For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

FEBUGOOD

1. Generic Name

Febuxostat Tablets 40, 80 and 120 mg

2. Composition

FEBUGOOD 40

Each film coated tablet contains:
Febuxostat…… 40 mg
Excipients……. q.s.
Colours: Yellow Oxide of Iron & Titanium Dioxide I.P.

FEBUGOOD 80

Each film coated tablet contains:
Febuxostat…….80 mg
Excipients……..q.s.
Colours: Sunset yellow FCF &Titanium Dioxide I.P.

FEBUGOOD 120

Each film coated tablet contains:
Febuxostat 120 mg
Colours: Titanium Dioxide I.P.,
Lake of Tartrazine & Lake of Brilliant blue

The excipients used are Maize starch, Polyvinyl pyrrolidone K30, Microcrystalline cellulose, Crospovidone, Isopropyl alcohol, Croscarmellose sodium, Aerosil, Magnesium stearate, Hypromellose, Polyethylene Glycol 6000, purified Talc, Titanium dioxide, Yellow Oxide of Iron, Dichloromethane, Sunset yellow FCF Lake.

3. Dosage form and strength

Dosage form: Film coated tablet
Strength: 40 mg, 80 mg and 120 mg

4. Clinical particulars

4.1 Therapeutic indication

Febuxostat is a Xanthine Oxidase (XO) inhibitor indicated for the treatment of chronic hyperuricemia in conditions where urate deposition has already occurred (including a history, or presence of tophus and / or gouty arthritis.)

4.2 Posology and method of administration

Recommended Dose

For treatment of hyperuricemia in patients with gout, FEBUGOOD is recommended at 40 mg or 80 mg once daily. The recommended starting dose of FEBUGOOD is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg per dL after 2 weeks with 40 mg, FEBUGOOD 80 mg is recommended. If serum uric acid is >6 mg/dl (357µmol/l) after 2-4 weeks, 120 mg once daily may be considered. Febuxostat works sufficienctly quickly to allow retesting of the serum uric acid after 2 weeks. The theapeutic target is to decrease

and maintain serum uric acid below 6 mg/dl (357 μmol/l). FEBUGOOD can be taken without regard to food or antacid use

Special Populations

No dose adjustment is necessary when administering FEBUGOOD in patients with mild to moderate renal impairment. The recommended starting dose of FEBUGOOD 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, FEBUGOOD 80 mg is recommended.

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

Uric Acid Level

Testing for the target serum uric acid level of less than 6 mg per dL may be performed as early as 2 weeks after initiating FEBUGOOD therapy.

Gout Flares

Gout flares may occur after initiation of FEBUGOOD due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended upon initiation of FEBUGOOD. Prophylactic therapy may be beneficial for up to six months.

If a gout flare occurs during FEBUGOOD treatment, FEBUGOOD need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient.

Use in Children and Elder patients

Pediatric use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric use

No dose adjustment is necessary in elderly patients. Of the total number of subjects in clinical studies of febuxostat, 16 percent were 65 and over, while 4 percent were 75 and over. Comparing subjects in different age groups, no clinically significant differences in safety or effectiveness were observed but greater sensitivity of some older individuals cannot be ruled out. The Cmax and AUC24 of febuxostat following multiple oral doses of febuxostat in geriatric subjects (≥ 65 years) were similar to those in younger subjects (18-40 years).

4.3 Contraindications

- Febuxostat is contraindicated in patients being treated with azathioprine, mercaptopurine, or theophylline.
- Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Cardio-vascular disorders

Treatment with febuxostat in patients with ischemic heart disease or congestive heart failure is not recommended and present evidence states that it increases the

cardiovascular-thrombo embolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in those subjects who are on febuxostat than allopurinol. A causal relationship with febuxostat has not been established.

Gout Flare
After initiation of febuxostat therapy, 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. If a gout flare occurs during febuxostat treatment, it should not be discontinued. The gout flare should be managed concurrently with NSAID or colchicine as appropriate for the individual patient. Continuous treatment with febuxostat decreases frequency and intensity of gout flares.

Liver Enzyme Elevations
During randomized controlled studies, transaminase elevations greater than 3 times the upper limit of normal were observed. Hence it is recommended that liver function should be monitored before initiation of therapy and thereafter.

