhea and abnormal liver function tests in the combined Phase 3 studies are more frequent in patients concomitantly treated with colchicine.

DRUG INTERACTIONS
Xanthine oxidase substrate drugs
Drugs metabolized by XO (i.e. mercaptopurine and azathioprine) are contraindicated with Febuxostat. Inhibition of XO by Febuxostat may cause increased plasma concentrations of these drugs leading to toxicity and hematological adverse effects.
Febuxostat does alter the metabolism of theophylline (a substrate of Xanthine oxidase) in humans. 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.

Naproxen and other inhibitors of glucuronidation
Febuxostat metabolism depends on Uridine Glucuronosyl Transferase (UGT) enzymes. Drugs 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 twice daily was associated with an increase in febuxostat exposure (Cmax 28%, AUC 41% and t1/2 26%). In clinical studies the use of naproxen or other NSAIDs/COX-2 inhibitors was not related to any clinically significant increase in adverse events. 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.

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.

USE IN SPECIAL POPULATIONS

Pregnancy
US FDA Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Febuxostat should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mother
Febuxostat is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Febuxostat is administered to a nursing woman.

Pediatrics
Safety and efficacy not established.

Elderly
No dose adjustment is necessary in elderly patients. The Cmax and AUC24 of febuxostat following multiple oral doses of febuxostat in geriatric subjects (≥65 years) were similar to those in younger subjects (18 to 40 years).

Renal impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment (Clcr 30 to 89 mL/min). The recommended starting dose of febuxostat is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg/dL after two weeks with 40 mg, 80 mg is recommended. There are insufficient data in patients with severe renal impairment (Clcr less than 30 mL/min); therefore, caution should be exercised in these patients.

Hepatic impairment
No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); therefore, caution should be exercised in these patients. In all categories of liver impairment it is advisable not to use more than 80 mg daily of Febuxostat.

OVER DOSAGE
Febuxostat was studied in healthy subjects in doses up to 300 mg 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 in case of an overdose.

PRESENTATION
Gouric® 40mg Tablet
Pack of 20 Tablets
Gouric® 80mg Tablet
Pack of 20 Tablets

INSTRUCTIONS
As advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, email at
reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

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