Summary of Product Characteristics
Febuxostat Tablets 40 mg (GOUTGESIC 40)

1. Name of the medicinal product
Febuxostat Tablets 40 mg

2. Qualitative and quantitative composition
Each Film coated tablet contains:

Febuxostat	40 mg
Excipients	QS

Approved colour used in coating
For excipients see section 6.1.

3. Pharmaceutical form
Film coated Tablet.
White colour round shaped Film coated Tablet.

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
The recommended oral dose of Febuxostat is 80 mg once daily without regard to food. If serum uric acid is > 6 mg/dL (357 μmol/L) after 2-4 weeks, Febuxostat 120 mg once daily may be considered.
Febuxostat works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks. The therapeutic target is to decrease and maintain serum uric acid below 6 mg/dL (357 μmol/L).
Gout flare prophylaxis of at least 6 months is recommended.

Elderly
No dose adjustment is required in the elderly.

Renal impairment
The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 mL/min.
No dose adjustment is necessary in patients with mild or moderate renal impairment.

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

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 use.
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 listed in section 6.1.

4.4 Special warnings and precautions for use

Cardio-vascular disorders

In patients with pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke or unstable angina), during the development of the product and in one post registrational study (CARES), a higher number of fatal cardiovascular events were observed with febuxostat when compared to allopurinol.

However, in a subsequent post registrational study (FAST), febuxostat was not inferior to allopurinol in the incidence of both fatal and non-fatal cardiovascular events.

Treatment of this patient group should be exercised cautiously and they should be monitored regularly.

Medicinal product allergy / hypersensitivity

Rare reports of serious allergic/hypersensitivity reactions, including life-threatening Stevens-Johnson Syndrome, Toxic epidermal necrolysis and acute anaphylactic reaction/shock, have been collected in the post-marketing experience. In most cases, these reactions occurred during the first month of therapy with febuxostat. Some, but not all of these patients reported renal impairment and/or previous hypersensitivity to allopurinol. Severe hypersensitivity reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) were associated with fever, haematological, renal or hepatic involvement in some cases. Patients should be advised of the signs and symptoms and monitored closely for symptoms of allergic/hypersensitivity reactions. Febuxostat treatment should be immediately stopped if serious allergic/hypersensitivity reactions, including Stevens-Johnson Syndrome, occur since early withdrawal is associated with a better prognosis. If patient has developed allergic/hypersensitivity reactions including Stevens-Johnson Syndrome and acute anaphylactic reaction/shock, febuxostat must not be re-started in this patient at any time.

Acute gouty attacks (gout flare)

Febuxostat treatment should not be started until an acute attack of gout has completely subsided. Gout flares may occur during initiation of treatment due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. At treatment initiation with febuxostat flare prophylaxis for at least 6 months with an NSAID or colchicine is recommended.

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

Xanthine deposition

In patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. As there has been no experience with febuxostat, its use in these populations is not recommended.

Mercaptopurine/azathioprine

Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine as inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of mercaptopurine/azathioprine that could result in severe toxicity.

Where the combination cannot be avoided, a reduction of the dose of mercaptopurine/azathioprine to the 20% or less of the previously prescribed dose is recommended in order to avoid possible haematological effects.

The patients should be closely monitored and the dose of mercaptopurine/azathioprine should be subsequently adjusted based on the evaluation of the therapeutic response and the onset of eventual toxic effects.

Organ transplant recipients

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

Theophylline

Co-administration of febuxostat 80 mg and theophylline 400 mg single dose in healthy subjects showed absence of any pharmacokinetic interaction. Febuxostat 80 mg can be used in patients concomitantly treated with theophylline without risk of increasing theophylline plasma levels. No data is available for febuxostat 120 mg.

Liver disorders

During the combined phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0%). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment.

Thyroid disorders

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

4.5 Interaction with other medicinal products and other forms of interaction

Mercaptopurine/azathioprine

On the basis of the mechanism of action of febuxostat on XO inhibition concomitant use is not recommended. Inhibition of XO by febuxostat may cause increased plasma concentrations of these drugs leading to myelotoxicity.

In case of concomitant administration with febuxostat, the dose of mercaptopurine/azathioprine should be reduced to 20% or less of the previously prescribed dose.

The adequacy of the proposed dose adjustment, which was based on a modelling and simulation analysis from preclinical data in rats, was confirmed by the results of a clinical drug-drug interaction study in healthy volunteers, receiving azathioprine 100 mg alone and a reduced dose of azathioprine (25 mg) in combination with febuxostat (40 or 120 mg).