Thyroid disorders
Increased TSH values (>5.5 µIU/ml) were observed in patients on long-term treatment with febuxostat (5.0%) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function.

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.

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.

4.5 Drugs interactions

Effect of Febuxostat on Other Drugs

Xanthine Oxidase Substrate Drugs-Azathioprine, Mercaptopurine, and Theophylline: 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 and theophylline. Azathioprine and mercaptopurine undergo metabolism via three major metabolic pathways, one of which is mediated by XO. Although febuxostat drug interaction studies with azathioprine and mercaptopurine have not been conducted, concomitant administration of allopurinol [a xanthine oxidase inhibitor] with

azathioprine or mercaptopurine has been reported to substantially increase plasma concentrations of these drugs. Because febuxostat is a XO inhibitor, it could inhibit the XO-mediated metabolism of azathioprine and mercaptopurine leading to increased plasma concentrations of azathioprine or mercaptopurine that could result in severe toxicity.

Theophylline is a CYP1A2 and XO substrate. Although no febuxostat drug interaction study with theophylline has been conducted, concomitant administration of theophylline with allopurinol, a xanthine oxidase inhibitor at doses ≥ 600 mg per day, has been reported to increase theophylline plasma concentrations. Because febuxostat is a xanthine oxidase inhibitor and theophylline is a low therapeutic index drug, febuxostat could inhibit the XO-mediated metabolism of theophylline leading to increased plasma concentrations of theophylline that could induce severe theophylline toxicity.

P450 Substrate Drugs:

In vitro studies have shown that febuxostat does not inhibit P450 enzymes CYP1A2, 2C9, 2C19, 2D6, or 3A4 and it also does not induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 at clinically relevant concentrations. As such, pharmacokinetic interactions between febuxostat and drugs metabolized by these CYP enzymes are unlikely.

Effect of Other Drugs on febuxostat

Febuxostat is metabolized by conjugation and oxidation via multiple metabolizing enzymes. The relative contribution of each enzyme isoform is not clear. A drug interaction between febuxostat and a drug that inhibits or induces one particular enzyme isoform is in general not expected.

***In Vivo* Drug Interaction Studies**

Colchicine: No dose adjustment is necessary for either febuxostat or colchicine when the two drugs are co-administered. Administration of febuxostat (40 mg once daily) with colchicine (0.6 mg twice daily) resulted in an increase of 12% in Cmax and 7% in AUC24 of febuxostat. In addition, administration of colchicine (0.6 mg twice daily) with febuxostat (120 mg daily) resulted in less than 11% change in Cmax or AUC of colchicine for both AM and PM doses. These changes were not considered clinically significant.

Naproxen: No dose adjustment is necessary for febuxostat or naproxen when the two drugs are co-administered. Administration of febuxostat (80 mg once daily) with naproxen (500 mg twice daily) resulted in a 28% increase in Cmax and a 40% increase in AUC of febuxostat. The increases were not considered clinically significant. In addition, there were no significant changes in the Cmax or AUC of naproxen (less than 2%).

Indomethacin: No dose adjustment is necessary for either febuxostat or indomethacin when these two drugs are co-administered. Administration of febuxostat (80 mg once daily) with indomethacin (50 mg twice daily) did not result in any significant changes in Cmax or AUC of febuxostat or indomethacin (less than 7%).

Hydrochlorothiazide: No dose adjustment is necessary for febuxostat when co-administered with hydrochlorothiazide. Administration of febuxostat (80 mg) with hydrochlorothiazide (50 mg) did not result in any clinically significant changes in Cmax

or AUC of febuxostat (less than 4%), and serum uric acid concentrations were not substantially affected.

Warfarin: No dose adjustment is necessary for warfarin when co-administered with febuxostat. Administration of febuxostat (80 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: Co-administration of drugs that are CYP2D6 substrates (such as desipramine) with febuxostat are not expected to require dose adjustment. Febuxostat was shown to be a weak inhibitor of CYP2D6 in vitro and in vivo. Administration of febuxostat (120 mg once daily) with desipramine (25 mg) resulted in an increase in Cmax (16%) and AUC (22%) of desipramine, which was associated with a 17% decrease in the 2-hydroxydesipramine to desipramine metabolic ratio (based on AUC).

