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.

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.

The proportion of patients with serum urate levels of < 6.0 mg/dL (357 µmol/L) at the final visit was 45% for 40 mg febuxostat, 67% for febuxostat 80 mg and 42% for allopurinol 300/200 mg, respectively. Several studies have been conducted on the efficacy of DSG show pregnancy failures around 1% per year. Only 3 pregnancies were reported in 13,290 women followed-up for almost 75,000 cycles, for the monophasic preparation. Others reported no pregnancies for the triphasic preparation in a study, involving 639 women followed-up for more than 3,000 cycles. Also 3 pregnancies were reported in 193 women who were followed-up for 6 months.

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 patients with severe kidney impairment and moderate liver impairment.

VI.2.4 Summary of safety concerns Table

21 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	Contact your doctor immediately if you experience muscle pain, tenderness or weakness.

Important Identified Risk	What is known	Preventability
	muscle breakdown.	
Drug-drug interaction with azathioprine or mercaptopurine	The following substances may interact with febuxostat and your doctor may wish to consider necessary measures: Mercaptopurine (used to treat cancer) Azathioprine (used to reduce immune response)	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, such as mercaptopurine, azathioprine, including medicines obtained without a prescription.

Table 22 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

Important potential risks	What is known
	(hypoesthesia, hemiparesis or paraesthesia), altered or reduced sense of taste (hyposmia). Contact your doctor immediately if you experience such events.
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.

Table 23 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.

Missing information	What is known
Limited experience in severe renal kidney impairment and moderate hepatic liver impairment	The efficacy and safety have not been fully evaluated in patients with severe renal kidney impairment. Limited information is available in patients with moderate hepatic liver impairment.

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 in the 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 *Important potential risks* - Cardiovascular events - Hepatic events - Renal events - Neuropsychiatric events - Haematological/ bleeding events - Thyroid events	Initial version for authorisation procedure

Version	Date	Safety Concerns	Comment
		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	