5 Part VI: Summary of the risk management plan by product

5.1 Part VI.1 Elements for summary tables in the EPAR

Table 5-1 Part VI.1.1 Summary table of safety concerns

Important identified risks	Serious skin / hypersensitivity reactions
	Rhabdomyolysis
	Drug-drug interaction with azathioprine or mercaptopurine
Important potential risks	Cardio vascular effects
	Hepatic
	Renal events
	Neuropsychiatric events
	Hematological / Bleeding events
	Thyroid events
	Off label use in the pediatric population (TLS specific)
Missing information	Children and adolescents
	Subjects in whom the rate of serum urate formation is greatly increased (eg: malignant disease and its treatment , Lesch-Nyhan Syndrome)
	Organ transplantation
	Severe hepatic impairment
	Pregnancy and lactation
	Limited experience in: female patients, elderly patients, severe renal impairment, moderate hepatic impairment
	Interaction with standard therapy of hematological malignancies (TLS specific)
	Off label use in patients with solid tumors (TLS specific)

Table 5-2 Part VI.1.2 Table of on-going and planned studies in the Post-authorization Pharmacovigilance Development Plan

None

Table 5-3 Part VI.1.3 Summary of Post authorization efficacy development plan

None

Table 5-4 Part VI.1.4 Summary table of risk minimization measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Serious skin / hypersensitivity reactions	Guidance is provided in the following sections of the SmPC: 4.3 Contraindications, 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects.	None
Rhabdomyolysis	Guidance is provided in section 4.8 of the	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	SmPC	
Drug-drug interaction with azathioprine or mercaptopurine	Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction	None
Cardio vascular effects	Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects.	None
Hepatic events	Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, 4.8 Undesirable effects, and 5.2 Pharmacokinetic properties.	None
Renal events	Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, 4.8 Undesirable effects, 5.1 Pharmacodynamic properties, 5.2 Pharmacokinetic properties and 5.3 Preclinical safety data.	None
Neuropsychiatric events	Guidance is provided in the following sections of the SmPC: 4.7 Effects on ability to drive and use machines, and 4.8 Undesirable effects.	None
Hematological / Bleeding events	Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects.	None
Thyroid events	Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects.	None
Children and adolescents	Guidance is provided in the section 4.2 Posology and method of administration of the SmPC	None
Off label use in the pediatric population (TLS specific)	Guidance is provided in the following sections of the SmPC: 4.1 Therapeutic indications and 4.2 Posology and method of administration	None
Subjects in whom the rate of serum urate formation is greatly increased (e.g: malignant disease and its treatment, Lesch-Nyhan Syndrome)	Guidance is provided in the following sections of the SmPC: 4.1 Therapeutic indications 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	None
Organ transplantation	Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, and 5.1	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Pharmacodynamic properties.	
Severe hepatic impairment	Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties.	None
Pregnancy and lactation	Guidance is provided in the following sections of the SmPC: 4.6 Fertility, pregnancy and lactation, and 5.3 Preclinical safety data.	None
Limited experience in: female patients, elderly patients, severe renal impairment, moderate hepatic impairment.	Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration, 5.1 Pharmacodynamic properties, 5.2 Pharmacokinetic properties, 5.3 Preclinical safety data.	None
Interaction with standard therapy of hematological malignancies (TLS specific)	Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.1 Pharmacodynamic properties	None
Off label use in patients with solid tumors (TLS specific)	Guidance is provided in section 4.1 Therapeutic indications of the SmPC.	None

5.2 Part VI.2 Elements for a Public Summary

5.2.1 Part VI.2.1 Overview of disease epidemiology

5.2.1.1 Treatment of high blood levels of uric acid in conditions where deposition has already occurred (including a history or presence of gout)

Febuxostat 80 mg is used to treat gout (type of arthritis), which is associated with an excess of a chemical called uric acid (urate) in the joints or soft tissues [Woods, 2010]. The frequency of gout varies across the globe, with an estimated frequency of 1% to 4% in North America and Western Europe. The frequency of gout increases with age in all countries; frequency in men is higher than in women, at a ratio of 3 to 4:1 [Gadol, 2015]. Looking at a certain time period, it has been estimated that 6.1 million people in the United States experience gout during their lifetime, and studies in the United Kingdom have reported a frequency approaching 7% [Baker, 2010].