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy
Pregnancy category C:
Febuxostat was not teratogenic in rats and rabbits at oral doses up to 48 mg per kg (40 and 51 times the human plasma exposure at 80 mg per 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 per kg (40 times the human plasma exposure at 80 mg per day) during organogenesis and through lactation period. 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. 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.

Nursing Mother
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
Not available

4.8 Undesirable effects
From randomized clinical trial experience, most common adverse reaction (≥1%) were liver function abnormality, nausea, diarrhea, arthralgia, rash, and dizziness. While less common adverse reaction (≥1%) were as follows:

Blood and Lymphatic System Disorders: Anemia, idiopathic thrombocytopenic purpura, leukocytosis/leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.

Cardiac Disorders: Angina pectoris, atrial fibrillation/flutter, cardiac murmur, ECG abnormal, palpitations, sinus bradycardia, tachycardia.

Ear and Labyrinth Disorders: Deafness, tinnitus, vertigo.

Eye Disorders: Vision blurred.
Gastrointestinal Disorders: Abdominal distention, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, frequent stools, gastritis, gastroesophageal reflux disease, gastrointestinal discomfort, gingival pain, haematemesis, hyperchlorhydria, hematochezia, mouth ulceration, pancreatitis, peptic ulcer, vomiting.

General Disorders and Administration Site Conditions: Asthenia, chest pain/discomfort, edema, fatigue, feeling abnormal, gait disturbance, influenza-like symptoms, mass, pain, thirst.

Hepatobiliary Disorders: Cholelithiasis/cholecystitis, hepatic steatosis, hepatitis, hepatomegaly.

Immune System Disorder: Hypersensitivity.

Infections and Infestations: Herpes zoster.

Procedural Complications: Contusion.

Metabolism and Nutrition Disorders: Anorexia, appetite decreased/increased, dehydration, diabetes mellitus, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypokalemia, weight decreased/increased.

Musculoskeletal and Connective Tissue Disorders: Arthritis, joint stiffness, joint swelling, muscle spasms/twitching/ tightness/weakness, musculoskeletal pain/stiffness, myalgia.

Nervous System Disorders: Altered taste, balance disorder, cerebrovascular accident, Guillain-Barré syndrome, headache, hemiparesis, hypoesthesia, hyposmia, lacunar infarction, lethargy, mental impairment, migraine, paresthesia, somnolence, transient ischemic attack, tremor.

Psychiatric Disorders: Agitation, anxiety, depression, insomnia, irritability, libido decreased, nervousness, panic attack, personality change.

Renal and Urinary Disorders: Hematuria, nephrolithiasis, pollakiuria, proteinuria, renal failure, renal insufficiency, urgency, incontinence.

Reproductive System and Breast Changes: Breast pain, erectile dysfunction, gynecomastia.

Respiratory, Thoracic and Mediastinal Disorders: Bronchitis, cough, dyspnea, epistaxis, nasal dryness, paranasal sinus hypersecretion, pharyngeal edema, respiratory tract congestion, sneezing, throat irritation, upper respiratory tract infection.

Skin and Subcutaneous Tissue Disorders: Alopecia, angio-edema, dermatitis, dermographism, ecchymosis, eczema, hair color changes, hair growth abnormal, hyperhidrosis, peeling skin, petechiae, photosensitivity, pruritus, purpura, skin discoloration/altered pigmentation, skin lesion, skin odor abnormal, bursitis, urticaria.

Vascular Disorders: Flushing, hot flush, hypertension, hypotension.

Laboratory Parameters: Activated partial thromboplastin time prolonged, creatine increased, bicarbonate decreased, sodium increased, EEG abnormal, glucose increased, cholesterol increased, triglycerides increased, amylase increased, potassium increased, TSH increased, platelet count decreased, hematocrit decreased, hemoglobin decreased, MCV increased, RBC decreased, creatinine increased, blood urea increased, BUN/creatinine ratio increased, creatine phosphokinase (CPK) increased, alkaline phosphatase increased, LDH increased, PSA increased, urine output increased/decreased, lymphocyte count decreased, neutrophil count decreased, WBC increased/ decreased, coagulation test abnormal, low density lipoprotein (LDL) increased, triglyceride increases, prothrombin time prolonged, urinary casts, urine positive for white blood cells and protein.

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 Mechanism of Action

Febuxostat is xanthine oxidase (XO) inhibitor and shows its action by decreasing serum uric acid level. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of XO. It is not expected to inhibit other enzymes (like guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase or purine nucleoside phosphorylase.) involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.

