EU RISK MANAGEMENT PLAN FOR ADENURIC (FEBUXOSTAT)

RMP version to be assessed as part of this application:

RMP Version number: 10.0

Data lock point for this RMP: 28 February 2021

Date of final sign off: 01 December 2021

Rationale for submitting an updated RMP:
The aim of the present RMP version is to consolidate the changes approved with the Type II variation to update the PI by including the results of the clinical study FAI-01 (Procedure number: EMEA/H/C/000777/II/0062) as well as the changes proposed through the Type II variation to update the PI by including the results of the clinical study FAST (Procedure number: EMEA/H/C/000777/II/0061).
In particular, this RMP version 10.0 has been updated starting from the RMP version 9.1 approved in the frame of the variation procedure EMEA/H/C/000777/II/0062 and includes all changes of the RMP versions 8.0 and 8.1 submitted in the frame of the assessment of the Type II variation EMEA/H/C/000777/II/0061.

Summary of significant changes in this RMP:

- No change to the safety concerns list has been performed.

- In Part II Module SVII, the important identified risk "Cardiovascular events", has been updated to include safety data from the completed FAST study.
Part V and VI have been revised accordingly.

Other RMP versions under evaluation:

RMP Version number: 8.1

Submitted on: 04-Aug-2021

Procedure number: EMEA/H/C/000777/II/0061

Details of the currently approved RMP:

Version number: 9.1

Approved with procedure: EMEA/H/C/000777/II/0062

Date of approval (opinion date): 11/11/2021

QPPV name: Dr. Francesco Sarlo, MD

QPPV [redacted]

TABLE OF CONTENT

LIST OF TABLES

PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Febuxostat
Pharmacotherapeutic group(s) (ATC Code)	M04AA03
Marketing Authorisation Holder	- Menarini International Operations Luxembourg S.A. (MIOL), 1 Avenue de la Gare, L-1611 Luxembourg, Grand Duchy of Luxembourg, MAH of Adenuric in European Economic Area (EEA) countries, Albania, Argentina, Armenia, Azerbaijan, Belarus, Costa Rica, El Salvador, Georgia, Guatemala, Honduras, Kazakhstan, Kyrgyzstan, Moldova, Nicaragua, Panama, Tajikistan, Turkmenistan, Ukraine, Uzbekistan. - A.Menarini Australia Pty Ltd MAH of Adenuric in Australia - A.Menarini AG MAH of Adenuric in Switzerland - A. Menarini New Zeland Pty limited MAH of Adenuric in New Zeland - Berlin-Chemie AG - Glienicker Weg MAH of Adenuric in Kosovo and Russia -Berlin Chemie Menarini BH d. o. o. MAH of Adenuric in Bosnia & Herzegovina - Septima Dooel - Adenuric in Montenegro - Takeda Pharmaceuticals USA Inc: MAH of Uloric in United States, Canada, Puerto Rico and Mexico. - Teijin Pharma Limited: MAH of Feburic in Japan - SK Chemicals Co, Limited: MAH of Feburic in Republic of Korea - UFSA Ilaç Sanayi ve Ticaret Anonim Şirketi in Turkey - Astellas Pharma Hong Kong Co, Ltd: MAH of Feburic in Hong Kong, Macau - Astellas Pharma Taiwan, Inc: MAH of Feburic in Taiwan - Algorithm SAL: MAH of Adenuric in Lebanon, Kuwait, Jordan, UAE and Saudi Arabia - Neopharm Limited: MAH of Feburic in Israel - Astellas Pharma (Thailand) Co., Ltd: MAH of Feburic in Thailand - Astellas Pharma Singapore Pte. Ltd: MAH of Feburic in Vietnam and Singapore - Astellas Pharma Malaysia Sdn. Bhd.: MAH of Feburic in Malaysia