Drug interaction studies of febuxostat with other cytotoxic chemotherapy have not been conducted. No data is available regarding the safety of febuxostat during other cytotoxic therapy.

Rosiglitazone/CYP2C8 substrates

Febuxostat was shown to be a weak inhibitor of CYP2C8 *in vitro*. In a study in healthy subjects, coadministration of 120 mg febuxostat QD with a single 4 mg oral dose of rosiglitazone had no effect on the pharmacokinetics of rosiglitazone and its metabolite N-desmethyl rosiglitazone, indicating that febuxostat is not a CYP2C8 enzyme inhibitor *in vivo*. Thus, co-administration of febuxostat with rosiglitazone or other CYP2C8 substrates is not expected to require any dose adjustment for those compounds.

Theophylline

An interaction study in healthy subjects has been performed with febuxostat to evaluate whether the inhibition of XO may cause an increase in the theophylline circulating levels as reported with other XO inhibitors. The results of the study showed that the co-administration of febuxostat 80 mg QD with theophylline 400 mg single dose has no effect on the pharmacokinetics or safety of theophylline. Therefore, no special caution is advised when febuxostat 80 mg and theophylline are given concomitantly. No data is available for febuxostat 120 mg.

Naproxen and other inhibitors of glucuronidation

Febuxostat metabolism depends on Uridine Glucuronosyl Transferase (UGT) enzymes. Medicinal products that inhibit glucuronidation, such as NSAIDs and probenecid, could in theory affect the elimination of febuxostat. In healthy subjects concomitant use of febuxostat and naproxen 250 mg twice daily was associated with an increase in febuxostat exposure (Cmax 28%, AUC 41% and t1/2 26%). In clinical studies the use of naproxen or other NSAIDs/Cox-2 inhibitors was not related to any clinically significant increase in adverse events.

Febuxostat can be co-administered with naproxen with no dose adjustment of febuxostat or naproxen being necessary.

Inducers of glucuronidation

Potent inducers of UGT enzymes might possibly lead to increased metabolism and decreased efficacy of febuxostat. Monitoring of serum uric acid is therefore recommended 1-2 weeks after start of treatment with a potent inducer of glucuronidation. Conversely, cessation of treatment of an inducer might lead to increased plasma levels of febuxostat.

Colchicine/indometacin/hydrochlorothiazide/warfarin

Febuxostat can be co-administered with colchicine or indomethacin with no dose adjustment of febuxostat or the co-administered active substance being necessary.

No dose adjustment is necessary for febuxostat when administered with hydrochlorothiazide.

No dose adjustment is necessary for warfarin when administered with febuxostat. Administration of febuxostat (80 mg or 120 mg once daily) with warfarin had no effect on the pharmacokinetics of warfarin in healthy subjects. INR and Factor VII activity were also not affected by the co- administration of febuxostat.

Desipramine/CYP2D6 substrates

Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro.* In a study in healthy subjects, 120 mg febuxostat QD resulted in a mean 22% increase in AUC of desipramine, a CYP2D6 substrate indicating a potential weak inhibitory effect of febuxostat on the CYP2D6 enzyme *in vivo*.

Thus, co-administration of febuxostat with other CYP2D6 substrates is not expected to require any dose adjustment for those compounds.

Antacids

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminium hydroxide has been shown to delay absorption of febuxostat (approximately 1 hour) and to cause a 32% decrease in Cmax, but no significant change in AUC was observed. Therefore, febuxostat may be taken without regard to antacid use.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data on a very limited number of exposed pregnancies have not indicated any adverse effects of febuxostat on pregnancy or on the health of the foetus/new born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition. The potential risk for human is unknown. Febuxostat should not be used during pregnancy.

Breast-feeding

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 breast-feeding.

Fertility

In animals, reproduction studies up to 48 mg/kg/day showed 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

1-10%

Liver function abnormalities (4.6-6.6%)

Rash (0.5-1.6%)

Nausea (1.1-1.3%)

Arthralgia (0.7-1.1%)

>1%
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, hematemesis, 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, urticarial

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 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 increased, prothrombin time prolonged, urinary casts, urine positive for white blood cells and protein.

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antigout preparation, preparations inhibiting uric acid production, ATC code: M04AA03

Mechanism of action

Uric acid is the end product of purine metabolism in humans and is generated in the cascade of hypoxanthine → xanthine → uric acid. Both steps in the above transformations are catalyzed by xanthine oxidase (XO). Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting XO. Febuxostat is a potent, non-purine selective inhibitor of XO (NP-SIXO) with an *in vitro* inhibition Ki value less than one nanomolar. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of XO. At therapeutic concentrations febuxostat does not inhibit other enzymes involved in purine or pyrimidine metabolism, namely, guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase or purine nucleoside phosphorylase.