5.2 Pharmacodynamic properties

Febuxostat shows dose dependent effect on the uric acid level. In healthy subjects it shows dose dependent decrease in 24 hour mean serum uric acid (sUA) level, and increases in the 24-hour mean xanthine concentration. In addition, there was a decrease in the total daily urinary uric acid excretion and also increase in the total daily urinary xanthine excretion. Percent reduction in 24-hour mean serum uric acid concentrations was 40% to 55% for 40mg to 80 mg of daily dosing.

The efficacy of febuxostat was demonstrated in two Phase 3 pivotal studies (APEX study and FACT study described below) that were conducted in 1832 patients with hyperuricemia and gout. In each phase 3 pivotal study, Febuxostat demonstrated superior ability to lower and maintain sUA levels compared to allopurinol. The primary efficacy endpoint in each study was the proportion of patients whose last 3 monthly sUA levels were < 6.0 mg/dl (357 µmol/l). No patients with organ transplant have been included in these studies.

APEX Study: The Allopurinol and Placebo-Controlled Efficacy Study of Febuxostat (APEX) was a Phase 3, randomized, double-blind, multicenter, 28-week study. One thousand and seventy-two (1072) patients were randomized: placebo (n=134),

FEBUXOSTAT 80 mg QD (n=267), FEBUXOSTAT 120 mg QD (n=269), FEBUXOSTAT 240 mg QD (n=134) or Allopurinol (300 mg QD [n=258] for patients with a baseline serum creatinine ≤ 1.5 mg/dl or 100 mg QD [n=10] for patients with a baseline serum creatinine>1.5 mg/dl and 2.0 mg/dl). Two hundred and forty mg febuxostat (2 times the recommended highest dose) was used as a safety evaluation dose.

The APEX study showed statistically significant superiority of both the FEBUXOSTAT 80 mg QD and the FEBUXOSTAT 120 mg QD treatment arms versus the conventionally used doses of allopurinol 300mg (n = 258) /100mg (n = 10) treatment arm in reducing the sUA below 6 mg/dl (357 µmol/l) (see Table 1).

FACT Study: The Febuxostat Allopurinol Controlled Trial (FACT) Study was a Phase 3, randomized, double-blind, multicenter, 52-week study. Seven hundred sixty (760) patients were randomized: FEBUXOSTAT 80 mg QD (n=256), FEBUXOSTAT 120 mg QD (n=251), or allopurinol 300 mg QD (n=253).

The FACT study showed the statistically significant superiority of both FEBUXOSTAT 80 mg and FEBUXOSTAT 120 mg QD treatment arms versus the conventionally used dose of allopurinol 300 mg treatment arm in reducing and maintaining sUA below 6 mg/dl (357 µmol/l).

Table 1 summarises the primary efficacy endpoint results:
Proportion of Patients with Serum Uric Acid Levels <6.0 mg/dl (357µmol/l)

Last Three Monthly Visits

Study	FEBUXOSTAT 80 mg QD	FEBUXOSTAT 120 mg QD	Allopurinol 300/100 mg QD[1]
APEX (28 weeks)	48 % * (n=262)	65% *, # (n=269)	22% (n=268)
FACT (52 weeks)	53%* (n=255)	62%* (n=250)	21% (n=251)
Combined Results	51%* (n=517)	63%*, # (n=519)	22% (n=519)

[1] results from subjects receiving either 100 mg QD (n=10: patients with serum creatinine >1.5 and ≤ 2.0 mg/dl) or 300 mg QD (n=509) were pooled for analyses.
* $p < 0.001$ vs allopurinol, # $p < 0.001$ vs 80 mg

The ability of FEBUXOSTAT to lower serum uric acid levels was prompt and persistent. Reduction in serum uric acid level to 1.5 mg/dl and ≤ 2.0 mg/dl). For renally impaired subjects who were randomized to allopurinol, the dose was capped at 100mg QD. FEBUXOSTAT achieved the primary efficacy endpoint in 44% (80 mg QD), 45% (120 mg QD), and 60% (240 mg QD) of patients compared to 0% in the allopurinol 100 mg QD and placebo groups. There were no clinically significant differences in the percent decrease in serum uric acid concentration in healthy subjects irrespective of their renal function (58 % in the normal renal function group and 55% in the severe renal dysfunction group).

