SUMMARY OF PRODUCT CHARACTERISTICS

Febuxostat Tablets 40 mg / 80 mg

1. NAME OF THE MEDICINAL PRODUCT

Febuday 40 (Febuxostat ablets 40 mg)

Febuday 80 (Febuxostat tablets 80 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains

Febuxostat 40 mg

Each film coated tablet contains

Febuxostat 80 mgwhen

For a full list of excipients, refer section 6.1

3. PHARMACEUTICAL FORM

Febuxostat 40 mg tablet: White colored round shaped biconvex film coated tablets, plain on both sides.

Febuxostat 80 mg tablet: White colored round shaped biconvex film coated tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

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

Febuxostat is indicated in adults.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

POSOLOGY:

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 mgper dL after 2 weeks with 40 mg, Febuxostat 80 mg is recommended.

Febuxostat can be administered without regard to food or antacid use.

Elderly

No dose adjustment is required in the elderly.

Renal impairment

No dosage adjustment is necessary in patients with mild or moderate renal impairment. The efficacy and safety have not been fully evaluated in patients with severe renal impairment.

Hepatic impairment

The recommended dosage in patients with mild hepatic impairment is 80 mg. Limited information is available in patients with moderate hepatic impairment.The efficacy and safety of febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh ClassC).

Organ transplant recipients

As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended

Paediatric 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.

METHOD OF ADMINISTRATION

Oral Route

Febuxostat should be taken by mouth and can be taken with or without food.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients. Febuxostat ia contraindicated in Patients being treated with azathioprine or mercatopurine or theophylline.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Gout Flare: An increase in gout flares is frequently reported during initiation of anti-hyperuricemic agents, including Febuxostat. If a gout flare occurs during treatment, Febuxostat need not be discontinued. Prophylactic therapy (i.e., non-steroidal anti-inflammatory drug (NSAID) or colchicine upon initiation of treatment) may be beneficial for up to six months.

Cardiovascular Events: A higher rate of cardiovascular thromboembolic events was reported in patients treated with Febuxostat than allopurinol in clinical trials. Monitor for signs and symptoms of MI and stroke.

Liver Enzyme Elevation: Transaminase elevations have been observed in Febuxostat-treated patients. Monitor liver function tests periodically.

Medicinal product allergy / hypersensitivity:

Rare reports of serious allergic/hypersensitivity reactions,including life-threatening Stevens–Johnson Syndrome and acute anaphylactic reaction/shock, reported in the post-marketing experience.

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.

Xanthine deposition:

As with other urate lowering medicinal products, 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.

Thyroid disorders :

Increased TSH values (>5.5 μIU/ml) were observed in patients on long-term treatment with febuxostat (5.5%) in the reported 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 Lapplactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Xanthine Oxidase Substrate Drugs:

Febuxostat is an XO inhibitor. drug interaction studies reported febuxostat altered the metabolism of theophylline (a substrate of XO) in humans. Therefore, use with caution when co-administering Febuxostat with theophylline.

Drug interaction studies of Febuxostat with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) are not reported. 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 or mercaptopurine.

Cytotoxic Chemotherapy Drugs:

Drug interaction studies of Febuxostat with cytotoxic chemotherapy have not been reported. 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.

Naproxen and other inhibitors of glucuronidation:

Febuxostat metabolism depends on 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 BID was associated with an increase in febuxostat exposure (Cmax 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.

Desipramine/CYP2D6 substrates:

Febuxostat was shown to be a weak inhibitor of CYP2D6 in vitro. In a study in healthy subjects, 120mg Febuxostat 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 1hour) 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.

4.6 PREGNANCY AND LACTATION

Pregnancy

Data on a very limited number of exposed pregnancies report have not indicated any adverse effects of febuxostat on pregnancy or on the health of the foetus/new born child. Report on 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.

Breast feeding

It is unknown whether febuxostat is excreted in human breast milk. Animal studies have reported 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 reported no dose-dependent adverse effects on fertility.The effect of Febuxostat on human fertility is unknown.