Medicinal products to which this RMP refers	Adenuric 80 and 120 mg in the following presentations in EEA countries: EU/1/08/447/001 EU/1/08/447/002 EU/1/08/447/003 EU/1/08/447/004 EU/1/08/447/005 EU/1/08/447/006 EU/1/08/447/007 EU/1/08/447/008 EU/1/08/447/009 EU/1/08/447/010 EU/1/08/447/011 EU/1/08/447/012 EU/1/08/447/013 EU/1/08/447/014 EU/1/08/447/015 EU/1/08/447/016 EU/1/08/447/017 EU/1/08/447/018 EU/1/08/447/019 EU/1/08/447/020 EU/1/08/447/021 EU/1/08/447/022 EU/1/08/447/023 EU/1/08/447/024
Invented name(s) in the European Economic Area (EEA)	Adenuric
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Febuxostat is a 2-arylthiazole derivative, is a potent, non-purine selective inhibitor of xanthine oxidase (XO)
	Summary of mode of action: Febuxostat exhibits antihyperuricemic activity by reducing the formation of uric acid.
	Important information about its composition The active ingredient is obtained by chemical synthesis and the medicinal product is released according to its list of specifications.
Hyperlink to the Product Information	- Product Information Adenuric 80 mg film-coated tablets - Product Information Adenuric 120 mg film-coated tablets
Indication(s) in the EEA	Current: Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis). Prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS). Febuxostat is indicated in adults.
	Proposed : Not applicable
Dosage in the EEA	Current: 80 mg or 120 mg orally once daily without regard to food.

	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: 80 mg film-coated tablets 120 mg film-coated tablets
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication: Gout

Adenuric is indicated for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).

Incidence:

In Western countries, both the prevalence and incidence of gout have increased in the past 4 decades (Bieber et al., 2004).
In the UK, an incidence of 11.9-18.0/10,000 had been reported (Mikuls et al., 2005). Similar annual incidence rates were reported for Germany and the UK during 2000 to 2004 (up to 0.09%) (IMS disease analyzer. September 2006). In the USA, incidence rates of 6.2/10,000 (Campion et al., 1987) and 0.1% to 4.9%, depending on serum urate levels, have been reported (Arromdee et al, 2002). More data from the UK general population estimates the incidence of gout in 2.68 per 1,000 patient-year (PY) (4.42 in men, 1.32 in women), where the incidence increase with age (Cea-Soriano et al., 2011).

Prevalence:

The prevalence of gout increases with age and with the increased prevalence of obesity (Choi et al, 2005). In industrialised nations, increased longevity may contribute to a higher gout prevalence through an association between gout and age-related diseases such as metabolic syndrome and hypertension, and treatments for these diseases (eg, thiazide diuretics) (Saag et al, 2006). In the UK, gout has a prevalence of 0.95% (Harris et al, 1995). In Germany, a prevalence of 1.4% was reported during the period 2000 to 2005 (Annemans et al, 2008). In the USA, a prevalence of 4.1% was reported in a managed care population of >75 year old (Kramer et al, 2002). More data (2007-2008) indicate that the prevalence of gout in US adults was 3.9%, corresponding to 8.3 million individuals (Zhu et al, 2011).
The prevalence of gout among men was 5.9% (6.1 million), and the prevalence among women was 2.0% (2.2 million) (Chandratre P, Roddy E, Clarson L, Richardson J, Hider SL, Mallen CD. Health-related quality of life in gout: a systematic review. Rheumatology (Oxford). 2013; 52(11): 2031–2040).

Demographics of the population in the authorised indication and risk factors for the disease:

Although considered to be primarily a male disease, the sex distribution of gout is closer among elderly subjects. In a managed care population in the USA, a male:female ratio of 4:1 was recorded in subjects aged <65 years and 3:1 in those aged >65 years (Wallace et al, 2004). In the US general population the prevalence of gout among men and women was 5.9% and 2.0%, respectively corresponding to 6.1 and 2.2 million individuals (Zhu et al, 2011). The overall male:female ratio ranged between 7:1 and 9:1 in the National Health and Nutrition Examination Survey III (Kramer et al, 2002). In Germany, the male:female ratio in a sample of gout subjects was 4:1 (Annemans et al, 2008). In a small sample of gout subjects in France (n = 260), 88% were male (IMS disease analyzer. September 2006).

In both men and women, gout becomes more common with increasing age. In subjects with gout, mean ages of 60.5 years in the UK (Mikuls et al., 2005), 63.1 years in Germany and 67.2 years in France have been reported (IMS disease analyzer. September 2006; Annemans et al, 2008). While an incidence of 33.1/10,000 PY has been reported for male subjects aged 45-64 years, the incidence was 7.6/10,000 for women of the same age (Mikuls et al., 2005). Women rarely experience attacks of gout before the menopause. Oestrogen exerts a uricosuric effect and may protect females from hyperuricaemia before the menopause (Saag et al, 2006). The frequency of gout varies according to ethnicity and geographical region, with higher rates of hyperuricaemia and gout found in the black compared to the white population (Hochberg et al, 1995).