Primary endpoint in the sub group of patients with sUA r10 mg/dl Approximately 40% of patients (combined APEX and FACT) had a baseline sUA of r10 mg/dl. In this

subgroup FEBUXOSTAT achieved the primary efficacy endpoint in 41% (80 mg QD), 48% (120 mg QD), and 66% (240 mg QD) of patients compared to 9% in the allopurinol 300 mg/100 mg QD and 0 % in the placebo groups.

Clinical Outcomes: proportion of patients requiring treatment for a gout flare and tophi size change
The proportion of subjects requiring treatment for a gout flare (APEX and FACT Study) was numerically lower in the groups that achieved an average post-baseline serum urate level <6.0 mg/dl, <5.0 mg/dl, or <4.0 mg/dl compared to the group that achieved an average post-baseline serum urate level r6.0 mg/dl during the last 32 weeks of the treatment period (Week 20-Week 24 to Week 48 - 52 intervals).

Two years of data from the Phase 3 Open Label Extension study showed that the maintenance of serum urate levels < 6 mg/dl (<357 µmol/l) resulted in a decrease in the incidence of gout flares with less than 3 % of subjects requiring treatment for a flare (i.e. more than 97 % of patients did not require treatment for a flare) at Month 16-24. This was associated with a reduction of tophus size leading to complete resolution in 54% of subjects at Month 24.

During the phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (3.5%). These rates were similar to the rates reported on allopurinol (3.6%). Increased TSH values (<5.5 µIU/ml) were observed in patients on long-term treatment with febuxostat (5.0%) and patients with allopurinol (5.8%) in the long term open label extension studies.

The total exposure to FEBUXOSTAT in phase 3 pivotal studies and long-term extension studies is greater than 2700 patient-years.

5.3 Pharmacokinetic properties

In healthy subjects, 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. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed for febuxostat. 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. Febuxostat pharmacokinetic parameters for patients with hyperuricemia and gout estimated by population pharmacokinetic analyses were similar to those estimated in healthy subjects.

Absorption: The absorption of febuxostat following oral dose administration was estimated to be 49% to 84%. Maximum plasma concentrations (tmax) of febuxostat occurred between 1 to 1.5 hours post-dose. 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 with or without 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 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. Hence, Febuxostat may be taken without regard to antacid use.

Distribution: The mean apparent steady state volume of distribution (Vss/F) of febuxostat was 29 to 75 L after oral doses of 10mg to 300mg. 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 while for active metabolite value ranges from 82 to 91%.

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 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 (t½) 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 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 (18-40 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/min), moderate (Clcr 30-49 mL/min) or severe renal impairment (Clcr 10-29 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 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.

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 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 20-30% 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 sUA 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. Caution should be exercised in subjects with severe hepatic impairment (Child-Pugh Class C) as there are no studies available for those subjects.

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 sUA concentrations was similar between genders. No dose adjustment is necessary based on gender.

6 Nonclinical properties

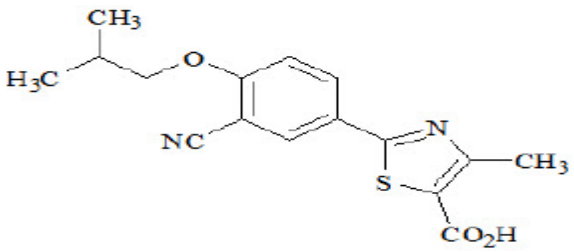
6.1 Animal Toxicology or Pharmacology

Not Available

7. Description

Febuxostat is a xanthine oxidase inhibitor. The Chemical name of febuxostat is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, with a molecular weight of 316.38. The empirical formula is C16H16N2O3S.

The chemical structure is:



Febugood 40 is Yellow coloured, round shaped, biconvex, plain on both sides, film coated tablets. The excipients used are Maize starch, Polyvinyl pyrrolidone K30, Microcrystalline cellulose, Crospovidone, Isopropyl alcohol, Croscarmellose sodium, Aerosil, Magnesium stearate, Hypromellose, Polyethylene Glycol 6000, purified Talc, Titanium dioxide, Yellow Oxide of Iron, Dichloromethane.