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

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 < 1/1000) adverse reactions occuring in patients treated with febuxostat are listed below.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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
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 maculo papular, rash papular Rare Stevens-Johnson Syndrome ,generalized rash(serious), erythema, 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 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
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.

Description of selected adverse reactions

Rare serious hypersensitivity reactions to febuxostat, including Stevens-Johnson Syndrome and anaphylactic reaction/shock, have occurred in the post-marketing experience. Stevens-Johnson Syndrome is 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 single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis).

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. As with other urate lowering medicinal products, gout flare prophylaxis is recommended.

4.9 OVERDOSE

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

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group : Antigout

ATC code : M04AA03

Mechanism of Action:

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.

Pharmacodynamics:

Effect on Uric Acid and Xanthine Concentrations: In healthy subjects, Febuxostat reported 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% to 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 reported in normal healthy subjects and in patients with gout.

5.2 PHARMACOKINETIC PROPERTIES

The maximum plasma concentrations (Cmax) and AUC of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life (t1/2) of approximately 5 to 8 hours.

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 to 1.5 hours post-dose. After multiple oral 40 mg and 80 mg once daily doses, Cmax is approximately 1.6 ± 0.6 mcg per mL (N=30), and 2.6 ± 1.7 mcg per mL (N=227), respectively. Absolute bioavailability of the febuxostat tablet has not been reported.

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 reported (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 reported to delay absorption of febuxostat

(approximately 1 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:

The mean apparent steady state volume of distribution (Vss/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 repoted to 40 mg and 80 mg doses.

Metabolism:

Febuxostat is extensively metabolized by both conjugation via uridine diphosphate glucuronosyl transferase (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 in vivo.

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 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 Populations:

Pediatric Use: The pharmacokinetics of Febuxostat in patients under the age of 18 years have not been reported.

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 (18-40 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 50-80 mL per min), moderate (Clcr 30-49 mL per min) or severe renal impairment (Clcr 10-29 mL pemin), the Cmax of febuxostat did not change relative to subjects with normal renal function (Clcr greater than 80 mL per 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 subjectswith renal impairment compared to those with normal renal function. Mean Cmax and AUC values for 3 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 [see Dosage and Administration (2) and Use in Specific Populations (8.6)]. The recommended starting dose of Febuxostat is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg per dL after 2 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 reported 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 20-30% 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.

Gender: Following multiple oral doses of Febuxostat, the Cmax and AUC24 of febuxostat were 30% and 14% higher in females than in males, respectively. However, weight-corrected Cmax and

AUC were similar between the genders. In addition, the percent decrease in serum uric acid concentrations was similar between genders. No dose adjustment is necessary based on gender.

Race: No specific pharmacokinetic data was available on the effects of race.

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 reported 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 genotoxicitydid not reveal any biologically relevant genotoxic effects for febuxostat.

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

There was no report on impaired fertility, vteratogenic 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 (Avicel 101), Hydroxy propyl cellulose (Klucel LF Pharm), Croscarmellose sodium (Ac-Di-Sol), Colloidal silicon dioxide, Magnesium stearate, *Coating:* Polyvinyl Alcohol Partially hydrolized, titaniumdioxide, poly ethylene glycol, Talc, Lecithin, .

6.2 INCOMPATIBILITIES:

Not applicable

6.3 SHELF LIFE:

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE:

Do not store above 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER:

10 tablets of FEBUDAY 40/80 (Febuxostat Tablets 40/80 mg) are sealed with plain aluminium foil on one side and printed Aluminium foil on the other side in the form of a blister pack and 3 such Alu-Alu blister packs are further packed in a printed carton along with instructions for use.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL:

Any unused product or waste material should be disposed off in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER:

MSN LABORATORIES PRIVATE LIMITED
MSN House, Plot No. : C-24, Industrial Estate,
Sanath Nagar, Hyderabad – 500 018
Telangana, India.

8. DATE OF REVISION OF THE TEXT: April 2017

LEGAL CATEGORY: POM (Prescription only medicine)