1.6 PRODUCT INFORMATION

1.6.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

GOUTGESIC 80 TABLETS

Active Ingredient(s) (INN or Scientific name): Febuxostat

Dosage Form and sub-form: TABLETS

Strength: 80 mg

Route of Administration: Oral

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film Coated Tablet Contains:

Febuxostat……80 mg

Colour: Titanium Dioxide BP

Batch Size: 0.45 Lac Tablets

S. No.	Ingredients	Label claim mg/Tablet	Specifi-cation	Overage in %	Qty per Tablet (mg)	Qty per batch (kg)	Therapeutic Category
Active Ingredient							
1	Febuxostat	80.0	IH	---	80.0	3.6	Xanthine oxidase inhibitor.
Excipients for Dry Mixing							
2	Lactose	---	BP	---	40.0	1.8	Diluent
3	Microcrystalline cellulose	---	BP	---	53.56	2.41	Excipients
4	Crosscarmellose sodium	---	BP	---	4.00	0.18	Disintegrants
5	Low substituted hydroxypropyl cellulose	---	BP	---	10.00	0.45	Excipient
Excipients for Lubrication							
6	Crosscarmellose sodium	---	BP	---	4.00	0.18	Disintegrants
7	Colloidal silicon dioxide	---	BP	---	2.00	0.09	Glidant
8	Magnesium stearate	---	BP	---	2.00	0.09	Lubricant
Coating Materials							
9	Intacoat IC-U-A05R01962	---	IH	---	7.20	0.324	Colouring agent
10	Isopropyl Alcohol	---	BP	---	43.46	1.956	Solvent
11	Methylene Chloride	---	BP	---	77.37	3.482	Solvent

Abbreviation: BP: British Pharmacopoeia, IH: In House Specification

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the chronic management of hyperuricemia in patients with gout

4.2 Posology and method of administration

For treatment of hyperuricemia in patients with gout, one tablet of Febuxostat-40 daily is recommended. Or two weeks after initiation, if serum uric acid levels are not below 6 mg/dl, the dose can be increased to one tablet of Goutgesic-80 daily, can be taken with or without food. Or As directed by the Physician.

4.3 Method of administration

Oral Administration

Special populations

Renal insufficiency: 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 (creatinine clearance < 30 ml/min)

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.

Elderly: No dose adjustment is required in the elderly.

4.4 Contraindications

Hypersensitivity to the active substance or to any of the Excipients.

GOUTGESIC-80 is contraindicated in patients being treated with azathioprine or mercaptopurine.

4.5 Special warnings and precautions for use

Gout Flare

After initiation of GOUTGESIC-80, an increase in gout flares is frequently observed. This increase is due to reduction in serum uric acid levels, resulting in mobilization of Urate from tissue deposits.

In order to prevent gout flares when GOUTGESIC-80 is initiated, concurrent prophylactic treatment with an NSAID or Colchicine is recommended.

Cardiovascular Events

In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with Febuxostat 40 mg, (0.74 per 100 P-Y [95% Confidence Interval (CI) 0.36-1.37]) than allopurinol (0.60 per 100 P-Y [95% CI 0.16-1.53]). A causal relationship with Febuxostat 40 mg has not been established. Monitor for signs and symptoms of myocardial infraction (MI) and stroke.

Hepatic Effects

There have been post marketing reports of fatal and non-fatal hepatic failure in patients taking Febuxostat, although the reports contain insufficient information necessary to establish the probable cause. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in Febuxostat, and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted.

Obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) as a baseline before initiating Febuxostat.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), GOUTGESIC-80 treatment should be interrupted and investigation done to establish the probable cause. GOUTGESIC-80 should not be restarted in these patients without another explanation for the liver test abnormalities.

Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury and should not be restarted on GOUTGESIC-80. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with GOUTGESIC-80 can be used with caution.

4.6 Paediatric population

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

4.7 Interaction with other medicinal products and other forms of interaction

Febuxostat may increase blood levels of mercaptopurine (Purinethol), azathioprine, and theophylline by reducing their breakdown in the body. Therefore, GOUTGESIC-80 should not be administered with mercaptopurine, azathioprine, and theophylline.

