Febuxostat

VI.1 Elements for summary tables in the European Public Assessment Report (EPAR)

VI.1.1 Summary table of Safety concerns

Table 22 Summary table of safety concerns

Summary of safety concerns	
Important identified risks	- Serious skin / hypersensitivity reactions[1] - Rhabdomyolysis[1] - Drug-drug interaction with azathioprine or mercaptopurine[1]
Important potential risks	- Cardiovascular events[1] - Hepatic events[1] - Renal events[1] - Neuropsychiatric events[1] - Haematological / Bleeding events[1] - Thyroid events[1] - Off label use in the paediatric population (TLS specific)
Missing information	- Children and adolescents[1] - Subjects in whom the rate of serum urate formation is greatly increased (eg, malignant disease and its treatment, Lesch-Nyhan syndrome) [1] - Organ transplantation[1] - Severe hepatic impairment[1] - Pregnancy and lactation[1] - Limited experience in: female patients, elderly patients, severe renal impairment and moderate hepatic impairment - Interaction with standard therapy of haematological malignancies (TLS specific) - Off label use in patients with solid tumors (TLS specific)

VI.1.2. Table of on-going and planned studies in the post-authorization pharmacovigilance development plan

Not applicable.

VI.1.3. Summary of post-authorisation efficacy development plan

Not applicable.

VI.1.4. Summary table of risk minimisation measures

Table 17 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Serious skin / hypersensitivity reactions	This risk is included in sections 4.4 and 4.8 of the SmPC and in sections 2 and 4 of the PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Rhabdomyolysis	This risk is included in section 4.8 of the SmPC and in section 4 of the PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Drug-drug interaction with azathioprine or mercaptopurine	This risk is included in sections 4.4 and 4.5 of the SmPC and in section 2 of the PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Cardiovascular events	This risk is included in sections 4.4 and 4.8 of the SmPC and in sections 2 and 4 of the PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Hepatic events	This risk is included in sections 4.4 and 4.8 of the SmPC and in sections 2 and 4 of the PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Renal events	This risk is included in sections 4.4 and 4.8 of the SmPC and in section 4 of the PIL. Other routine risk minimisation measures:	None proposed

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	Prescription only medicine.	
Neuropsychiatric events	This risk is included in section 4.8 of the SmPC and in section 4 of the PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Haematological/ Bleeding events	This risk is included in sections 4.4 and 4.8 of the SmPC and in section 4 of the PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Thyroid events	This risk is included in sections 4.4 and 4.8 of the SmPC and in sections 2 and 4 of the PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Off label use in the paediatric population (TLS specific)	This risk is not included in or PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Children and adolescents	This risk is included in section 4.2 of the SmPC and in section 2 of the PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Subjects in whom the rate of serum urate formation is greatly increased (eg, malignant disease and its treatment, Lesch-Nyhan syndrome)	This risk is included in section 4.4 of the SmPC and in section 2 of the PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Organ transplantation	This risk is included in section 4.4 of the SmPC. Other routine risk minimisation measures: Prescription only medicine.	None proposed

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Severe hepatic impairment	This risk is included in sections 4.2 and 5.2 of the SmPC and in section 2 of the PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Pregnancy and lactation	This risk is included in section 4.6 and 5.3 of the SmPC and in section 2 of the PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Limited experience in: female patients, elderly patients, severe renal impairment and moderate hepatic impairment	This risk is included in section 4.2 of the SmPC. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Interaction with standard therapy of haematological malignancies (TLS specific)	This risk is included in section 4.4 of SmPC. Other routine risk minimisation measures: Prescription only medicine.	None proposed
Off label use in patients with solid tumors (TLS specific)	This risk is not included in SmPC or PIL. Other routine risk minimisation measures: Prescription only medicine.	None proposed

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Febuxostat is a medicine used in adults with gout to reduce high levels of uric acid in the blood. Gout results from a build-up of uric acid crystals in and around the joints, especially in the toes, which causes pain and swelling. Lowering the level of uric acid in the blood can prevent the formation of uric acid crystals and reduce uric acid deposits.

Gout is the most common inflammatory arthritis globally. The frequency of gout worldwide has increased in the last decades. This might be related to an increase of obesity, sugar drinks and alcohol intake. Gout is estimated to be 4 times more frequent in men than women and, in general, increases with age.