Beyond hyperuricaemia, risk factors for gout include gender, age and modifiable risk factors that include obesity, consumption of purine-rich foods some alcoholic beverages and some drugs (Saag et al, 2006; Richette and Bardin, 2010).

The main existing treatment options:

Standard symptomatic pharmacological management of acute gout attacks consists in the administration of colchicine and / or Non-Steroidal Anti-inflammatory Drugs (NSAIDs), or corticosteroids. Other pharmacological options for the treatment of gout consist of urate lowering drugs; these drugs must be administered chronically to decrease serum urate levels and to dissolve tissue urate crystals. Urate lowering drugs include uricosuric agents such as probenicid, sulfinpyrazone and benzbromarone, and inhibitor of xanthine oxidase such as allopurinol or febuxostat. Another urate lowering drug is represented by rasburicase, a recombinant urate-oxidase enzyme, which catalyses the oxidation of uric acid to the more soluble allantoin; however this product is only indicated for the treatment of tumor lysis syndrome (Richette and Bardin, 2010; Perez-Ruiz and Herreo-Beites, 2012). In a large US retrospective study it has been estimated that about 42% of patients treated for gout takes NSAIDs, 32% allopurinol, 21% corticosteroids, 17% colchicine and 1% probenecid (Primatesta et al, 2011).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Gout is not generally considered as a lethal disease, but it is associated with a worse health-related quality of life and significant disability. Mortality associated with gout generally results from comorbid conditions or complications such as hypertension, renal damage and reduction of motility. Although the link is unclear, hyperuricaemia has been associated with an increased risk of mortality from a number of causes, including cardiovascular events (Fang et al, 2000; Niskanen et al, 2004) and stroke (Mazza et al, 2001). In a retrospective study on 9,924 hyperuricaemic veterans, 1,021 died (all cause mortality) during a follow-up lasting for 23,903 person-year (Luk et al, 2009).

Important co-morbidities:

Beyond the above mentioned drugs taken for the treatment of gout, gout patients can take a number of other drugs because of the multiple important comorbidities associated with this disease. Therefore, in a cohort of hyperucaemic patients not taking allopurinol (n = 7,441), 38% of patients were treated with HMG CoA reductase inhibitors (statins), 38% with Angiotensin-Converting Enzyme (ACE) inhibitors, 33% with beta-blockers, 26% with hydrochlorithiazide, 18% with calcium channel blockers, 17% with acetylsalicylic acid, 14%

with loop diuretics, 6% with sartans (excluding losartan), 5% with fibrates, 5% with insulin, and 2% with losartan which is endowed with uricosuric properties. 25% of this population used NSAIDs (Luk et al, 2009).
This picture well matches, for a qualitative point of view at least, with the concomitant treatments administered to patients involved in the clinical development program, where the safety has been evaluated in patients participating in phase III clinical trials randomised to placebo, allopurinol, or febuxostat (n = 4,101) and taking NSAIDs/COX-2 inhibitors (41% of patients), colchicine (24%), acetylsalicylic acid (20%), nitrates (2%), ACE inhibitors (24%), beta-blockers (18%), statins (22%), insulin (2%), acetaminophen (13%), corticosteroids (16%), warfarin (3%), thiazides (2%), and calcium channel blockers (11%) (Febuxostat Integrated Summary of Safety 2008: Tables 6.3.1.1.1 to 6.3.1.1.13).

It is well known that gout is associated with various comorbid conditions, including cardiovascular and renal disease.
The association between alcohol consumption and gout is also well documented.
These comorbidities were reflected in the demographics of the subjects enrolled into the clinical programme supporting this application (see Module 2.7.4, Section 4.1.3). In the Phase III studies, more than half of the subjects classified as obese (BMI ≥30 kg/m2). At least 59% of subjects in each group reported the use of alcohol. The most common medical conditions at baseline were histories of hypertension (46-53% of subjects), hyperlipidaemia (33-39%) and atherosclerotic disease (11-18%), and 48-63% of subjects had impaired renal function (defined as calculated Clcr <90 mL/min).

