MICRO LABS LIMITED, INDIA
SUMMARY OF PRODUCT CHARACTERISTICS
FEBUXOSTAT TABLETS 80 mg

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name

Febuxostat Tablets

1.2 Strength

80 mg

2. QUALITATIVE AND QUANTITAVE COMPOSITION

Each film- coated tablet contains:

Febuxostat…80 mg

Excipients :

Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium

Sodium Lauryl Sulphate, Purified Water, Hydroxypropyl cellulose, Colloidal Anhydrous Silica

Magnesium Stearate, Instacoat universal Yellow (A05D10519)

3. PHARMACEUTICAL FORM

Film-coated Tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications :

Febuxostat is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout.
Febuxostat is not recommended for the treatment of asymptomatic hyperuricemia.

4.2 Posology and method of administration :

For treatment of hyperuricemia in patients with gout, Febuxostat is recommended at 40 mg or 80 mg once daily.
The recommended starting dose of Febuxostat is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg/dL after two weeks with 40 mg, Febuxostat 80 mg is recommended.
Febuxostat can be taken without regard to food or antacid use.

Special Populations

No dose adjustment is necessary when administering Febuxostat in patients with mild to moderate renal impairment. The recommended starting dose of Febuxostat is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg/dL after two weeks with 40 mg, Febuxostat 80 mg is recommended.

No dose adjustment is necessary in patients with mild to moderate hepatic impairment.

4.3 Contraindications:

Febuxostat is contraindicated in patients being treated with azathioprine, mercaptopurine, or theophylline.

4.4 Special warnings and precautions for use:

Gout Flare

- 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

Cardiovascular Events

- In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients

treated with Febuxostat (0.74 per 100 P-Y [95% Confidence Interval (CI) 0.36-1.37]) than allopurinol (0.60 per 100 P-Y [95% CI 0.16-1.53]). A causal relationship with Febuxostat has not been established. Monitor for signs and symptoms of myocardial infarction (MI) and stroke.

Hepatic Effects

- There have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking Febuxostat, although the reports contain insufficient information necessary to establish the probable cause. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in Febuxostat and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted
- Obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) as a baseline before initiating Febuxostat.
- Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), Febuxostat treatment should be interrupted and investigation done to establish the probable cause. Febuxostat should not be restarted in these patients without another explanation for the liver test abnormalities.
- Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury and should not be restarted on Febuxostat. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with Febuxostat can be used with caution.

4.5 Interaction with other medicinal products and other forms of interaction.

Xanthine Oxidase Substrate Drugs

Febuxostat is an XO inhibitor. Drug interaction studies of Febuxostat with drugs that are metabolized by XO (e.g., theophylline, mercaptopurine, azathioprine) have not been conducted. Inhibition of XO by Febuxostat may cause increased plasma concentrations of these drugs leading to toxicity. Febuxostat is contraindicated in patients being treated with azathioprine, mercaptopurine, or theophylline.

Cytotoxic Chemotherapy Drugs

Drug interaction studies of Febuxostat with cytotoxic chemotherapy have not been conducted. No data are available regarding the safety of Febuxostat during cytotoxic chemotherapy.

In Vivo Drug Interaction Studies

Based on drug interaction studies in healthy subjects, Febuxostat does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or Desipramine. Therefore, Febuxostat may be used concomitantly with these medications.

4.6 Pregnancy and lactation

Pregnancy:

There are no adequate and well-controlled studies in pregnant women. Febuxostat should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Febuxostat was not teratogenic in rats and rabbits at oral doses up to 48 mg/kg (40 and 51 times the human plasma exposure at 80 mg/day for equal body surface area, respectively) during organogenesis. However, increased neonatal mortality and a reduction in the neonatal body weight gain were observed when pregnant rats were treated with oral doses up to 48 mg/kg (40 times the human plasma exposure at 80 mg/day) during organogenesis and through lactation period.

Lactation

Febuxostat is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Febuxostat is administered to a nursing woman.

4.7 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.

4.8 Undesirable effects :

Adverse reactions have been identified during post approval use of febuxostat. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

Hepatobiliary Disorders: hepatic failure (some fatal), jaundice, serious cases of abnormal liver function test results, liver disorder.