Febugood 80 is Orange coloured, round shaped, biconvex, plain on both sides, film coated tablets. The excipients used are Maize starch, Polyvinyl pyrrolidone K30, Microcrystalline cellulose, Crospovidone, Isopropyl alcohol, Croscarmellose sodium, Aerosil, Magnesium stearate, Hypromellose, Polyethylene Glycol 6000, purified Talc, Titanium dioxide, Sunset yellow FCF Lake, Dichloromethane.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

FEBUGOOD 40, 80 and 120 are available as blister strip of 10 tablets.

8.4 Storage and handing instructions

Store below 30°C. Protect from light and moisture.
Keep out of reach of children.

9. Patient Counselling Information

Read all of this leaflet carefully before you start taking this medicine because it contains
important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

9.1 What FEBUGOOD is and what it is used for

FEBUGOOD tablets contain the active substance febuxostat and are used to treat gout, which is associated with an excess of a chemical called uric acid (urate) in the body. In

some people, the amount of uric acid builds up in the blood and may become too high to remain soluble. When this happens, urate crystals may form in and around the joints and kidneys. These crystals can cause sudden, severe pain, redness, warmth and swelling in a joint (known as a gout attack). Left untreated, larger deposits called tophi may form in and around joints. These tophi may cause joint and bone damage.

FEBUGOOD works by reducing uric acid levels. Keeping uric acid levels low by taking FEBUGOOD once every day stops crystals building up, and over time it reduces symptoms. Keeping uric acid levels sufficiently low for a long enough period can also shrink tophi.

FEBUGOOD 120 mg tablets is also used to treat and prevent high blood levels of uric acid that may occur when you start to receive chemotherapy for blood cancers.

When chemotherapy is given, cancer cells are destroyed, and uric acid levels increase in the blood accordingly, unless the formation of uric acid is prevented.

FEBUGOOD is for adults.

9.2 What you need to know before you take FEBUGOOD
Do not take FEBUGOOD
- If you are allergic to febuxostat or any of the other ingredients of this medicine.

Warnings and precautions
Talk to your doctor before taking FEBUGOOD:
- If you have or have had heart failure or heart problems
- If you have or have had renal disease and/or serious allergic reaction to Allopurinol (a medication used for the treatment of Gout)
- If you have or have had liver disease or liver function test abnormalities
- If you are being treated for high uric acid levels as a result of Lesch-Nyhan syndrome (a rare inherited condition in which there is too much uric acid in the blood)
- If you have thyroid problems.

Should you experience allergic reactions to FEBUGOOD, stop taking this medicine. Possible symptoms of allergic reactions might be:
- rash including severe forms (e.g. blisters, nodules, itchy-, exfoliative rash), itchiness
- swelling of limbs or face
- difficulties in breathing
- fever with enlarged lymph nodes
- but also serious life threatening allergic conditions with cardiac and circulatory arrest.

Your doctor might decide to permanently stop treatment with FEBUGOOD.

There have been rare reports of potentially life-threatening skin rashes (Stevens-Johnson Syndrome) with the use of FEBUGOOD, appearing initially as reddish target-like spots or circular patches often with central blister on the trunk. It may also include ulcers in the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes). The rash may progress to widespread blistering or peeling of the skin.
If you have developed Stevens-Johnson Syndrome with the use of febuxostat, you must not be restarted on FEBUGOOD at any time. If you develop a rash or these skin symptoms, seek immediate advice from a doctor and tell that you are taking this medicine.

If you are having a gout attack at the moment (a sudden onset of severe pain, tenderness, redness, warmth and swelling in a joint), wait for the gout attack to subside before first starting treatment with FEBUGOOD.

For some people, gout attacks may flare up when starting certain medicines that control uric acid levels. Not everyone gets flares, but you could get a flare-up even if you are taking FEBUGOOD, and especially during the first weeks or months of treatment. It is important to keep taking FEBUGOOD even if you have a flare, as FEBUGOOD is still working to lower uric acid. Over time, gout flares will occur less often and be less painful if you keep taking FEBUGOOD every day.

Your doctor will often prescribe other medicines, if they are needed, to help prevent or treat the symptoms of flares (such as pain and swelling in a joint).

In patients with very high urate levels (e.g. those undergoing cancer chemotherapy), treatment with uric acid-lowering medicines could lead to the build-up of xanthine in the urinary tract, with possible stones, even though this has not been observed in patients being treated with FEBUGOOD for Tumor Lysis Syndrome.