Cardiovascular comorbidities:

Cardiovascular disease is relatively common in subjects with gout, with studies reporting 24.9% of subjects to have comorbid coronary artery disease (Mikuls et al., 2005) and 15.5% and 10.5%, respectively, to have coronary atherosclerosis and cardiac arrhythmias (Riedel et al, 2004). A German study population reported hypertension in 18.5%, heart failure in 10.8% and myocardial infarction in 5.8% of subjects with gout (Annemans et al, 2008).
In the general population of the UK, cardiovascular diseases account for 30% of deaths each year (North of England Hypertension Guideline Development Group 2004). Hyperuricaemia has been linked to an increased risk of cardiovascular events, as well as cardiovascular mortality, in a number of studies (Fang et al, 2000; Niskanen et al, 2004; Johnson et al, 2003; Baker et al, 2005), although the association remains unclear. A major difficulty is that other common comorbidities in subjects with gout, such as hypertension, may contribute to an increased risk of cardiovascular events.
Cardiovascular disorders are frequent comorbidities in subjects with gout, with frequencies of 24.9%, 15.5% and 10.5% reported for coronary artery disease (Mikuls et al, 2005), coronary atherosclerosis and cardiac arrhythmias (Riedel et al, 2004), respectively.
Krishnan et al. (2008), in a study of 9,105 men at above-average risk for coronary artery disease from 1982 to 1999 reported that the unadjusted mortality rates from cardiovascular disease were 10.3 per 1000 person-years and 8.0 per 1000 person-years for men with and without gout respectively, representing an 30% greater risk (hazard ratio=1.30, 95% confidence interval [CI], 1.07-1.58). After adjusting for traditional risk factors, use of diuretics and aspirin, and serum creatinine level, the hazard ratio (gout vs no gout) was 1.21 (95% CI, 0.99-1.49) for death from CVD overall, 1.35 (95% CI, 1.06-1.72) for CHD mortality, and 1.35 (95% CI, 0.94-1.93) for MI mortality (Krishnan et al, 2008). . A higher mortality rate was found in patients with gout and coronary artery disease as compared to subjects without gout (Teng et al., 2012).

Another independent prospective study of male participants (n=51,297) of the Health Professionals Follow-Up Study from 1986 to 2000 found that gout was associated with a 38, 55, and 59% increased risk for cardiovascular death (hazard ratio=1.38, 95% CI, 1.15-1.66), coronary heart disease mortality (hazard ratio=1.55, 95% CI, 1.24-1.93), and non-fatal myocardial infarction (hazard ratio=1.59, 95% CI, 1.04-2.41), respectively (Choi et al, 2007).
A large prospective study was established on 83,683 Austrian men cohort (mean age 41.6 years) prospectively followed for a median of 13.6 years, and confirmed the independent relationship between elevated sUA and mortality from coronary heart failure and stroke. The highest quintile of sUA concentration (>398.81 mumol/L) was significantly related to mortality from cardiac heart failure (P = 0.03) and stroke (P <0.0001); adjusted hazard ratios (95% confidence interval) for the highest vs lowest quintiles of sUA were 1.51 (1.03-2.22) and 1.59 (1.23-2.04), respectively (Strasak et al, 2008a).
Similarly, sUA showed to be an independent predictor for all major forms of death from cardiovascular disease including acute, subacute and chronic forms of congestive heart disease, cardiac heart failure and stroke in elderly, post-menopausal women. In a large cohort of 28,613 elderly Austrian women (mean age 62.3 years), followed-up for a median of 15.2 years., sUA in the highest quartile (≥ 5.41 mg/dL) was significantly associated with mortality from total CVD (p< 0.0001), showing a clear dose–response relationship; the adjusted hazard ratio (95%CI) in comparison to the lowest sUA quartile was 1.35 (1.20–1.52). In subgroup analyses sUA was independently predictive for deaths from acute and subacute (p < 0.0001) and chronic forms (p = 0.035) of coronary heart disease, yielding adjusted hazard ratios for the highest versus lowest sUA quartile of 1.58 (1.19–2.10) and 1.25 (1.01–1.56), respectively. sUA was further significantly related to fatal congestive heart failure (CHF) (p<0.0001) and stroke (p=0.018); the adjusted hazard ratios for the highest versus lowest sUA quartile were 1.50 (1.04–2.17) and 1.37 (1.09–1.74), respectively (Strasak et al 2008b).
The above figures have been confirmed in a more study which have analysed all-cause and cardiovascular mortality in Taiwan for the period 2000 – 2006 (Kuo et al., 2010). Among 61 527 subjects, 1383 deaths (198 cardiovascular deaths) were identified, corresponding to a crude mortality rate of 4.86 deaths per 1000 person-years. Crude mortality rates were 4.50, 5.61 and 10.46 deaths per 1000 person-years for subjects with normouricaemia, hyperuricaemia and gout, respectively. Compared with subjects with normouricaemia, the hazard ratios (HRs) of all-cause mortality were 1.46 (95% CI 1.12, 1.91) for individuals with gout and 1.07 (95% CI 0.94, 1.22) for those with hyperuricaemia, respectively, after adjustments were made for age, sex, component number of metabolic syndrome and proteinuria. The adjusted HRs of cardiovascular mortality were 1.97 (95% CI 1.08, 3.59) for individuals with gout and 1.08 (95% CI 0.78, 1.51) for those with hyperuricaemia. Moreover, the risk of all-cause or cardiovascular mortality for gout remained unchanged when limiting the data to those with an estimated glomerular filtration of >60 ml/min/1.73 m2.
In another prospective study in the Taiwanese population (Chen et al., 2009), 41,879 men and 48,514 women ages > or = 35 years were analysed for all causes mortality, total cardiovascular disease (CVD), ischemic stroke, congestive heart failure, hypertensive disease, and coronary heart disease. It was found that hyperuricemia was an independent risk factor of mortality from all causes, total CVD, and ischemic stroke in the Taiwanese general population, in high-risk groups, and potentially in low-risk groups.
An association between hyperuricemia (baseline serum uric acid >or=6 mg/dL for women and >or=7 mg/dL for men) and heart failure has been remarked in a study on 5,461 community-dwelling aged 65 y and more, 1,505 of which had hyperuricemia (Ekundayo et al., 2010). Incident HF occurred in 21% and 18% of participants respectively with and without hyperuricemia during 8.1 years of mean follow-up (hazard ratio {HR} for hyperuricemia versus no hyperuricemia, 1.30; 95% confidence interval {CI}, 1.05-1.60; P=0.015).