5.2.1.2 Prevention and treatment of high blood levels of uric acid that may occur during chemotherapy for blood cancers in adult patients at risk of Tumor Lysis Syndrome (TLS).

When chemotherapy is given, cancer cells are destroyed, and uric acid levels increase in the blood (hyperuricemia), unless the formation of uric acid is prevented. Hyperuricemia and its associated complications are the most frequently recognized manifestations of tumor lysis syndrome (a group of metabolic abnormalities that can occur as a complication due to destruction of tumor cells) [Hochberg, 2008]. The frequency of TLS varies greatly depending on the underlying tumor. The tumors that begin in the cells of blood-forming tissue, carry the greatest risk. Among adults, TLS is commonly seen after treatment for leukemia (cancer in the bone marrow) and Burkitt's lymphoma (cancer of the lymphatic system). Males and females of any age or ethnic group can be affected. Advanced age may increase the risk of developing TLS due to reduced kidney filtration function rate [Wilson and Berns, 2014].

5.2.2 Part VI.2.2 Summary of treatment benefits

Febuxostat is the first drug approved and marketed for the treatment of gout and is a new option for treating excess of uric acid in the blood and gout, in patients who are unable to use or tolerate allopurinol.

A Febuxostat versus Allopurinol clinical study was conducted in 762 patients to compare the safety and efficacy of febuxostat 80 mg/120 mg with that of allopurinol 300 mg. A higher number of patients treated with febuxostat reached normal values of urate levels in blood (6 mg/dL) in comparison with allopurinol.

An efficacy study of Febuxostat compares the efficacy and safety of febuxostat (80, 120, or 240 mg), allopurinol (100 or 300 mg), and placebo (drug without effect) in 1,072 patients with normal and impaired kidney function. Higher and significant number of patients with blood urate levels of below 6 mg/dL were observed with febuxostat than with allopurinol or placebo.

The efficacy and safety of Oral Febuxostat 80 mg, 40 mg in 2,269 subjects with Gout compares daily febuxostat with allopurinol 300 mg. Urate-lowering efficacy was greater in 80 mg dose when compared to both 40 mg dose and allopurinol [Woods, 2010].

5.2.3 Part VI.2.3 Unknowns relating to treatment benefits

The efficacy of febuxostat has not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 mL/min).

The efficacy of febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh Class C) and limited information is available in patients with moderate hepatic impairment.

The efficacy of febuxostat in children below the age of 18 years has not been established.

The effect of febuxostat on human fertility is unknown.

There has been no experience of febuxostat in organ transplant recipients.

The efficacy and safety of febuxostat has not been established in patients with severe TLS, e.g. in patients who failed on other urate lowering therapies.

5.2.4 Part VI.2.4 Summary of safety concerns

Table 5-5 Important identified risks

Risk	What is known	Preventability
Serious skin and allergic reactions (Serious skin / hypersensitivity reactions)	Side effects which are uncommon may affect up to 1 to 100 people include dermatitis (inflammation of the skin), urticaria (appearance of wheals), pruritus (sensation of itching), skin discoloration, skin lesion, petechial (pertaining to tiny red or purple spots on the skin), rash macular (skin eruption in which the lesions are flat), rash maculopapular (characterized by a flat, red area on the skin that is covered with small bumps) and rash papular (skin eruption or reaction consisting of small, round, raised bumps that have clear borders). Side effects which are rare and may affect up to 1 in 1000 people include anaphylactic reactions, drug hypersensitivity, potentially life-threatening skin rashes characterized by formation of blisters and shedding of the skin and inner surfaces of body cavities, e.g. mouth and genitals, painful ulcers in the mouth and/or	Patient should not take febuxostat if they are allergic to febuxostat or any other ingredient of this medicine. Before taking febuxostat, doctor should be informed if the patient have or have had any serious allergic reaction to allopurinol (a medication used for the treatment of Gout). Doctor should be informed if the patient experiences any of the mentioned symptoms, so that the doctor might decide to permanently stop the treatment with febuxostat. If the patient develops potentially life-threatening skin rashes (Stevens-Johnson Syndrome) with the use of febuxostat, then the patient must not be re-started on febuxostat at any point of time.

