INSERT	Size:135 x 395mm
Specification:	Printing Numb. of Side:Front-Back
	Colour:Black
	Art work No.: Material Code:

Dt;06_12_2021

Front

back

Febuxostat

Febxuscare

40 mg Film-Coated Tablet
Antigout

℞

FORMULATION:
Each film-coated tablet contains:
Febuxostat ..... 40 mg
Excipients Q.S.
Colour: Yellow oxide of Iron &Titanium Dioxide BP

PRODUCT DESCRIPTION:
Yellow coloured round shaped biconvex both side plain film-coated tablets.

PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Antigout preparation, preparations inhibiting uric acid production.

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.

PHARMACOKINETIC PROPERTIES:
In healthy subjects, 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 ($t_{1/2}$) of approximately 5 to 8 hours.
Population pharmacokinetic/pharmacodynamic analyses were conducted in 211 patients with hyperuricaemia and gout, treated with Febuxostat 40-240 mg QD. In general, febuxostat pharmacokinetic parameters estimated by these analyses are consistent with those obtained from healthy subjects, indicating that healthy subjects are representative for pharmacokinetic/pharmacodynamic assessment in the patient population with gout.
Absorption
Febuxostat is rapidly (t_{max} 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 when 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%.
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 acylglucuronide 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 Febuxostat 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 Febuxostat 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 Febuxostat in elderly as compared to younger healthy subjects.
Gender
Following multiple oral doses of Febuxostat, 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.

INDICATIONS:
Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of tophus and/or gouty arthritis).

DOSAGE AND ADMINISTRATION:
Posology
The recommended oral dose of Febuxostat is 40 mg or 80 mg once daily without regard to food. The recommended starting dose of Febuxostat is 40 mg once daily. If serum uric acid is > 6 mg/dL(357 µmol/L) after 2-4 weeks, Febuxostat 80 mg once daily may be considered.
Febuxostat 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 (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).
The recommended dose in patients with mild hepatic impairment is 80 mg. Limited information is available in patients with moderate hepatic impairment.
Pediatric population
The safety and the efficacy of Febuxostat in children aged below the age of 18 years have not been established. No data are available.
Route of Administration: For oral administration only
Febuxostat should be taken by mouth and can be taken with or without food. Or as prescribed by the physician.

CONTRAINDICATIONS:
Hypersensitivity to febuxostat or to any other ingredients in the product.

SPECIAL WARNING AND PRECAUTION FOR USE:
Cardiovascular 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-star ted 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 as inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of mercaptopurine/azathioprine that could result in severe toxicity. No interaction studies have been performed in humans.
Where the combination cannot be avoided, a reduction of the dose of mercaptopurine/azathioprine is recommended. Based on modelling and simulation analysis of data from a pre-clinical study in rats, when coadministered with febuxostat, the dose of mercaptopurine/azathioprine should be reduced to the 20% or less of the previously prescribed dose in order to avoid possible haematological effects. The patients should be closely monitored and the dose of mercaptopurine/azathioprine should be subsequently adjusted based on the evaluation of the therapeutic response and the onset of eventual toxic 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 400 mg 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.
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.

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 (except theophylline) that are metabolized by XO have not been performed in humans.
Modelling and simulation analysis of data from a pre-clinical study in rats indicates that, in case of concomitant administration with febuxostat, the dose of mercaptopurine/azathioprine should be reduced to 20% or less of the previously prescribed dose.
Drug interaction studies of febuxostat with other cytotoxic chemotherapy have not been conducted. No data is available regarding the safety of febuxostat during other cytotoxic therapy.
Rosiglitazone/CYP2C8 substrates
Febuxostat was shown to be a weak inhibitor of CYP2C8 *in vitro*. In a study in healthy subjects, co-administration 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 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 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 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.

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
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 breastfeeding.

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 DRUG 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 1: Adverse reactions in combined phase 3, long-term extension studies and post-marketing experience.

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 gastroesophageal
Respiratory, thoracic and mediastinal 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
Hepatobiliary 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 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 disorders	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, 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.
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).
Gout flares were commonly observed soon after the start of treatment and during th first months. Thereafter, the frequency of gout flare decreases in a time-dependent manner. Gout flare prophylaxis is recommended.

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

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

Keep all medicines out of reach of children.

AVAILABILITY:
Alu-Alu Blister Pack x 10's (Box of 30's)

DRP-10512-09
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