Summary Product Characteristics (SPC)

1. **Name of the Medicinal Product**
   Fibron 80 mg film coated Tablets

2. **Qualitative and Quantitative Composition**
   Each film coated tablet contains 80 mg of Febuxostat.

3. **Pharmaceutical Form**
   Film coated Tablet

   Excipients with known effects: lactose

4. **Clinical Particulars**

4.1 Therapeutic Indications

Treatment of chronic hyperuricaemia in conditions.

4.2 Posology and Method of administration

The recommended oral dose of is 80 mg once daily without regard to food. If serum uric acid is > 6 mg/dL (357 μmol/L) after 2-4 weeks, 120 mg once daily may be considered.
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.
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. 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 in children aged below the age of 18 years have not been established. No data are available.

Method of administration

Oral use

4.3 Contraindication

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 pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke or unstable angina) should be avoided, unless no other therapy options are appropriate.

Medicinal product allergy / hypersensitivity

Rare reports of serious allergic/hypersensitivity reactions, including lifethreatening 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.

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 toxicity. Drug interaction studies of Febuxostat with drugs (except theophylline) that are metabolized by XO have not been performed in humans.

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, co-administration 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. 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.

4.6 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.

Breastfeeding

It is unknown whether Febuxostat is excreted in human breast milk. Animal studies
this active substance in breast milk and an impaired development of suckling pups. A
cannot be excluded. Febuxostat should not be used while breastfeeding.

Fertility

In animals, reproduction studies up to 48 mg/kg/day showed no dose-dependent ad

4.7 Effects on ability to drive and use machines

Somnolence, dizziness, paraesthesia and blurred vision have been reported with the u
should exercise caution before driving, using machinery or participating in dangerou

4.8 Undesirable effects

Blood and lymphatic system disorders	Rare Pancytopenia, thrombocytopenia, agranulocytosis	
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 Rare Sudden cardiac death
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, liver injury
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 maculopapular, rash papular Rare Toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, drug reaction with eosinophilia and systemic symptoms, generalized rash (serious), erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic, rash erythematous, rash morbillifom, alopecia, hyperhidrosis

Reporting of suspected adverse reactions:

Healthcare professionals are requested to report any suspected adverse reactions via the national Pharmacovigilance Electronic Reporting Systems to the respective national regulatory authorities.

4.9 Overdose

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

5 Pharmacological Properties

5.1 Pharmacodynamic Properties

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 2arylthiazole 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

Bio-Equivalence was done by comparative dissolution profiles with the innovator product.

Absorption

Febuxostat is rapidly (t_{max} of 1.0-1.5 h) and well absorbed (at least 84%). After single or multiple oral 80 and 120 mg once daily doses, C_{max} is approximately 2.83.2 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 C_{max} and a 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).

Distribution

The apparent steady state volume of distribution (V_{ss}/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 ^{14}C-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%).

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 coadministered 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.

6. Pharmaceutical Particulars

6.1 List of Excipients

FLOCEL 101 USP
Hydroxypropyl cellulose BP
Lactose BP
Croscarmellose sodium Dried
Aerosil
Magnesium stearate
FILM COATING
Opadry II Yellow
Composition of Opadry II Yellow:
Polyvinyl alcohol part hydrolyzed USP, FCC, Ph.Eur,JPE
Titanium dioxide USP, FCC, Ph.Eur, JP, ChP, GB
Macrogol USP, FCC, Ph.Eur, JECFA, JP
Purified talc USP, FCC, Ph.Eur, JECFA, JP
Iron oxide yellow JECFA, JPE, NF, ChP

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

2 Years

6.4 Special precautions for storage

Store in a dry place below 30˚C. Protect from light. Keep all medicines out o the reach of children.

6.5 Nature and contents of container PVDC blister pack.

6.6 Instructions for use, handling and disposal No special requirements.

7. MARKETING AUTHORIZATION HOLDER

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9. DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION:

01/December/2022

10. DATE OF REVISION OF TEXT

01/December/2022