Your doctor may ask you to have blood tests to check that your liver is working normally.

Children and adolescents
Do not give this medicine to children under the age of 18 because the safety and efficacy have not been established.

Other medicines and FEBUGOOD
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.
It is especially important to tell your doctor or pharmacist if you are taking medicines containing any of the following substances as they may interact with FEBUGOOD and your doctor may wish to
consider necessary measures:

- Mercaptopurine (used to treat cancer)
- Azathioprine (used to reduce immune response)
- Theophylline (used to treat asthma)

Pregnancy and breast-feeding
It is not known if FEBUGOOD may harm your unborn child. FEBUGOOD should not be used during pregnancy. It is not known if FEBUGOOD may pass into human breast milk. You should not use FEBUGOOD if you are breast feeding, or if you are planning to breastfeed.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Be aware that you may experience dizziness, sleepiness, blurred vision and numbness or

tingling sensation during treatment and should not drive or operate machines if affected.

FEBUGOOD contains lactose
FEBUGOOD tablets contain lactose (a type of sugar). If you have been told that you have an intolerance to some sugars contact your doctor before taking this medicine.

9.3 How to take FEBUGOOD
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- The usual dose is one tablet daily. The back of the blister pack is marked with the days of the week to help you check that you have taken a dose each day.
- The tablets should be taken by mouth and can be taken with or without food.

Gout
FEBUGOOD is available as either an 80 mg tablet or a 120 mg tablet. Your doctor will have prescribed the strength most suitable for you.

Continue to take FEBUGOOD every day even when you are not experiencing gout flare or attack.

Prevention and treatment of high uric acid levels in patients undergoing cancer chemotherapy
FEBUGOOD is available as a 120 mg tablet.
Start taking FEBUGOOD two days before chemotherapy and continue its use according to your doctor's advice. Usually treatment is short-term.

The score line on the 80 mg tablet is only there to help you break the tablet if you have difficulty swallowing it whole.

If you take more FEBUGOOD than you should
In the event of an accidental overdose ask your doctor what to do, or contact your nearest accident and emergency department.

If you forget to take FEBUGOOD
If you miss a dose of FEBUGOOD take it as soon as you remember unless it is almost time for your next dose, in which case miss out the forgotten dose and take your next dose at the normal time. Do not take a double dose to make up for a forgotten dose.

If you stop taking FEBUGOOD
Do not stop taking FEBUGOOD without the advice of your doctor even if you feel better. If you stop taking FEBUGOOD your uric acid levels may begin to rise and your symptoms may worsen due to the formation of new crystals of urate in and around your joints and kidneys.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking this medicine and contact your doctor immediately or go to an emergency department nearby if the following rare (may affect up to 1 in 1,000 people) side effects occur, because a serious allergic reaction might follow:

- anaphylactic reactions, drug hypersensitivity
- potentially life-threatening skin rashes characterised by formation of blisters and shedding of the skin and inner surfaces of body cavities, e.g. mouth and genitals, painful ulcers in the mouth and/or genital areas, accompanied by fever, sore throat and fatigue (Stevens- Johnson Syndrome/ Toxic Epidermal Necrolysis), or by enlarged lymph nodes, liver enlargement, hepatitis (up to liver failure), raising of the white-cells count in the blood (drug reaction with eosinophilia and systemic symptoms-DRESS)
- generalised skin rashes

The common side effects (may affect up to 1 in 10 people) are:

- abnormal liver test results
- diarrhoea
- headache
- rash (including various types of rash, please see below under "uncommon" and "rare" sections)
- nausea
- increase in gout symptoms
- localised swelling due to retention of fluids in tissues (oedema)

Other side effects which are not mentioned above are listed below.

Uncommon side effects (may affect up to 1 in 100 people) are:

- decreased appetite, change in blood sugar levels (diabetes) of which a symptom may be excessive thirst, increased blood fat levels, weight increase
- loss of sex drive
- difficulty in sleeping, sleepiness
- dizziness, numbness, tingling, reduced or altered sensation (hypoaesthesia, hemiparesis or paraesthesia), altered sense of taste, diminished sense of smell (hyposmia)
- abnormal ECG heart tracing, irregular or rapid heartbeats, feeling your heart beat (palpitation)
- hot flushes or flushing (e.g. redness of the face or neck), increased blood pressure, bleeding (hemorrhage, seen only in patients taking chemotherapy for blood disorders)
- cough, shortness of breath, chest discomfort or pain, inflammation of nasal passage and/or throat (upper respiratory tract infection), bronchitis
- dry mouth, abdominal pain/discomfort or wind, heartburn/indigestion, constipation, more frequent passing of stools, vomiting, stomach discomfort
- itching, hives, skin inflammation, skin discoloration, small red or purple spots on the skin, small, flat red spots on the skin, flat, red area on the skin that is covered with small confluent bumps, rash, areas of redness and spots on the skin, other type of skin conditions
- muscle cramp, muscle weakness, pain/ache in muscles/joints, bursitis or arthritis (inflammation of joints usually accompanied by pain, swelling and/or stiffness), pain in extremity, back pain, muscle spasm
- blood in the urine, abnormal frequent urination, abnormal urine tests (increased level of protein in the urine), a reduction in the ability of the kidneys to function properly
- fatigue, chest pain, chest discomfort

- stones in the gallbladder or in bile ducts (cholelithiasis)
- increase in blood thyroid stimulating hormone (TSH) level
- changes in blood chemistry or amount of blood cells or platelets (abnormal blood test results)
- kidney stones
- erectile difficulties

Rare side effects (may affect up to 1 in 1,000 people) are:
- muscle damage, a condition which on rare occasions can be serious. It may cause muscle problems and particularly, if at the same time, you feel unwell or have a high temperature it may be caused by an abnormal muscle breakdown. Contact your doctor immediately if you experience muscle pain, tenderness or weakness
- severe swelling of the deeper layers of the skin, especially around the lips, eyes, genitals, hands, feet or tongue, with possible sudden difficult breathing
- high fever in combination with measles-like skin rash, enlarged lymph nodes, liver enlargement, hepatitis (up to liver failure), raising of the white-cells count in the blood (leukocytosis, with or without eosinophilia)
- reddening of the skin (erythema), rash in various types (e.g. itchy, with white spots, with blisters, with blisters containing pus, with shedding of the skin, measles-like rash), widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes, resulting in exfoliation and possible sepsis (Stevens-Johnson Syndrome/Toxic epidermal necrolysis)
- nervousness
- feeling thirsty
- ringing in the ears
- blurred vision, change in vision
- hair loss
- mouth ulceration
- inflammation of the pancreas: common symptoms are abdominal pain, nausea and vomiting
- increased sweating
- weight decrease, increased appetite, uncontrolled loss of appetite (anorexia)
- muscle and/or joint stiffness
- abnormally low blood cell counts (white or red blood cells or platelets)
- urgent need to urinate
- changes or decrease in urine amount due to inflammation in the kidneys (tubulointerstitial nephritis)
- inflammation of the liver (hepatitis)
- yellowing of the skin (jaundice)
- liver damage
- increased level of creatine phosphokinase in blood (an indicator of muscle damage)

9.5 How to store FEBUGOOD
- Keep this medicine out of the sight and reach of children.
- Store below 30°C. Protect from light and moisture
- Do not use this medicine after the expiry date which is stated on the carton and the tablet blister foil after 'EXP.' The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

9.6 Contents of the pack and other information

What FEBUGOOD contains
The active substance is febuxostat.
Each film coated tablet contains 40, 80 and 120 mg of febuxostat.

The excipients used are Maize starch, Polyvinyl pyrrolidone K30, Microcrystalline cellulose, Crospovidone, Isopropyl alcohol, Croscarmellose sodium, Aerosil, Magnesium stearate, Hypromellose, Polyethylene Glycol 6000, purified Talc, Titanium dioxide, Yellow Oxide of Iron, Dichloromethane, Sunset yellow FCF Lake.

What FEBUGOOD looks like and contents of the pack
FEBUGOOD 40, 80 and 120 are available as blister strip of 10 tablets.

10. Details of manufacturer
Theon Pharmaceuticals Ltd.
Vill. Saini Majra, Tehsil Nalagarh,
Dist. Solan, HP-174 101

11. Details of permission or licence number with date
Licence No. MNB/06/409 issued on date 09.12.2016

12. Date of revision
June 2019

MARKETED BY
torrent PHARMA
TORRENT PHARMACEUTICALS LTD.
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IN/FEBUGOOD 40,80,120 mg/JUN-19/02/PI