Tumor Lysis Syndrome (TLS) is the most common disease-related emergency encountered by physicians caring for patients with haematologic cancers. It represents a critical and possibly fatal complication resulting from the rapid lysis of large numbers of tumour cells, observed most often after initial treatment with chemotherapy.

Febuxostat is indicated for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS).

VI.2.2 Summary of treatment benefits

The efficacy of febuxostat was demonstrated in different studies, that were conducted in 4101 patients with excess of uric acid in the blood (hyperuricaemia) and gout. In each study, febuxostat demonstrated superior ability to lower and maintain uric acid levels in the blood compared to allopurinol.

The safety and efficacy of febuxostat 40 mg and 80 mg was evaluated, in comparison with allopurinol 300 mg or 200 mg, in patients with gout and excess of uric acid in the blood (hyperuricaemia). Two thousand and two hundred and sixty-nine (2269) patients were treated: Febuxostat 40 mg once daily (n=757), febuxostat 80 mg once daily (n=756), or allopurinol 300/200 mg once daily (n=756). At least 65% of the patients had mild to moderate kidney insufficiency (with creatinine clearance of 30-89 mL/min). Treatment against gout flares was compulsory over the 26-week period.

Febuxostat at a dose of 120mg per day is an acceptable therapeutic option in the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of TLS.

The Phase III pivotal study showed that febuxostat is superior over allopurinol in terms of reduction of sUA (a well-established surrogate endpoint for TLS and renal impairment), in patients undergoing chemotherapy for haematological malignancies at intermediate to high risk of TLS. Moreover, results of this trial provide evidence that febuxostat is effective in preserving renal function.

The efficacy profile of febuxostat is maintained regardless of baseline hyperuricaemia (sUA level >7.5 mg/dL), creatinine level, type of HM, ECOG PS score and TLS risk grade as confirmed by the exploratory

analyses performed in subpopulations of patients with different baseline characteristics.

A significantly higher sUA reduction compared to allopurinol is achieved after only 24 hours, which is a relevant factor in the prevention of urate-nephropathy, especially in patients in whom chemotherapy cannot be delayed.

VI.2.3 Unknowns relating to treatment benefit

The safety and efficacy of febuxostat in adolescents below 18 years, pregnancy and lactation, patients in whom serum urate formation is increased, organ transplantation and patients with severe liver impairment has not yet been established. No data is available. Limited experience is available in : female patients, elderly patients, patients with severe kidney impairment and moderate liver impairment.

Interaction with standard therapy of haematological malignancies (TLS specific) and off label use in patients with solid tumors (TLS specific) has not yet been established.

VI.2.4 Summary of safety concerns

Table 24 Important identified risks

Important Identified Risk	What is known	Preventability
Serious skin or allergic reactions	Serious allergic reactions (anaphylactic reactions), drug allergy and skin rashes may affect up to 1 in 1,000 people.	Stop taking this medicine and contact your doctor immediately or go to an emergency department nearby you. Febuxostat should not be used in patients with previous allergy to this active substance.
Abnormal muscle breakdown (Rhabdomyolysis)	A muscle damage, a condition which on rare occasions (may affect up to 1 in 1,000 people) can be serious. It may cause muscle problems and particularly, if at the same time, you feel unwell or have a high temperature it may be caused by an abnormal muscle breakdown.	Contact your doctor immediately if you experience muscle pain, tenderness or weakness.
Drug-drug interaction with azathioprine or	The following substances may interact with febuxostat and	Tell your doctor or pharmacist if you are taking, have recently

Important Identified Risk	What is known	Preventability
mercaptopurine	your doctor may wish to consider necessary measures: • Mercaptopurine (used to treat cancer) • Azathioprine (used to reduce immune response)	taken or might take any other medicines, such as mercaptopurine, azathioprine, including medicines obtained without a prescription.

