Rx Prescription Drug

FEBUSTAD

1. Name of the medicinal product

FEBUSTAD FILM-COATED TABLETS 40MG
FEBUSTAD FILM-COATED TABLETS 80MG

2. Special notice and recommendation

Keep out of reach of children
Read the package insert carefully before use

3. Composition

FEBUSTAD FILM-COATED TABLETS 40MG*:*

Each	film-coated	tablet	contains:
Febuxostat			40 mg

FEBUSTAD FILM-COATED TABLETS 80MG*:*

Each	film-coated	tablet	contains:
Febuxostat			80 mg

4. Pharmaceutical form

Film-coated tablet.
FEBUSTAD FILM-COATED TABLETS 40MG*:* Yellow, round-shaped film-coated tablet, biconvex, plain on both sides.
FEBUSTAD FILM-COATED TABLETS 80MG*:* Yellow, caplet-shaped, film-coated tablet, biconvex, engraved with "80" on one side, break line on the other side.

5. Indications

- Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).
- FEBUSTAD is indicated in adults.

6. Administration and dosage

Dosage

Adult

The recommended oral dose of FEBUSTAD is 40 mg or 80 mg once daily without regard to food.
The recommended starting dose of FEBUSTAD tablet is 40 mg once daily. If serum uric acid is > 6.0 mg/dL (357 µmol/L) after 2-4 weeks, FEBUSTAD 80 mg once daily may be considered.
FEBUSTAD 80 mg tablet can be divided into equal halves. In order to provide a 40 mg dose, the tablet should be split just before use. Prescribers should advise patients on how to break the tablets in half and to keep the other half for the next dose.
FEBUSTAD tablet 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 6.0 mg/dL (357 µmol/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).
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).
No dose adjustment is necessary in patients with mild hepatic impairment. Limited information is available in patients with moderate hepatic impairment.

Paediatric population

The safety and the efficacy of FEBUSTAD in children aged below the age of 18 years have not been established. No data are available.

Method of administration

Oral use
FEBUSTAD should be taken by mouth and can be taken with or without food.

7. Contraindications

FEBUSTAD is contraindicated in patients with hypersensitivity to any component of this product.

8. Special warnings and precautions for use

Cardio-vascular disorders

Treatment with febuxostat in patients with pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke or unstable angina) should be avoided, unless no other therapy options are appropriate. Caution should be exercised for exacerbation and/or onset of cardiovascular disease when administering this drug.
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. In the post registrational CARES study in gout patients with established CV disease (see section Pharmacodynamic properties for detailed characteristics of the study) the rate of major adverse cardiovascular events (MACE) defined as the composite of CV death, nonfatal MI, nonfatal stroke, or unstable angina with urgent coronary revascularization was similar in febuxostat versus allopurinol treated patients (hazard ratio [HR] 1.03; 95% CI 0.89-1.21), but a higher rate of cardiovascular deaths was observed (4.3% vs. 3.2% of patients; HR 1.34; 95% CI 1.03-1.73).

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, LeschNyhan 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 people 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.

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.

Lactose

Febuxostat tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

9. 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/newborn 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.

Lactation

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 breast-feeding.

Fertility

In animals, reproduction studies up to 48 mg/kg/day showed no dose-dependent adverse effects on fertility. The effect of febuxostat on human fertility is unknown.

10. 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.

11. 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. 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.
- 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 people, 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 people 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.

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 people concomitant use of febuxostat and naproxen 250 mg 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 were 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 people. 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 people, 120 mg febuxostat QD 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.

12. Adverse reactions

Summary of the safety profile

The most commonly reported adverse reactions in clinical trials (4,072 subjects treated at least with a dose from 10 mg to 300 mg) and post-marketing experience are gout flares, liver function abnormalities, diarrhoea, nausea, headache, rash and oedema. These adverse reactions were mostly mild or moderate in severity. Rare serious hypersensitivity reactions to febuxostat, some of which were associated to systemic symptoms, have occurred in the post- marketing experience.

