VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Gout is the most common cause of inflammatory arthritis worldwide. In the United Kingdom (UK), epidemiological studies in general practice have shown the prevalence of gout per 1000 to have been steadily increasing from 2.6 in 1975, 3.4 in 1987, to 9.5 in 1993. More recent work has shown that incidence and prevalence were both significantly higher in 2012 than 1997, with a 63.9% increase in prevalence and 29.6% increase in incidence over this period. It is found predominantly in middle-aged-to-elderly men

VI.2.2 Summary of treatment benefits

Febuxostat was more effective than allopurinol and placebo in treating hyperuricaemia by reducing blood uric acid levels. In the first study, 48% of the patients taking 80 mg Febuxostat once a day (126 out of 262) and 65% of the patients taking 120 mg once a day (175 out of 269) had levels of uric acid below 6 mg/dl in the final three measurements. This was compared with 22% of the patients taking allopurinol (60 out of 268) and none of the 134 patients taking placebo. Similar results were seen in the second study after a year.

In patients with blood cancer who were undergoing chemotherapy, Febuxostat was as effective as allopurinol in controlling blood levels of uric acid: in 98.3 % of patients (170 out of 173) on Febuxostat blood levels of uric acid normalised compared with 96 % (166 out of 173) of patients on allopurinol.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of Febuxostat in children aged below the age of 18 years have not been established.

In addition the efficacy and safety of febuxostat has not been established in patients with acute severe Tumor Lysis Syndrome, e.g. in patients who failed on other urate lowering therapies.

It has to be noted though, that in a submitted study, patients with only certain types of blood cancer (chronic lymphocytic leukaemia (CLL), acute leukaemia (AL) and Lymphoma) were included. Therefore no data is available regarding other medicinal products used in blood cancer other than those involved in the study and possible interactions of these with Febuxostat, with the risk of having an impact on its efficacy, cannot be excluded at this point.

In patients in whom urate formation is greatly increased (e.g. cancer and its treatment, juvenile gout) febuxostat concentration in urine could, in rare cases, increase sufficiently to allow deposition in the urinary tract. As there has been no experience with febuxostat, its use in these populations is not recommended.

Also the efficacy and safety have not been fully evaluated in patients with severe kidney damage (creatinine clearance < 30 mL/min and moderate liver damage.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Safety concern in lay language *(medical term)*	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Medical product allergy (Serious skin / Hypersensitivity reactions)	Patients should be aware of signs and symptoms like rash, dermatitis, itchy skin and trouble breathing that may indicate a severe life threatning situation	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.
Breakdown of muscle fibers (Rhabdomyolisis)	Rhabdomyolysis is a condition in which damaged skeletal muscle breaks down rapidly. Symptoms may include muscle pains, weakness, vomiting, and confusion. There may be tea-colored urine or an irregular heartbeat. Muscle breakdown may cause kidney damage.	Yes, by consultation of a doctor.
Taking azathioprine or mercaptopurine with febuxostat (Drug – drug interaction	You shouln't use the same time with flebuxostat, drugs that contains mercaptopurine or azathioprine.	Yes, by consultation of a doctor about the drugs you receive or you are going to receive.

with azathioprine or mercaptopurine)		

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Cardiovascular events	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 (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. 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. Also patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome treated with febuxostat should be under cardiac monitoring as clinically appropriate.
Hepatic events	During the combined phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0 %). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment. Thirteen subjects reported an adverse event as a primary reason for premature discontinuation. The most common AEs that led to withdrawal from the study were abnormal liver function tests (LFTs; n = 3), cancers (n = 3) and increased serum creatinine (n = 2). Of these AEs, all three instances of abnormal LFTs and one instance of increased serum creatinine were considered related to the study drug treatment. These resolved within 10–106 days. All subjects with abnormal LFTs had elevated values at baseline prior to exposure to febuxostat, and two subjects reported regular use of alcohol (10 drinks per week).
Renal events	Hypersensitivity reactions to febuxostat can be associated to single or multiple organ involvement, liver and kidney including tubulointestitial nephritis.
Neuropsychiatric events	Cases reported psychiatric and nervous system disorders include decreased sexual desire, dizziness, headache, lack of sleep, tingling, reduced sense, altered taste and smell.

