SUMMARY OF PRODUCT CHARACTERISTICS

1. **NAME OF THE MEDICINAL PRODUCT: FEBULIV**
(Febuxostat Tablets)

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION:**
Febuliv 40 (Febuxostat Tablets 40 mg)
Each film coated tablet contains:
Febuxostat ….. 40 mg

Febuliv 80 (Febuxostat Tablets 80 mg)
Each film coated tablet contains:
Febuxostat ….. 80 mg

Excipient(s) with known effects:
40 mg: Each tablet contains 58.38 mg of lactose (as monohydrate).
80 mg: Each tablet contains 116.75 mg of lactose (as monohydrate).
For the full list of excipients, see section “Excipients”.

3. **PHARMACEUTICAL FORM:**
Film Coated Tablets
Febuliv 40: White colored, round shaped, biconvex, film coated tablets, plain on both sides.
Febuliv 80: White colored, round shaped, biconvex, film coated tablets with break line on one side & plain on other side.
The score line is not intended for division of the tablet for dose adjustment. The tablet should be swallowed whole.

4. **CLINICAL PARTICULARS:**

4.1 **Therapeutic indications:**
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:**

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 Tablets 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 Tablets in children aged below the age of 18 years have not been established. No data are available.

Method of administration:

For Oral Use

4.3 **Contraindications:**

Hypersensitivity to the active substance or to any of the excipients of the

4.4 **Special warnings and precautions for use:**

Cardio-vascular disorders

Treatment of chronic hyperuricaemia

Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended.

A numerical greater incidence of investigator-reported cardiovascular APTC events (defined endpoints from the Anti-Platelet Trialists' Collaboration (APTC) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was observed in the febuxostat total group compared to the allopurinol group in the APEX and FACT studies (1.3 vs. 0.3 events per 100 Patient Years (PYs)), but not in the CONFIRMS study (see section 5.1 for detailed characteristics of the studies). The incidence of investigator-reported cardiovascular APTC events in the combined Phase 3 studies (APEX, FACT and CONFIRMS studies) was 0.7 vs. 0.6 events per 100 PYs. In the long-term extension studies the incidences of investigator-reported APTC events were 1.2 and 0.6 events per 100 PYs for febuxostat and allopurinol, respectively. No statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure.

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.

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 concomit use is not recommended. Inhibition of XO by febuxostat may cause increas plasma concentrations of these drugs leading to toxicity. Drug interaction studies febuxostat with drugs (except theophylline) that are metabolized by XO have been performed in humans.

Modelling and simulation analysis of data from a pre-clinical study in rats indica that, in case of concomitant administration with febuxostat, the dose mercaptopurine/azathioprine should be reduced to 20% or less of the previou prescribed dose.

Interaction studies of febuxostat with other cytotoxic chemotherapy have not be conducted.

Rosiglitazone/CYP2C8 substrates

Febuxostat was shown to be a weak inhibitor of CYP2C8 in vitro. In a study healthy subjects, coadministration of 120 mg febuxostat QD with a single 4 mg o dose of rosiglitazone had no effect on the pharmacokinetics of rosiglitazone and metabolite N-desmethyl rosiglitazone, indicating that febuxostat is not a CYP2 enzyme inhibitor in vivo. Thus, co-administration of febuxostat with rosiglitazone other CYP2C8 substrates is not expected to require any dose adjustment for th compounds.

Theophylline

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

No data is available for febuxostat 120 mg.

Naproxen and other inhibitors of glucuronidation

Febuxostat metabolism depends on Uridine Glucuronosyl Transferase (UG enzymes. Medicinal products that inhibit glucuronidation, such as NSAIDs a probenecid, could in theory affect the elimination of febuxostat. In healthy subje concomitant use of febuxostat and naproxen 250 mg twice daily was associated w an increase in febuxostat exposure (C_{max} 28%, AUC 41% and $t_{1/2}$ 26%). In clin studies the use of naproxen or other NSAIDs/Cox-2 inhibitors was not related to a clinically significant increase in adverse events.