Risk	What is known	Preventability
	genital areas, accompanied by fever, sore throat and fatigue (Stevens- Johnson Syndrome/ Toxic Epidermal Necrolysis), or by enlarged lymph nodes, liver enlargement, hepatitis (up to liver failure), raising of the white-cells count in the blood (drug reaction with eosinophilia and systemic symptoms-DRESS), possible sepsis, and also serious life threatening allergic conditions with cardiac and circulatory arrest.	If the patient develops any rash or any other skin symptoms, then immediate advice from the doctor should be taken and the doctor should be informed regarding the use of febuxostat. Patient should stop taking this medicine and contact the doctor immediately or visit an emergency department nearby if the mentioned side effects occur.
Disintegration of muscle fibers with excretion of myoglobin in the urine (Rhabdomyolysis)	Adverse reactions which are rare and may affect up to 1 in 1000 people include muscle damage. Febuxostat may cause muscle problems and particularly, if at the same time, the patient experiences a high temperature. These symptoms may be caused by an abnormal muscle breakdown.	Patients should contact their doctor immediately if they experience muscle pain, tenderness or weakness.
Drug-drug interaction with medication used to reduce immune response and to treat cancer called azathioprine and mercaptopurine respectively. (Drug-drug interaction with azathioprine or mercaptopurine)	Febuxostat may cause increased plasma concentrations of medications used to reduce immune response such as azathioprine leading to toxicity. Drug interaction studies of febuxostat with cytotoxic (substances which are destructive to cells) chemotherapy have not been conducted. No data is available regarding the safety of febuxostat during cytotoxic therapy.	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. It is especially important to tell your doctor or pharmacist if you are taking medicines containing any of the following substances as they may interact with febuxostat and your doctor may wish to consider necessary measures: • Mercaptopurine (used to treat cancer) • Azathioprine (used to reduce immune response) Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine. Where the combination cannot be avoided patients should be closely monitored. A reduction of dosage of mercaptopurine or azathioprine is recommended in order to avoid possible responses on blood cells.

Table 5-6 Important potential risks

Risk	What is known
Side-effects of heart and blood vessels (Cardiovascular effects)	Treatment with febuxostat in patients with any heart disease or heart failure is not recommended. Before taking febuxostat, doctor should be informed regarding the history of any heart failure or heart problems. Side effects which are uncommon and may affect up to 1 in 100 people include abnormal ECG heart tracing, irregular or rapid heartbeats, feeling one's own heart beat (palpitation), chest pain and chest discomfort.
Liver effects (Hepatic events)	Before taking febuxostat, doctor should be informed regarding the history of any liver disease or liver function test abnormalities and the doctor might advise the patient to undergo blood tests to ensure that the liver is working properly. Side effects of febuxostat which are common and may affect up to 1 in 10 people include abnormal liver test results. Side effects which are rare and may affect up to 1 in 1000 people include yellowing of the skin (jaundice), liver enlargement, inflammation of the liver (up to liver failure) and liver damage. Limited information is available in patients with moderate liver damage and no studies have been conducted in patients with severe liver damage.
Effects on kidney due to the use of drug (Renal events)	Patient should not stop taking febuxostat without the advice of the doctor even if feeling better as it might lead to rise in uric acid levels and the symptoms may worsen due to the formation of new crystals of urate in and around your joints and kidneys. No dose adjustment is necessary in patients with mild or moderate kidney damage. Side effects which are uncommon and may affect up to 1 in 100 people include blood in the urine, abnormal frequent urination, abnormal urine tests (increased level of proteins in the urine), a reduction in the ability of the kidneys to function properly and kidney stones. Side effects which are rare and may affect up to 1 in 1000 people include urgent need to urinate, changes or decrease in urine amount due to inflammation in the kidneys (tubulointerstitial nephritis).
Drug induced side effects on brain, spine and the nerves that connect them including mental illness (Neuropsychiatric events)	Patient might experience dizziness, sleepiness, blurred vision and numbness or tingling sensation during treatment and should not drive or operate machines if affected. Side effects which are uncommon and may affect up to 1 in 100 people include dizziness, numbness, tingling, reduced or altered sensation (hypoesthesia, hemiparesis or paresthesia), altered or