Tabulated list of adverse reactions
Common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000) adverse reactions occurring in patients treated with febuxostat are listed below.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Table of Adverse reactions in combined phase 3, long-term extension studies and post-marketing experience.

Blood and lymphatic system disorders	*Rare* Pancytopenia, thrombocytopenia, agranulocytosis*, eosinophilia*
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 (including various types of rash reported with lower frequencies, see below) *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, erythema multiform*, 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, haematuria, pollakiuria, proteinuria *Rare* Tubulointerstitial nephritis*, micturition urgenc
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, haemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, haematocritic decrease, blood lactate dehydrogenase increased, blood potassium increase *Rare* Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase, blood creatine phosphokinase increase*
* Adverse reactions coming from post-marketing experience ** Treatment-emergent non-infective diarrhoea and abnormal liver function tests in the combined Phase 3 studies are more frequent in patients concomitantly treated with colchicine. *** See section 15. Pharmacokinetic properties for incidences of gout flares in the individual Phase 3 randomized controlled studies	

Description of selected adverse reactions
Rare serious hypersensitivity reactions to febuxostat, including Stevens-Johnson Syndrome, Toxic epidermal necrolysis and anaphylactic reaction/shock, have occurred in the post-marketing experience. Stevens-Johnson Syndrome and Toxic epidermal necrolysis are characterised by progressive skin rashes associated with blisters or mucosal lesions and eye irritation. Hypersensitivity reactions to febuxostat can be associated to the following symptoms: skin reactions characterised by infiltrated maculopapular eruption, generalised or exfoliative rashes, but also skin lesions, facial oedema, fever, haematologic abnormalities such as thrombocytopenia and eosinophilia, and single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis) (see section 8. Special warnings and precautions for use).

Gout flares were commonly observed soon after the start of treatment and during the first months. Thereafter, the frequency of gout flare decreases in a time-dependent manner. Gout flare prophylaxis is recommended (see sections 6. Administration and dosage and 8. Special warnings and precautions for use).

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

14. Pharmacodynamic properties
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.

15. Pharmacokinetic properties
In healthy people, maximum plasma concentrations (C_{max}) and area under the plasma concentration time curve (AUC) of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed for febuxostat. There is no appreciable accumulation when doses of 10 mg to 240 mg are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life (t1/2) of approximately 5 to 8 hours.
In general, febuxostat pharmacokinetic parameters estimated by these analyses are consistent with those obtained from healthy people, indicating that healthy people are representative for pharmacokinetic/ pharmacodynamic assessment in the patient population with gout.
Population pharmacokinetic/pharmacodynamic analyses were conducted in 211 patients with hyperuricaemia and gout, treated with febuxostat 40-240 mg QD.
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, C_{max} 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 C_{max} and a 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, FEBUSTAD may be taken without regard to food.
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 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.
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%).
Renal impairment
In a dedicated phase I pharmacokinetics study, following multiple doses of 80 mg of febuxostat in patients with mild, moderate or severe renal impairment, the Cmax 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 Cmax 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.
Based on population pharmacokinetic analysis, following multiple 40 mg or 80 mg doses of febuxostat, the mean oral clearance (CL/F) values of febuxostat in patients with gout and mild (n=334), moderate (n=232) or severe (n=34) renal impairment were decreased by 14%, 34%, and 48%, respectively, compared to patients with normal (n=89) renal function. The corresponding median AUC values of febuxostat at steady-state in patients with renal impairment were increased by 18%, 49%, and 96% after 40 mg dose, and 7%, 45% and 98% after 80 mg dose, respectively, compared to patients with normal renal function.
Hepatic impairment
Following multiple doses of 80 mg of FEBUSTAD 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 people 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 FEBUSTAD in elderly as compared to younger healthy people.
Gender
Following multiple oral doses of FEBUSTAD, 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.

16. Packaging
Alu-PVC/PE/PVDC blister pack of 10 tablets. Box of 3 blisters.

17. Storage condition, shelf-life
Store at or below 30°C. Store in the original package to protect from light and moisture.
The expiry date of this pack is printed on the box. Do not use this pack after this date.

18. Name, address of manufacturer

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