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

Inducers of glucuronidation

Potent inducers of UGT enzymes might possibly lead to increased metabolism a decreased efficacy of febuxostat. Monitoring of serum uric acid is theref

4.6 Pregnancy and lactation:

Pregnancy

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

Breastfeeding

It is unknown whether febuxostat is excreted in human breast milk. Animal stuc have shown excretion of this active substance in breast milk and an impai development of suckling pups. A risk to a suckling infant cannot be exclud Febuxostat should not be used while breastfeeding.

Fertility

In animals, reproduction studies up to 48 mg/kg/day showed no dose-depend adverse effects on fertility.

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 Tablets does not adversely affect performance.

4.8 Undesirable effects:

Summary of the safety profile

The most commonly reported adverse reactions in clinical trials (4,072 subje treated at least with a dose from 10 mg to 300 mg) and post-marketing experie are gout flares, liver function abnormalities, diarrhoea, nausea, headache, rash a oedema. These adverse reactions were mostly mild or moderate in severity. R serious hypersensitivity reactions to febuxostat, some of which were associate systemic symptoms, and rare events of sudden cardiac death, have occurred in post-marketing experience.

Tabulated list of adverse reactions

Common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,00 <1/1,000) adverse reactions occurring in patients treated with febuxostat are lis below.

The frequencies are based on studies and post-marketing experience in g patients.

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

Table 1: Adverse reactions in combined phase 3, long-term extension studies a post-marketing experience

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, hypoaesthe hyposmia

Ear and labyrinth disorders Rare

Tinnitus

Cardiac disorders Uncommon

Atrial fibrillation, palpitations, ECG abnormal

Rare

Sudden cardiac death*

Vascular disorders Uncommon

4.9 **Overdose:**

Patients with an overdose should be managed by symptomatic and supportive ca

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.

Clinical efficacy and safety

The efficacy of febuxostat was demonstrated in three Phase 3 pivotal studies (the two pivotal APEX and FACT studies, and the additional CONFIRMS study described below) that were conducted in 4101 patients with hyperuricaemia and gout. In each phase 3 pivotal study, febuxostat demonstrated superior ability to lower and maintain serum uric acid levels compared to allopurinol. The primary efficacy endpoint in the APEX and FACT studies was the proportion of patients whose last 3 monthly serum uric acid levels were < 6.0 mg/dL (357 µmol/L). In the additional phase 3 CONFIRMS study, for which results became available after the marketing authorisation for febuxostat was first issued, the primary efficacy endpoint was the proportion of patients whose serum urate level was < 6.0 mg/dL at the final visit. 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 300 mg (n = 258) /100 mg (n = 10) treatment arm in reducing the sUA below 6 mg/dL (357 µmol/L)

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

5.2 **Pharmacokinetic properties:**

In healthy subjects, maximum plasma concentrations (C_{max}) 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 ($t_{1/2}$) 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 (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 2.8-3.2 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 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). Thus, Febuxostat Tablets may be taken without regard to food.

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 hydroxy 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%).

Renal impairment

Following multiple doses of 80 mg of Febuxostat in patients with mild, moderate or severe renal impairment, the C_{max} 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 C_{max} and AUC of active

5.3 Preclinical safety data:

Effects in non-clinical studies were generally observed at exposures in excess o 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:

Core: Lactose Monohydrate, Croscarmellose Sodium, Sodium Lauryl Sulphate Hypromellose, Microcrystalline Cellulose, Colloidal Anhydrous Silica, Magnesium Stearate

Coating: Polyvinyl Alcohol, Titanium Dioxide, Macrogol / PEG and Talc

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

2 years

6.4 Special precautions for storage:

Store below 30°C.

Keep out of reach of children.

6.5 Nature and contents of container:

1. Blister of 10 tablets. Three such blisters are packed in carton along with pack insert.
2. HDPE bottle of 30 Tablets packed in carton along with pack insert.

6.6 Special precautions for disposal:

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

7 **MARKETING AUTHORISATION HOLDER**:
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8 **MARKETING AUTHORISATION NUMBER(S):** NA

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:** NA

10. **DATE OF REVISION OF THE TEXT:**
First Date: 17.03.2021
Revised Date: 06.04.2022
Revised Date: 01.08.2022