Risk	What is known
	reduced sense of taste (hyposmia), difficulty in sleeping, sleepiness and loss of sex drive.
Drug induced disorders of blood and its components / Bleeding events (Hematological / Bleeding events)	Side effects which are uncommon and may affect up to 1 in 100 people include changes in blood chemistry or amount of blood cells or platelets (abnormal blood test results). Additionally, bleeding (hemorrhage) may be seen in patients taking chemotherapy for blood disorders. Side effects which are rare and may affect up to 1 in 1000 people include abnormally low blood cell counts (white or red blood cells or platelets). Patient should inform the doctor or pharmacist if he/she is taking medicines containing mercaptopurine (used to treat cancer) and azathioprine (used to reduce immune response) as they may interact with febuxostat and the doctor may wish to consider necessary measures to avoid possible hematological effects.
Drug induced fluctuation in releasing hormones by thyroid gland (Thyroid events)	Before taking febuxostat, doctor should be informed if the patient has any thyroid problems. Caution is required when febuxostat is used in patients with alteration of thyroid function. Side effects which are uncommon and may affect up to 1 in 100 people include increase in blood TSH level.
Not approved use of febuxostat in children with tumor lysis syndrome (Off label use in the pediatric population (TLS specific))	This medicine should not be used in children under the age of 18 because the safety and efficacy have not been established.

Table 5-7 Missing information

Risk	What is known
Children and adolescents	This medicine should not be used in children under the age of 18 because the safety and efficacy have not been established.
Safety in patients in whom the rate of serum urate formation is greatly increased (eg: Lesch-Nyhan Syndrome, an inherited disorder with high uric acid in blood, or malignant disease and its treatment) (Subjects in whom the rate of serum urate formation is greatly increased (e.g: malignant disease and its treatment, Lesch-Nyhan Syndrome))	In patients with very high urate levels (e.g. those undergoing cancer chemotherapy), treatment with uric acid-lowering medicines could lead to the build-up of xanthine in the urinary tract, with possible stones, even though this has not been observed in patients being treated with febuxostat for Tumor Lysis Syndrome (a group of metabolic abnormalities that can occur as a complication during the treatment of cancer). As there has been no experience with febuxostat, its use in patients with Lesch-Nyhan Syndrome is not recommended.
Organ transplantation	As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended
Pregnancy and lactation	It is not known if febuxostat may harm your unborn child.

Risk	What is known
	Febuxostat should not be used during pregnancy. It is not known if febuxostat may pass into human breast milk. Patient should not use febuxostat during breast feeding, or if planning to breastfeed. Advice must be taken from doctor or pharmacist before taking febuxostat if the patient is pregnant or breast-feeding, think might be pregnant or planning to have a baby.
Limited experience of the use of febuxostat in women, elderly patients, patients with severe kidney and moderate liver damage (Limited experience in: female patients, elderly patients, severe renal impairment, moderate hepatic impairment)	There are limited data on the efficacy and safety of febuxostat in female patients, elderly patients and patients with kidney and liver damage. Limited information is available in patients with moderate liver impairment. Patients should talk to their doctor if they have or have had renal disease and / or liver disease or liver function test abnormalities
Interaction with therapies for types of cancer that affect blood, bone marrow and lymph nodes (specifically metabolic abnormalities during chemotherapy) (Interaction with standard therapy of hematological malignancies (TLS specific))	No data are available on interactions of febuxostat with medications used in the treatment of cancer that affect blood, bone marrow and lymph nodes, like leukemia or lymphoma.
Not approved use in patients with malignant and abnormal mass of tissue (specifically metabolic abnormalities during chemotherapy) (Off label use in patients with solid tumors (TLS specific))	No data are available on the not approved use of febuxostat in patients with tumors which form a discrete mass for the prevention or treatment of high blood levels of uric acid that may occur when a patient gets chemotherapy. (When chemotherapy is given, cancer cells are destroyed, and uric acid levels increase in the blood accordingly, unless the formation of uric acid is prevented.)

5.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

5.2.6 Part VI.2.6 Planned post authorization development plan

None

5.2.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

N/A (first submission).