Immune System Disorders: anaphylaxis, anaphylactic reaction.

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis.

Psychiatric Disorders: psychotic behavior including aggressive thoughts.

Renal and Urinary Disorders: tubulointerstitial nephritis.

Skin and Subcutaneous Tissue Disorders: generalized rash, Stevens Johnson Syndrome, hypersensitivity skin reactions.

4.9 Overdose:

Febuxostat was studied in healthy subjects in doses up to 300 mg daily for seven days without evidence of dose-limiting toxicities. No overdose of Febuxostat was reported in clinical studies. Patients should be managed by symptomatic and supportive care should there be an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Febuxostat, a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. Febuxostat is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.

Effect on Uric Acid and Xanthine Concentrations: In healthy subjects, Febuxostat resulted in a dose dependent decrease in 24-hour mean serum uric acid concentrations and an increase in 24-hour mean serum xanthine concentrations. In addition, there was a decrease in the total daily urinary uric acid excretion. Also, there was an increase in total daily urinary xanthine excretion. Percent reduction in 24-hour mean serum uric acid concentrations was between 40% and 55% at the exposure levels of 40 mg and 80 mg daily doses.

Effect on Cardiac Repolarization: The effect of Febuxostat on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy subjects and in patients with gout. Febuxostat in doses up to 300 mg daily, at steady-state, did not demonstrate an effect on the QTc interval.

5.2 Pharmacokinetic properties*:*

Absorption

The absorption of radiolabeled Febuxostat following oral dose administration was estimated to be at least 49% (based on total radioactivity recovered in urine). Maximum plasma

concentrations of Febuxostat occurred between 1 and 1.5 hours post-dose. After multiple oral 40 mg and 80 mg once daily doses, Cmax is approximately 1.6 ± 0.6 mcg/mL (N=30), and 2.6 ± 1.7 mcg/mL (N=227), respectively. Absolute bioavailability of the Febuxostat tablet has not been studied.

Following multiple 80 mg once daily doses with a high fat meal, there was a 49% decrease in Cmax and an 18% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed (58% fed vs. 51% fasting). Thus, Febuxostat may be taken without regard to food.

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminum hydroxide with an 80 mg single dose of Febuxostat has been shown to delay absorption of Febuxostat (approximately one hour) and to cause a 31% decrease in Cmax and a 15% decrease in AUC∞. As AUC rather than Cmax was related to drug effect, change observed in AUC was not considered clinically significant. Therefore, Febuxostat may be taken without regard to antacid use.

Distribution and Plasma Protein Binding

The mean apparent steady state volume of distribution (V_{ss}/F) of Febuxostat was approximately 50 L (CV ~40%). The plasma protein binding of Febuxostat is approximately 99.2% (primarily to albumin), and is constant over the concentration range achieved with 40 mg and 80 mg doses.

Metabolism

Febuxostat is extensively metabolized by both conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes including UGT1A1, UGT1A3, UGT1A9, and UGT2B7 and oxidation via cytochrome P450 (CYP) enzymes including CYP1A2, 2C8 and 2C9 and non-P450 enzymes. The relative contribution of each enzyme isoform in the metabolism of Febuxostat is not clear. The oxidation of the isobutyl side chain leads to the formation of four

pharmacologically active hydroxy metabolites, all of which occur in plasma of humans at a much lower extent than Febuxostat.

In urine and feces, acyl glucuronide metabolites of Febuxostat (~35% of the dose), and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4, a secondary metabolite from 67M-1 (~14% of the dose), appeared to be the major metabolites of Febuxostat *invivo*.

Elimination

Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of14C-labeledFebuxostat, approximately 49% of the dose was recovered in the urine as unchanged Febuxostat (3%), the acyl glucuronide of the drug (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 feces as the unchanged Febuxostat (12%), the acyl glucuronide of the drug (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

The apparent mean terminal elimination half-life (t1/2) of Febuxostat was approximately 5 to 8 hours.

Special Population

Pediatric Use:

The pharmacokinetics of Febuxostat in patients under the age of 18 years has not been studied.