The impact of hyperuricemia on the outcome of adverse events in patients with heart failure has been also studied (Hamaguchi et al., 2011). Of the total cohort of HF patients, 56% had hyperuricemia defined as UA>/=7.0mg/dl. Patients with UA>/=7.4mg/dL had higher rates of all-cause death, cardiac death, rehospitalization, and all-cause death or rehospitalization due to worsening HF. After multivariable adjustment, higher UA levels were a significant and independent predictor for all-cause death (adjusted hazard ratio [HR] 1.413, 95% confidence interval [CI] 1.094-1.824, P=0.008) and cardiac death (adjusted HR 1.399, 95% CI 1.020-1.920, P=0.037).

A study on the association between hyperuricemia and the outcome of events in patients hospitalised for acute stroke, found that the admission serum uric acid levels also independently predicted worse outcome and a higher rate of repeated stroke or other cardiovascular event (Weir et al., 2003), an association confirmed in a published meta-analysis (Kim et al., 2009). Likewise in a retrospective study (Krishnan et al, 2012) on participants to the Aspirin Myocardial Infarction Study where patients with acute myocardial infarction were followed up for 3 years, the risk of all-cause death, CHD mortality, coronary incidence, and stroke were investigated by quartile of baseline sUA. Amongst the 4,352 patients analyzed all outcomes were greatest for patients in the fourth sUA quartile. In multivariate regression models, the hazard ratios (HR) for patients in the highest quartile were 1.88 for all-cause mortality (95% confidence interval (CI), 1.45 to 2.46), 1.99 for CHD mortality (95% CI, 1.49 to 2.66), and 1.36 for coronary incidence (95% CI, 1.08 to 1.70). Participants with untreated gout had an adjusted hazard ratio ranging from 1.5 to 2.0 (all $P < 0.01$) for these outcomes.

