Goutstat Tablets

Each film-coated tablet contains: Febuxostat 40mg, 80mg

Qualitative & quantitative composition:
Goutstat 40 mg: Each film-coated tablet contains: Febuxostat 40mg
Goutstat 80 mg: Each film-coated tablet contains: Febuxostat 80mg
Pharmaceutical form
Film coated tablets
Pharmacological properties
Pharmacodynamic properties
Pharmacotherapeutic group: Antigout preparation, preparations inhibiting uric acid production, ATC code: M04AA03
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, hypoxanth1ne guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase or purine nucleos1de phosphorylase.
Pharmacokinetics
Absorption
Febuxostat 1s rapidly and extensively absorbed following oral dose administration, with (tmax 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, Cmax 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 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.
Distribution
The apparent steady state volume of distribution (V_{ss}/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 40 and 80 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 glucuronosyl transferase (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 ^{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 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
Following multiple doses of 80 mg of Goutstat in patients with mild, moderate or severe renal impairment, the C_{max} of febuxostat did not change, relative to subjects with normal renal function. The mean total AUC of febuxostat increased by approximately 1.8-fold from 7.5 µg ·h/mL in the normal renal function group to 13.2 µg .h/mL in the severe renal dysfunction group. The C_{max} and AUC of active metabolites increased up to 2- and 4-fold, respectively. However, no dose adjustment is necessary in patients with mild or moderate renal impairment.
Hepatic impairment
Following multiple doses of 80 mg of Goutstat in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, the C_{max} 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 Goutstat in elderly as compared to younger healthy subjects.
Gender
Following multiple oral doses of Goutstat, the C_{max} and AUC were 24% and 12% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. No dose adjustment is needed based on gender.
Therapeutic indications
Febuxostat is indicated for the treatment of chronic hyperuricemia in patients with gout.
Posology and method of administration
Method of administration: Oral use.
Dosage and administration
For oral administration
For treatment of hyperuricemia in patients with gout, Febuxostat is recommended at 40mg or 80mg once daily.
The recommended starting dose of Febuxostat is 40mg once daily. For patients who do not achieve a serum uric acid (SUA) less than 6mg per dl after 2 weeks with 40mg, Febuxostat 80mg is recommended. Febuxostat can be taken without regard to food or antacid use.
No dose adjustment is necessary when administering Febuxostat in patients with mild to moderate renal insufficiency.
Hepatic Insufficiency
No dose adjustment is necessary in patients with mild to moderate hepatic insufficiency.
Contraindications
Febuxostat is contraindicated in patients with:
- Hypersensitivity to the active substance or to any of the excipients.
- Being treated with azathioprine, mercaptopurine, or theophylline.
- Asymptomatic hyperuricemia.

Precautions & Warnings
- Treatment with Febuxostat in patients with ischemic heart disease or 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:
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 concentrations of these drugs leading to toxicity. Drug interaction studies of febuxostat with drugs that are metabolized by XO have not been performed.
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. In a study in healthy subjects, coadministration of 120 mg febuxostat QD 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.
Theophylline
An interaction study in healthy subjects has been performed with febuxostat to evaluate whether the inhibition of XO may cause an increase in the theophylline circulating levels as reported with other XO inhibitors. The results of the study showed that the 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. No data is available for febuxostat 120 mg.
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. In healthy subjects concomitant use of febuxostat and naproxen 250mg twice daily was associated with an increase in febuxostat exposure (C_{max}28%, AUC 41% and $t_{1/2}$ 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.
Colchicine/indomethacin/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*. In a study in healthy subjects, 120 mg resulted in a mean 22% increase in AUC of desipramine, a CYP2D6 substrate indicating a potential weak inhibitory effect of febuxostat on the CYP2D6 enzyme *in vivo*. Thus, 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 C_{max}, but no significant change in AUC was observed. Therefore, febuxostat may be taken without regard to antacid use.

Pregnancy and Lactation

Pregnancy

Febuxostat should not be used during pregnancy.

Lactation

Febuxostat should not be used while breast-feeding.

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.

Undesirable effects

Common: Headache, Diarrhea, Nausea, Rash, LFT Abnormalities.

Uncommon: Blood amylase increase, platelet count decrease, blood creatinine increase, hemoglobin decrease, blood urea increase , LOH increase, triglycerides increase, dizziness, paraesthesia, somnolence, altered taste, abdominal pain, gastro-oesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort, nephrolith1asis, 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, libido decreased.

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

Overdose:

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

Shelf life: 36 months from the date of manufacture.

Special precautions for storage

Store in a cool dry place, below 30^{0}C, protected from direct sunlight.

Keep all medicines out of reach of children.

Presentation

Blisters pack of 1 x 10's in a Unit box

Manufactured By:

DAWA Limited, Plot No. 7879/8, Baba Dogo Road, Ruaraka
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Ref: Lf /DL/ Goutstat/01

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