4.8 Additional information on special populations

Geriatric Use

No dose adjustment is necessary in elderly patients. Of the total number of subjects in clinical studies of Febuxostat, 16% were 65 and over, while 4% 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

4.10 Pregnancy and Lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. GOUTGESIC-80 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Nursing Mothers

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 GOUTGESIC-80 is administered to a nursing woman.

4.11 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. As with other xanthine oxidase inhibitors adverse reactions such as somnolence, dizziness and paraesthesia have been reported. Patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that GOUTGESIC does not adversely affect performance**.**

4.12 Undesirable effects

Common reactions to febuxostat include nausea, rash, joint pain, gout flares, and liver problems. Less common side effects include stroke, heart attack, anemia, hepatitis, hypersensitivity, and weight loss.

4.13 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

GOUTGESIC-80, a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. GOUTGESIC-80 is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.

Effect on Uric Acid and Xanthine Concentrations

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

Effect on Cardiac Repolarization

The effect of GOUTGESIC-80 on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy subjects and in patients with gout. GOUTGESIC-80 in doses up to 300 mg daily, at steady-state, did not demonstrate an effect on the QTc interval.

5.2 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. There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) 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 radiolabeled febuxostat following oral dose administration was estimated to be at least 49% (based on total radioactivity recovered in urine). Maximum plasma concentrations of febuxostat occurred between 1 and 1.5 hours post-dose. After multiple oral 40 mg and 80 mg once daily doses, Cmax is approximately 1.6 ± 0.6 mcg/mL (N=30), and 2.6 ± 1.7 mcg/mL (N=227), respectively. Absolute bioavailability of the febuxostat tablet has not been studied.

Following multiple 40 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, GOUTGESIC-80 may be taken without regard to food.

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminium hydroxide with 40 mg single dose of GOUTGESIC-80 has been shown to delay absorption of Febuxostat (approximately one hour) and to cause a 31% decrease in Cmax and a 15% decrease in AUC∞. As AUC rather than Cmax was related to drug effect, change observed in AUC was not considered clinically significant. Therefore, GOUTGESIC-80 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 achieved with 40 mg and 80 mg doses.

Metabolism

Febuxostat is extensively metabolized by both conjugation via uridinediphosphateglucuronosyltransferase (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.

5.3 Preclinical safety data

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

Carcinogenesis, mutagenesis, impairment of fertility:

In male rats, a statistically significant increase in urinary bladder tumours (transitional cell papilloma and carcinoma) was found only in association with xanthine calculi in the high dose group, at approximately 11 times human exposure. There was no significant increase in any other tumour type in either male or female mice or rats. These findings are considered a consequence of species specific purine metabolism and urine composition and of no relevance to clinical use. A standard battery of test for genotoxicity did not reveal any biologically relevant genotoxic effects for febuxostat. Febuxostat at oral doses up to 48 mg/kg/day was found to have no effect on fertility and reproductive performance of male and female rats. There was no evidence of impaired fertility, teratogenic effects, or harm to the foetus due to febuxostat. There was high dose maternal toxicity accompanied by a reduction in weaning index and reduced development of offspring in rats at approximately 4.3 times human exposure. Teratology studies, performed in pregnant rats at approximately 4.3 times and pregnant rabbits at approximately 13 times human exposure did not reveal any teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Lactose
- Microcrystalline cellulose
- Low substituted hydroxypropyl cellulose
- Crosscarmellose sodium
- Colloidal silicon dioxide
- Magnesium stearate
- Instacoat IC-U-A05R01962
- Isopropyl Alcohol

- Methylene chloride BP

6.2 Incompatibilities

None known

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in a dry, well-ventilated place at a temperature not exceeding 30^0C. Protect from light.

6.5 Nature and contents of container

1 Blister of 10 tablets packed in cartons along with Product insert. (1×10's Blisters pack)

7. MARKETING AUTHORISATION HOLDER

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