Geriatric Use:

The Cmax and AUC of Febuxostat and its metabolites following multiple oral doses of Febuxostat in geriatric subjects (≥65 years) were similar to those in younger subjects (18 to 40

years). In addition, the percent decrease in serum uric acid concentration was similar between elderly and younger subjects. No dose adjustment is necessary in geriatric patients.

Renal Impairment:

Following multiple 80 mg doses of Febuxostat in healthy subjects with mild (Clcr 50 to 80 mL/min), moderate (Clcr 30 to 49 mL/min) or severe renal impairment (Clcr 10 to 29 mL/min), the Cmax of Febuxostat did not change relative to subjects with normal renal function (Clcr greater than 80 mL/min). AUC and half-life of Febuxostat increased in subjects with renal impairment in comparison to subjects with normal renal function, but values were similar among three renal impairment groups. Mean Febuxostat AUC values were up to 1.8 times higher in subjects with renal impairment compared to those with normal renal function. Mean Cmax and AUC values for three active metabolites increased up to 2- and 4-fold, respectively. However, the percent decrease in serum uric acid concentration for subjects with renal impairment was comparable to those with normal renal function (58% in normal renal function group and 55% in the severe renal function group).

No dose adjustment is necessary in patients with mild to moderate renal impairment. The recommended starting dose of Febuxostat is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg/dL after two weeks with 40 mg, Febuxostat 80 mg is recommended. There is insufficient data in patients with severe renal impairment; caution should be exercised in those patients.

Febuxostat has not been studied in end stage renal impairment patients who are on dialysis.

Hepatic Impairment:

Following multiple 80 mg doses of Febuxostat in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an average of 20% to 30% increase was observed for both Cmax and AUC24 (total and unbound) in hepatic impairment groups compared to subjects with normal hepatic function. In addition, the percent decrease in serum

uric acid concentration was comparable between different hepatic groups (62% in healthy group, 49% in mild hepatic impairment group, and 48% in moderate hepatic impairment group). No dose adjustment is necessary in patients with mild or moderate hepatic impairment. No studies have been conducted in subjects with severe hepatic impairment (Child-Pugh Class C); caution should be exercised in those patients.

5.3 Preclinical safety data:

Effects in non-clinical studies were generally observed at exposures in excess of the maximum human exposure.

Carcinogenesis, mutagenesis, impairment of fertility

In male rats, a statistically significant increase in urinary bladder tumours (transitional cell papilloma and carcinoma) was found only in association with xanthine calculi in the high dose group, at approximately 11 times human exposure. There was no significant increase in any other tumour type in either male or female mice or rats. These findings are considered a consequence of species specific purine metabolism and urine composition and of no relevance to clinical use.

A standard battery of test for genotoxicity did not reveal any biologically relevant genotoxic effects for febuxostat.

Febuxostat at oral doses up to 48 mg/kg/day was found to have no effect on fertility and reproductive performance of male and female rats.

There was no evidence of impaired fertility, teratogenic effects, or harm to the foetus due to febuxostat. There was high dose maternal toxicity accompanied by a reduction in weaning index and reduced development of offspring in rats at approximately 4.3 times human exposure. Teratology studies, performed in pregnant rats at approximately 4.3 times and

pregnant rabbits at approximately 13 times human exposure did not reveal any teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate

Microcrystalline Cellulose

Croscarmellose Sodium

Sodium Lauryl Sulphate

Purified Water

Hydroxypropyl cellulose

Colloidal Anhydrous Silica

Magnesium Stearate

Instacoat universal Yellow (A05D10519)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precautions for storage

Store below 30 °C. Keep out from the reach of children.

6.5 Nature and contents of container

Febuxostat Tablets 80 mg(Mebux – 80) are packed in Alu - Alu Blister pack of 10 tablets, 3 such blisters in a laminated outer carton along with pack Insert.

7. Marketing Authorization Holder

Manufactured by:

MICRO LABS LIMITED

92, SIPCOT,

HOSUR– 635126, INDIA

Applicant

[illegible] CEUTICALS IND LTD
[illegible] Oregun, Lagos, Nigeria

8. Marketing Authorization Number

NAFDAC Reg.No.B4-9650

9. Date of first authorization/renewal of authorization

12.03.2019

10. Date of revision of text

July 2017