20200

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Fibron® (Tablets)

Febuxostat

Xanthine oxidase inhibitor

FIBRON® 40MG TABLETS (FILM COATED)
FIBRON® 80MG TABLETS (FILM COATED)

PRESENTATION:

Fibron® 40mg Film Coated Tablet: Yellow, circular, biconvex tablet embossed 'COSMOS' on one side and a breakline on the other side. Each film coated tablet contains: Febuxostat 40 mg, Lactose and other excipients.
Fibron® 80mg Film Coated Tablet: Yellow, circular, biconvex tablet embossed 'C' on one side and a breakline on the other side. Each film coated tablet contains: Febuxostat 80 mg, Lactose and other excipients.

CLINICAL PHARMACOLOGY:

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 phosphoribosyl transferase, orotate phosphoribosyl transferase, orotidine monophosphate decarboxylase or purine nucleoside phosphorylase.

PHARMACOKINETICS:

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 120mg once daily doses, C_{max} is approximately 2.8-3.2 μg/mL, and 5.0-5t.3 μg/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 C_{max} 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 (80mg 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 10-300mg. The plasma protein binding of Febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 80 and 120mg 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.

Elimination

Febuxostat is eliminated by both hepatic and renal pathways. Following an 80mg 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%).

USES:

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

DOSAGE AND ADMINISTRATION:

Adult: Initially 80 mg once daily, if after 2–4 weeks of initial dose, serum uric acid greater than 6 mg/100mL then increase dose; increased if necessary to 120 mg once daily. Prophylaxis and treatment of acute hyperuricemia with initial chemotherapy for hematologic malignancies,
Adult: 120 mg once daily, to be started 2 days before start of cytotoxic therapy and continued for 7–9 days, according to chemotherapy duration.

CONTRA-INDICATIONS:

Not a treatment for acute gout but continues if attack develops when already receiving Febuxostat, and treat attack separately.
Hypersensitivity to the active substance or to any of the excipients.

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ADVERSE EFFECTS:
Common or very common:
Diarrhoea, Gout aggravated headache, hepatic disorders, nausea, oedema, and skin reactions.
Uncommon:
Appetite abnormal, arthritis, chest discomfort, cholelithiasis, constipation, cough, diabetes mellitus, dizziness, dry mouth, dyspnoea, fatigue, gastro-intestinal discomfort, insomnia.

WARNINGS AND PRECAUTIONS:
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.
Rare reports of serious allergic/hypersensitivity reactions, including life-threatening Stevens-Johnson syndrome, Toxic epidermal necrolysis and acute anaphylactic reaction/shock have been occurred during the first month of therapy with Febuxostat. 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.

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

INTERACTIONS:
Rosiglitazone/CYP2C8 substrates
Febuxostat was shown to be a weak inhibitor of CYP2C8 in vitro. In a study in healthy subjects, co-administration of 120mg Febuxostat QD with a single 4mg 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.
Naproxen and other inhibitors of glucuronidation
Febuxostat metabolism depends on Uridine Glucuronosyltransferase (UGT) enzymes. Medicinal products that inhibit glucuronidation, such as NSAIDs and probenecid, could in theory affect the elimination of Febuxostat. Febuxostat can be co-administered with naproxen with no dose adjustment of Febuxostat or naproxen being necessary.

PREGNANCY AND LACTATION:
Febuxostat should not be used during pregnancy. 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.

PHARMACEUTICAL PRECAUTIONS:
Store in a dry place below 30°C. Protect from light. Keep all medicines out of the reach of children.

LEGAL CATEGORY:
Prescription Only Medicine (POM)

®Regd. TM

COSMOS

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