5.2 Pharmacokinetic properties

In healthy subjects, maximum plasma concentrations (Cmax) and area under the plasma concentration time curve (AUC) of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed for febuxostat. There is no appreciable accumulation when doses of 10 mg to 240 mg are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life (t1/2) of approximately 5 to 8 hours.

Population pharmacokinetic/pharmacodynamic analyses were conducted in 211 patients with hyperuricaemia and gout, treated with febuxostat 40-240 mg QD. In general, febuxostat pharmacokinetic parameters estimated by these analyses are consistent with those obtained from healthy subjects, indicating that healthy subjects are representative for pharmacokinetic/pharmacodynamic assessment in the patient population with gout.

Absorption

Febuxostat is rapidly (tmax of 1.0-1.5 h) and well absorbed (at least 84%). After single or multiple oral 80 and 120 mg once daily doses, Cmax is approximately 2.8-3.2 μg/mL, and 5.0-5.3 μg/mL, respectively. Absolute bioavailability of the febuxostat tablet formulation has not been studied.

Following multiple oral 80 mg once daily doses or a single 120 mg dose with a high fat meal, there was a 49% and 38% decrease in Cmax 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 (80 mg multiple dose). Thus, febuxostat may be taken without regard to food.

Distribution

The apparent steady state volume of distribution (Vss/F) of febuxostat ranges from 29 to 75 L after oral doses of 10-300 mg. The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 80 and 120 mg doses. Plasma protein binding of the active metabolites ranges from about 82% to 91%.

Biotransformation

Febuxostat is extensively metabolized by conjugation *via* uridine diphosphate glucuronosyltransferase (UDPGT) enzyme system and oxidation *via* the cytochrome P450 (CYP) system. Four pharmacologically active hydroxyl metabolites have been identified, of which three occur in plasma of humans. *In vitro* studies with human liver microsomes showed that those oxidative metabolites were formed primarily by CYP1A1, CYP1A2, CYP2C8 or CYP2C9 and febuxostat glucuronide was formed mainly by UGT 1A1, 1A8, and 1A9.

Elimination

Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of 14C-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the active substance (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the faeces as the unchanged febuxostat (12%), the acyl glucuronide of the active substance (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

Renal impairment

Following multiple doses of 80 mg of febuxostat in patients with mild, moderate or severe renal impairment, the Cmax of febuxostat did not change, relative to subjects with normal renal function. The mean total AUC of febuxostat increased by approximately 1.8-fold from 7.5 μg·h/mL in the normal renal function group to 13.2 μg.h/mL in the severe renal dysfunction group. The Cmax and AUC of active metabolites increased up to 2- and 4-fold, respectively. However, no dose adjustment is necessary in patients with mild or moderate renal impairment.

Hepatic impairment

Following multiple doses of 80 mg of febuxostat in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, the Cmax and AUC of febuxostat and its metabolites did not change significantly compared to subjects with normal hepatic function. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

Age

There were no significant changes observed in AUC of febuxostat or its metabolites following multiple oral doses of febuxostat in elderly as compared to younger healthy subjects.

Gender

Following multiple oral doses of febuxostat, the Cmax and AUC were 24% and 12% higher in females than in males, respectively. However, weight-corrected Cmax and AUC were similar between the genders. No dose adjustment is needed based on gender.

5.3 Preclinical safety data

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

Pharmacokinetic modelling and simulation of rat data suggests that, when co-administered with febuxostat, the clinical dose of mercaptopurine/azathioprine should be reduced to 20% or less of the previously prescribed dose in order to avoid possible haematological effects.

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

Mannitol, Microcrystalline Cellulose, Purified Talc, Magnesium Stearate, Crospovidone, Colloidal anhydrous Silica, Polacrillin Potassium (As Kyron-T-314), Hypromellose (E-15), Colour Titanium Dioxide, Polyethylene Glycol (As 6000), Iso Propyl Alcohol & Dichloromethane.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life: 36 months

6.4 Special precautions for storage:

Stored at a temperature not exceeding 30ºC, in a cool and dark place, protect from direct sunlight.

6.5 Nature and contents of container

1 x 10 pack: 10 tablets packed in alu-alu blister and such 1 blister is packed in single carton along with pack insert.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder

Galaxy Vitacare Pvt. Ltd.
B No. 37, Gala No. 1,
Bhiwandi, Thane (Mumbai)
M.S. India.

Manufacturer

Saitech Medicare Pvt. Ltd.
Trilokpur road, Kala-Amb
Dist. Sirmor, Himachal Pradesh (INDIA).