Summary of Product Characteristics
(Product Data Sheet)

1.	**Name of the Medical Product**
	1.1 Product Name: **FEBURIC 40** (Febuxostat Tablets 40mg)
	1.2 Strength : **FEBURIC 40** **(Febuxostat Tablets 40mg)** Each film coated tablet contains: Febuxostat 40mg
	1.3 Pharmaceutical Dosage Form : Film Coated Tablets
2.	**Qualitative & Quantitative Composition:** **FEBURIC 40** **(Febuxostat Tablets 40mg)** Each film coated tablet contains: Febuxostat 40mg Colour: Titanium Dioxide For a full list of excipients, see section 6.1 of SmPC
3.	**Pharmaceutical Form:** White to off-white, circular, biconvex, film coated tablets with break line on one side and plain on other side.
4.	**Clinical Particulars**
	4.1 Therapeutic Indications: Febuxostat is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout. Febuxostat is not recommended for the treatment of asymptomatic hyperuricemia.
	4.2 Posology and Method of administration: For treatment of hyperuricemia in patients with gout, Febuxostat is recommended at 40 mg or 80 mg once daily. The recommended starting dose of Febuxostat is 40 mg once daily. For patients who do

	not achieve a serum uric acid (sUA) less than 6 mg/dL after two weeks with 40 mg, Febuxostat 80 mg is recommended. Febuxostat can be taken without regard to food or antacid use. **Special Populations** No dose adjustment is necessary when administering Febuxostat in patients with mild or 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/dL after two weeks with 40 mg, Febuxostat 80 mg is recommended. The dose of Febuxostat is limited to 40 mg once daily in patients with severe renal impairment 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/dL may be performed as early as two weeks after initiating Febuxostat therapy. ***Gout Flares*** Gout flares may occur after initiation of Febuxostat 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 Febuxostat. Prophylactic therapy may be beneficial for up to six months. If a gout flare occurs during Febuxostat treatment, Febuxostat need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient.
	4.3 Contraindications: Hypersensitivity to the active substance or to any of the excipients listed. Febuxostat is contraindicated in patients being treated with azathioprine or mercaptopurine.

4.4 Special warning and precautions for use:

Gout Flare

After initiation of febuxostat, 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 febuxostat 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 (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 has not been established. Monitor for signs and symptoms of myocardial infarction (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), Febuxostat treatment should be interrupted and investigation done to establish the probable cause. Febuxostat 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 febuxostat. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with febuxostat can be used with caution. ***Serious Skin Reactions*** Post-marketing reports of serious skin and hypersensitivity reactions, including Stevens - Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermalnecrolysis (TEN) have been reported in patients taking febuxostat. Discontinue febuxostat if serious skin reactions are suspected. Many of these patients had reported previous similar skin reactions to allopurinol. Febuxostat should be used with caution in these patients.
	4.5 Interactions with other medicinal products and other forms of Interactions : ***Xanthine Oxidase Substrate Drugs*** Febuxostat is an XO inhibitor. Based on a drug interaction study in healthy subjects, febuxostat altered the metabolism of theophylline (a substrate of XO) in humans. Therefore, use with caution when co-administering Febuxostat with theophylline. Drug interaction studies of Febuxostat with other drugs that are metabolized by XO (e.g., mercaptopurine and 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 or mercaptopurine. ***Cytotoxic Chemotherapy Drugs*** Drug interaction studies of febuxostat with cytotoxic chemotherapy have not been conducted. No data are available regarding the safety of febuxostat during cytotoxic chemotherapy. ***In Vivo Drug Interaction Studies*** Based on drug interaction studies in healthy subjects, febuxostat does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide,

	warfarin or desipramine. Therefore, febuxostat may be used concomitantly with these medications.
	4.6 Pregnancy and Lactation: **Pregnancy** *Risk Summary* Limited available data with febuxostat use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. No adverse developmental effects were observed in embryofetal development studies with oral administration of febuxostat to pregnant rats and rabbits during organogenesis at doses that produced maternal exposures up to 40 and 51 times, respectively, the exposure at the maximum recommended human dose (MRHD). No adverse developmental effects were observed in a pre- and postnatal development study with administration of febuxostat to pregnant rats from organogenesis through lactation at an exposure approximately 11 times. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. *Data* Animal Data In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation Days 7 – 17, febuxostat was not teratogenic and did not affect fetal development or survival at exposures up to approximately 40 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation Days 6 – 18, febuxostat was not teratogenic and did not affect fetal development at exposures up to approximately 51 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day). In a pre- and postnatal development study in pregnant female rats dosed orally from gestation Day 7 through lactation Day 20, febuxostat had no effects on delivery or growth and development of offspring at a dose approximately 11 times the MRHD (on an AUC

basis at a maternal oral dose of 12 mg/kg/day).

However, increased neonatal mortality and a reduction in neonatal body weight gain were observed in the presence of maternal toxicity at a dose approximately 40 times the MRHD (on an AUC basis at a maternal oral dose of 48 mg/kg/day).

Febuxostat crossed the placental barrier following oral administration to pregnant rats and was detected in fetal tissues.

Lactation

Risk Summary

There are no data on the presence of febuxostat in human milk, the effects on the breastfed infant, or the effects on milk production. Febuxostat is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for febuxostat and any potential adverse effects on the breastfed child from febuxostat or from the underlying maternal condition.

Data

Animal Data

Orally administered febuxostat was detected in the milk of lactating rats at up to approximately 7 times the plasma concentration.

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% 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 C_{max} and AUC_{24} of febuxostat following multiple oral doses of Febuxostat in geriatric subjects (≥65 years) were similar to those in younger subjects (18 to 40 years).

Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (Cl_{cr} 30 to 89 mL/min). The recommended starting dose of febuxostat is 40 mg once daily. For

patients who do not achieve a sUA less than 6 mg/dL after two weeks with 40 mg, febuxostat 80 mg is recommended. For patients with severe renal impairment (Cl_{cr} 15 to 29 mL/min), the dose of ULORIC is limited to 40 mg once daily

Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); therefore, caution should be exercised in these patients.

Secondary Hyperuricemia

No studies have been conducted in patients with secondary hyperuricemia (including organ transplant recipients); febuxostat is not recommended for use in patients whom the rate of urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). The concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract.

4.7 Effects on ability to drive and use machine:

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:

Most Common Adverse Reactions

In clinical studies, which were six to 12 months in duration, the following adverse reactions were reported by the treating physician as related to study drug. Table 1 summarizes adverse reactions reported at a rate of at least 1% in Febuxostat treatment groups and at least 0.5% greater than placebo**.**

Table 1: Adverse Reactions Occurring in ≥1% of Febuxostat -Treated Patients and at Least 0.5%
Greater than Seen in Patients Receiving Placebo in Controlled Studies

Adverse Reactions	**Placebo**	Febuxostat	**allopurinol ***

	(N=134)	40 mg daily (N=757)	80 mg daily (N=1279)	(N=1277)
Liver Function Abnormalities	0.7%	6.6%	4.6%	4.2%
Nausea	0.7%	1.1%	1.3%	0.8%
Arthralgia	0%	1.1%	0.7%	0.7%
Rash	0.7%	0.5%	1.6%	1.6%

* Of the subjects who received allopurinol, 10 received 100 mg, 145 received 200 mg, and 1122 received 300 mg, based on level of renal impairment.

The most common adverse reaction leading to discontinuation from therapy was liver function abnormalities in 1.8% of febuxostat 40 mg, 1.2% of febuxostat 80 mg, and in 0.9% of allopurinol-treated subjects.

In addition to the adverse reactions presented in Table 1, dizziness was reported in more than 1% of febuxostat -treated subjects although not at a rate more than 0.5% greater than placebo.

Less Common Adverse Reactions

In Phase 2 and 3 clinical studies the following adverse reactions occurred in less than 1% of patients and in more than one subject treated with doses ranging from 40 mg to 240 mg of febuxostat. This list also includes adverse reactions (less than 1% of patients) associated with organ systems.

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

Cardiovascular Safety

Cardiovascular events and deaths were adjudicated to one of the pre-defined endpoints from the Anti-Platelet Trialists' Collaborations (APTC) (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in the randomized controlled and long-term

	extension studies. In the Phase 3 randomized controlled studies, the incidences of adjudicated APTC events per 100 patient-years of exposure were: Placebo 0 (95% CI 0.00-6.16), febuxostat 40 mg 0 (95% CI 0.00-1.08), febuxostat 80 mg 1.09 (95% CI 0.44-2.24), and allopurinol 0.60 (95% CI 0.16-1.53). In the long-term extension studies, the incidences of adjudicated APTC events were: febuxostat 80 mg 0.97 (95% CI 0.57-1.56), and allopurinol 0.58 (95% CI 0.02-3.24). Overall, a higher rate of APTC events is observed in febuxostat than in allopurinol-treated patients. A causal relationship with febuxostat has not been established. Monitor for signs and symptoms of MI and stroke. **Post-marketing Experience** The following adverse reactions have been identified during post approval use of febuxostat. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Blood and Lymphatic System Disorders*: agranulocytosis, eosinophilia. *Hepatobiliary Disorders:* hepatic failure (some fatal), jaundice, serious cases of abnormal liver function test results, liver disorder. *Immune System Disorders:* anaphylaxis, anaphylactic reaction. *Musculoskeletal and Connective Tissue Disorders:* rhabdomyolysis. *Psychiatric Disorders:* psychotic behavior including aggressive thoughts. *Renal and Urinary Disorders:* tubulointerstitial nephritis. *Skin and Subcutaneous Tissue Disorders:* generalized rash, Stevens - Johnson syndrome, hypersensitivity skin reactions, erythema multiforme, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis.
	4.9 Overdosage: 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: **Mechanism of Action** Febuxostat, a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. Febuxostat is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.
	5.2 Pharmacokinetics 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 (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 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 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, febuxosta may be taken without regard to 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 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, febuxostat 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 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 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.
6.	**Pharmaceutical particulars**
	6.1 List of Excipients: Lactose Monohydrate (Granulac 200) USPNF, Microcrystalline Cellulose BP, Low-Substituted Hydroxypropyl Cellulose USPNF, Croscarmellose Sodium USPNF, Sodium Lauryl Sulfate (Kolliphor SLS fine) BP, Colloidal Silicon Dioxide USPNF, Magnesium Stearate BP, Opadry OY-IN-58910 White IH, Isopropyl Alcohol BP, Purified Water IP/BP/USP/Ph.Eur./IH.
	6.2 Incompatibilities: Not applicable
	6.3 Shelf life: 36 months from the date of manufacturer
	6.4 Special Precautions for storage: Store below 30°C. Protect from light.
	6.5 Nature and contents of container: 10 tablets are packed in Alu-Alu blister, 3 such blisters are packed in a carton along with Pack insert.
	6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product, if appropriate : Not applicable
7.	**Marketing Authorization Holder:** Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (West), Mumbai- 400 067, India **Manufacturing Site Address:** Ajanta Pharma Ltd. Plot No. B – 4/5/6, MIDC Industrial Area, Paithan, Aurangabad - 431 148. Maharashtra

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8.	**Registration certificate number(s) :** Not Applicable
9.	**Date of first registration/ re-registration:** Not Applicable
10.	**Date of revision of the SPC's text :** April 30, 2021