FEXOTA 40

Febuxostat Tablets 40 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION:
Label Claim:
Each film coated tablet contains:

Febuxostat	40 mg
Excipients	q. s.
Colour: Ferric Oxide of Red IH	

List of Excipients:
Maize Starch BP
Microcrystalline Cellulose BP
Dibasic calcium Phosphate BP
Purified Talc BP
Magnesium stearate BP
Sodium Starch Glycolate BP
Colloidal Silicon Dioxide BP
Fine Coat
Ferric Oxide of Red IH
Polyethylene Glycol 6000 BP
Methyl Paraben Sodium BP
Propyl Paraben Sodium BP

INDICATION:
FEXOTA 40 is indicated for the Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).
FEXOTA 40 is indicated in adults.

PHARMACEUTICAL FORM
FEXOTA 40 is Film-coated Tablets contains Febuxostat 40 mg indicated for the Treatment of chronic hyperuricaemia
A Reddish coloured, round, biconvex film coated tablet having score line on one side and plain on the other side

DOSAGE AND ADMINISTRATION
Posology
The recommended oral dose of FEXOTA 40 is 40 mg once daily without regard to food. If serum uric acid is > 6 mg/dL (357 µmol/L) after 2-4 weeks, FEXOTA 120 mg once daily may be considered.
FEXOTA 40 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 (357µmol/L).
Gout flare prophylaxis of at least 6 months is recommended.
Elderly
No dose adjustment is required in the elderly.
Renal impairment
The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 mL/min).
Adults and adolescents (over 12 years and weighing 35kg or more)
No dose adjustment is necessary in patients with mild or moderate renal impairment.
Hepatic impairment
The efficacy and safety of Febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh Class C).
The recommended dose in patients with mild hepatic impairment is 80 mg. Limited information is available in patients with moderate hepatic impairment.
Paediatric population
The safety and the efficacy of FEXOTA 40 in children aged below the age of 18 years have not been established. No data are available.
Method of administration
For oral administration.

CONTRAINDICATION:
Hypersensitivity to the active substance

SPECIAL WARNING AND PRECAUTION FOR USE:
Cardio-vascular disorders
Treatment with Febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended.
A numerical greater incidence of investigator-reported cardiovascular APTC events (defined endpoints from the Anti-Platelet Trialists' Collaboration (APTC) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was observed in the Febuxostat total group compared to the allopurinol group in the APEX and FACT studies (1.3 vs. 0.3 events per 100 Patient Years (PYs)), but not in the CONFIRMS study . The incidence of investigator-reported cardiovascular APTC events in the combined Phase 3 studies (APEX, FACT and CONFIRMS studies) was 0.7 vs. 0.6 events per 100 PYs. In the long-term extension studies the incidences of investigator-reported APTC events were 1.2 and 0.6 events per 100 PYs for Febuxostat and allopurinol, respectively. No statistically significant differences were found and no causal relationship with Febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure.
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 in the post-marketing experience. In most cases, 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 advised of the signs and symptoms 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. If 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 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.
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. Where the combination cannot be avoided patients should be closely monitored. A reduction of dosage of mercaptopurine or azathioprine is recommended in order to avoid possible haematological effects.
Organ transplant recipients
As there has been no experience in organ transplant recipients, the use of Febuxostat in such patients is not recommended.
Theophylline
Co-administration of Febuxostat 80 mg and theophylline 400mg single dose in healthy subjects showed absence of any pharmacokinetic interaction Febuxostat 80 mg can be used in patients concomitantly treated with theophylline without risk of increasing theophylline plasma levels. No data is available for Febuxostat 120 mg.
Liver disorders
During the combined phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with Febuxostat (5.0%). 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 (5.5%) in the long term open label extension studies. Caution is required when Febuxostat is used in patients with alteration of thyroid function.

ADVERSE REACTION:
The adverse drug reactions are ranked below by frequency, using the following convention: very common (≥1/10), common (≥1/100, to <1/10); uncommon (≥ 1/1,000, to <1/100); rare (≥1/10,000, to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from available data).
· 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
· 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, 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, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash popular; 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

INTERACTION WITH OTHER MEDICINE AND CONCOMITANT USE:
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 (Cmax28%, 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.
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.
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 FEXOTA 40 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 Cmax, but no significant change in AUC was observed. Therefore, Febuxostat may be taken without regard to antacid use.

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/new born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition. 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. Animal studies have shown excretion of this active substance in breast milk and an impaired development of suckling pups. A risk to a suckling infant cannot be excluded. Febuxostat should not be used while breastfeeding.
Fertility
In animals, reproduction studies up to 48 mg/kg/day showed no dose-dependent adverse effects on fertility. The effect of FEXOTA 40 on human fertility is unknown.

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 FEXOTA 40 does not adversely affect performance.

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

PHARMACOLOGICAL PROPERTIES
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 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 where tested (80 mg multiple dose). Thus, ADENURIC 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 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.

PHARMACODYNAMICS:
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 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.
In accordance with ICH—E14 guidelines, a thorough QT study was performed. This study included a placebo, an active comparator and a positive control and was conducted in healthy subjects with up to 80 mg per day 10 or 20 mg administered 4 times a day of domperidone. This study found a maximal difference of QTc between domperidone and placebo in LS-means in the change from baseline of 3.4 msec for 20 mg domperidone administered 4 times a day on Day 4. The 2-sided 90 % CI (1.0 to 5.9 msec) did not exceed 10 msec. No clinically relevant QTc effects were observed in this study when domperidone was administered at up to 80 mg/day (i.e., more than twice the maximum recommended dosing).
However, two previous drug-drug interaction studies showed some evidence of QTc prolongation when domperidone was administered as monotherapy (10 mg 4 times a day).The largest time-matched mean difference of QTcF between domperidone and placebo was 5.4 msec (95 % CI: -1.7 to 12.4) and 7.5 msec (95 % CI: 0.6 to 14.4), respectively.

PACKAGING:
10 tablets are packed in Alu-PVC blister and such 3 blisters are packed in a carton along with insert.

STORAGE CONDITION:
Store in dry place below 30°C.
Keep out of reach of children.

SHELF LIFE:
36 months

MANUFACTURED BY:
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