Table 18 Important potential risks

Important potential risks	What is known
Heart problems (Cardiovascular events)	Uncommon side effects (may affect up to 1 in 100 people) are: abnormal ECG heart tracing, irregular or rapid heartbeats, feeling your heart beat (palpitation). Talk to your doctor before taking febuxostat, if you have or have had heart failure or heart problems.
Liver problems (Hepatic events)	Rare side effects (may affect up to 1 in 1,000 people): Liver enlargement, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver damage. Common side effects (may affect up to 1 in 10 people): abnormal liver test results. If any of these signs occur, stop taking this medicine and consult your doctor immediately or go to an emergency department nearby you.
Kidney problems (Renal events)	Uncommon side effects (may affect up to 1 in 100 people) are: 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, kidney stones. Rare side effects (may affect up to 1 in 1,000 people) are: Changes or decrease in urine amount due to inflammation in the kidneys (tubulointerstitial nephritis). Stop taking this medicine and contact your doctor immediately or go to an emergency department nearby if the any of these signs occurred.
Neuropsychiatric events	Uncommon side effects (may affect up to 1 in 100 people) are: Difficulty in sleeping, sleepiness, dizziness, numbness, tingling, reduced or altered sensation (hypoesthesia, hemiparesis or paraesthesia), altered or reduced sense of taste (hyposmia). Contact your doctor immediately if you experience such events.

Important potential risks	What is known
Haematological / Bleeding events	Rare blood cells abnormalities such as thrombocytopenia (decreased number of platelets) and eosinophilia (increased number of eosinophils), and single or multiple organ involvement.
Thyroid events	Uncommon side effects (may affect up to 1 in 100 people) are: Increase in blood thyroid stimulating hormone (TSH) level. Talk to your doctor before taking febuxostat, if you have thyroid problems.
Off label use in the paediatric population (TLS specific)	No studies available at the moment.

Table 19 Missing information

Missing information	What is known
Children and adolescents	Do not give this medicine to children under the age of 18 because the safety and efficacy have not been established.
Subjects in whom the rate of serum urate formation is greatly increased (eg, 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.
Organ transplantation	As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended.
Severe liver impairment	The efficacy and safety of febuxostat has not been studied in patients with severe liver impairment (Child Pugh Class C).
Pregnancy and lactation	It is not known if febuxostat may harm your unborn child. Febuxostat should not be used during pregnancy. It is not known if febuxostat may pass into human breast milk. You should not use febuxostat if you are breast feeding, or if you are planning to breastfeed. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
Limited experience in: female patients,	The efficacy and safety have not been fully evaluated in

Missing information	What is known
elderly patients, severe renal kidney impairment and moderate hepatic liver impairment	patients with severe renal kidney impairment. Limited information is available in patients with moderate hepatic liver impairment.
Interaction with standard therapy of haematological malignancies (TLS specific)	Patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome should be under cardiac monitoring as clinically appropriate.
Off label use in patients with solid tumors (TLS specific)	No studies available at the moment.

VI.2.5 Summary of additional risk minimisation measures by safety concern

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

The Summary of Product Characteristics and the Package leaflet for febuxostat can be found on the web pages of the national competent authorities in the EU.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

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

Version	Date	Safety Concerns	Comment
1.0	26/July/2017	*Important identified risks* - Serious skin/ hypersensitivity reactions - Rhabdomyolysis - Drug-drug interaction with azathioprine or mercaptopurine	Initial version for authorisation procedure

Version	Date	Safety Concerns	Comment
		Important potential risks - Cardiovascular events - Hepatic events - Renal events - Neuropsychiatric events - Haematological/ bleeding events - Thyroid events *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 severe renal impairment and moderate hepatic impairment	
2.0	21/03/2018	*Important identified risks* - Serious skin/ hypersensitivity reactions - Rhabdomyolysis - Drug-drug interaction with azathioprine or mercaptopurine *Important potential risks* - Cardiovascular events - Hepatic events - Renal events - Neuropsychiatric events - Haematological/ bleeding events - Thyroid events - Off label use in the paediatric population (TLS specific) *Missing information* - Children and adolescents - Subjects in whom the rate of serum urate formation is greatly increased	

Version	Date	Safety Concerns	Comment
		(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 and moderate hepatic impairment - Interaction with standard therapy of haematological malignancies (TLS specific) - Off label use in patients with solid tumors (TLS specific)	
3.0	21/08/2018	- Update day 120: Inclusion of "female patients, elderly patients"; "drug interactions" was removed; "DSG was removed". Inclusion of Annex 7: especific follow-up forms forcutaneous adverse reactions and hepatic events	
4.0	28/09/2018	- Update day 180: The requested follow-up forms for cutaneous adverse reactions and hepatic events to be able to gather more detailed information on the case reports are not routine risk minimisation measures but are routine pharmacovigilance measures and have be included as such in the RMP in line with the RMP of the reference product.	