Haematological / bleeding events	Hypersensitivity reactions to febuxostat can be associated to haematologic abnormalities such as thrombocytopenia and eosinophilia. 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 dose of mercaptopurine or azathioprine is recommended in order to avoid possible haematological effects.
Thyroid events	Increased TSH values (> 5.5 µIU/mL) were observed in patients on long-term treatment with febuxostat (5.5 %) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function
Off label use in the paediatric population (TLS specific)	The safety and efficacy of [Invented name] in children aged below the age of 18 years have not been established. No data are available.

Missing information

Risk	**What is known**
Children and adolescents	The safety and efficacy of [Invented name] in children aged below the age of 18 years have not been established. No data are available.
Subjects in whom the rate of serum urate formation is greatly increased (eg. malignant disease and its treatment, Lesch-Nyhan syndrome)	In patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. As there has been no experience with febuxostat, its use in these populations 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.
Severe hepatic impairment	No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).
Pregnancy and lactation	Data on a very limited number of exposed pregnancies have not indicated any adverse reactions of febuxostat on pregnancy or on the health of the foetus/new born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition. The potential risk for human is unknown. [Invented name] should not be used during pregnancy. Breast-feeding It is unknown whether febuxostat is excreted in human breast milk. Animal studies have shown excretion of this active substance in breast milk and an impaired development of suckling pups. A risk to a suckling infant cannot be excluded. [Invented name] should not be used while breast-feeding.
Off label use in patients with solid tumours (TLS specific)	There is no experience on using febuxostat in patients with solid tumors (TLS specific.)
Interaction with standard	The efficacy and safety of febuxostat in the prevention and treatment

therapy of haematological malignancies (TLS specific)	of Tumor Lysis Syndrome was evaluated in the FLORENCE (FLO-01) study. Febuxostat showed a superior and faster urate lowering activity compared to allopurinol. In the FLORENCE study febuxostat demonstrated a superior control of serum uric acid level compared to allopurinol in patients scheduled to receive the latter medicine. No data comparing febuxostat with rasburicase are currently available. The efficacy and safety of febuxostat has not been established in patients with acute severe TLS, e.g. in patients who failed on other urate lowering therapies.
Limited experience in severe renal impairment	The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance < 30 mL/min.
Limited experience in moderate hepatic impairment	Following multiple doses of 80 mg of febuxostat in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, the Cmax and AUC of febuxostat and its metabolites did not change significantly compared to subjects with normal hepatic function. Following multiple oral doses of febuxostat, the Cmax and AUC were 24 % and 12 % higher in females than in males, respectively. However, weight-corrected Cmax and AUC were similar between the genders. No dose adjustment is needed based on gender.

VI.2.5 Summary of 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 (PIL). The measures in these documents are known as routine risk minimisation measures.

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	Change
1.0	18.05.2017	**Important identified risks** • Medicinal product allergy / hypersensitivity • Rhabdomyolysis • Drug-drug interaction with azathioprine or mercaptopurine **Important potential risks** • Cardiovascular events • Hepatic events • Renal events	Initial version

		• Neuropsychiatric events • Haematological events • Thyroid events • Off label use in the paediatric population (TLS specific) **Missing information** • 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, severe renal impairment, moderate hepatic impairment • Interaction with standard therapy of haematological malignancies (TLS specific)	
1.0	30.03.2018	**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** No experience in: • 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 • Off label use in patients with solid tumours (TLS specific)	Day 70 and day 106 responses. Follow up form co nstruction

		• Interaction with standard therapy of haematological malignancies (TLS specific) Limited experience: • Severe renal impairment • Moderate hepatic impairment	
1.0	13.07.2018		Follow up form co ncerning hepatic a dverse events is inc luded and PIL_Sm PC update