The characteristics of Scottish patients which had urate concentrations measurements in the period 2000-2002 and were aged 60 years old and over was studied: this population was followed up for 5 years (Wei et al., 2011). The analysis involved allopurinol users (n = 1035) and non-urate lowering therapy using patients (n = 6042) and both populations were homogeneous for urate concentration strata. The group of allopurinol users was further divided according to the dose administered (100, 200, and 300 mg and more). Main differences between these 2 populations concerned the gender (62.5% of allopurinol users were male), previous hospitalisations for gout or hyperuricaemia (significantly higher in the allopurinol users: 1.8 vs 0.4%), for renal diseases (significantly higher in the allopurinol users: 7.4 vs 3.5%) and for CV diseases (significantly higher in the allopurinol users: 9.7 vs 7.2%). Because of these co-morbidities, allopurinol users were more frequently co-treated with aspirin, anti-coagulants, angiotensin-converting enzyme inhibitors, beta-blockers, cardiac glycosides, calcium channel blockers, thiazide diuretics and diuretics in general, nitrates, statins, non-steroideal anti-inflammatory drugs and colchicine. CV event rate (APTC events) was 38.5 per 1000 patient-year (PY) in allopurinol non-users, 48.5 for allopurinol non-users with urate concentrations >6mg/dl, and 61.4 per 1000 PY in allopurinol users; these differences were not statistically significant. Amongst allopurinol users, the group taking 300 mg and over had significantly less CV events (47.6 per 1000 PY) than the group taking 100 mg (74 per 1000 PY), whereas the 200 mg group had an intermediate value (69.7 per 1000 PY). Interestingly, only 24% of the 100 mg group achieved urate concentrations < 6.0 mg/dl, whereas 47 and 65% of patients in the 200 and 300 mg and over groups attained to the targeted urate concentrations.

Another study involved a nested case-control analysis of a large population from Quebec which included patients aged 66 years or older discharged from the hospital with a primary diagnosis of heart failure (HF) between 1998 and 2004 and followed up to the event date (hospital re-admission for HF or death) for a maximum of one year since the end of enrolment (Thanassoulis et at., 2010). Study population consisted of 25,090 patients (mean age 77 years) which experienced 14,327 events of HF re-admission or CV deaths (52.9 and 47.1%,

respectively). Case patients had a higher burden of co-morbidities, renal failure and history of myocardial infarction, in particular. History of gout was recorded in 7.3% of cases as compared to the 4.6% of controls. In cases with gout, patients had a significantly increased risk for HF re-admission or CV death than patients without gout, and an acute episode of gout was associated with an increased risk of CV events. Patients with gout using allopurinol were compared with disease-matched non-users. Allopurinol users had a significantly reduced risk for HF re-admission or CV death than non-users and the CV risk in the former group was not higher than in HF population without gout.
In a re-analysis of the PRAISE trial on amlodipine where HF patients (79% white) with NYHA class IIIb or IV and urate levels records and clinical data were available (Wu et al., 2010), patients not using allopurinol were divided into 4 strata according to the quartiles of urate levels (1st 2.2-7.1; 2nd 7.2-8.6; 3rd 8.7-10.4; 4th >10.4) and compared with allopurinol users, which had, however, a mean uric acid level (8.1 mg/dl) higher than recommended. The higher urate quartile and allopurinol user groups had a greater proportion of men, class IV NYHA HF, renal diseases, hyponatremia and diuretic usage. The median follow-up was 14 months. The higher urate quartile and allopurinol user groups had the highest total mortality (424 and 417 events per 1000 PY, respectively) and combined morbididty-mortality (510 and 456 events per 1000 PY, respectively). Furthermore, results of multivariate Cox regression predicting mortality indicated that, beyond high levels of urate and allopurinol use, ischemic etiology, more severe HF (class IV NHYA), white race, increased total bilirubin, leucocytosis, and diuretic dosage were significant risk factors for a poor prognosis. The Authors discussed that the association between allopurinol use and the increased risk of mortality-morbidity reflected the elevated urate levels and worse clinical conditions in patients taking allopurinol rather than a direct causal relationship between allopurinol treatment and an adverse CV outcome and that higher doses of allopurinol are needed to achieve optimal clinical benefits.

In conclusion, the above mentioned evidence indicates a higher rate of cardiovascular adverse events is to be expected in gout patients as compared to the general population independently from other pre-existing cardiovascular co-morbidities.

Renal comorbidities:

Renal impairment is a common comorbidity in subjects with gout and a major risk factor for developing the disease (Luk et al, 2005; Perez-Ruiz et al, 1999). Published studies of patients with gout/hyperuricaemia have reported some degree of renal impairment in approximately 33% of patients (Akkasilpa et al, 2004), although renal failure is less common (1-17%) (Mikuls et al., 2005; Koh et al, 1998). Approximately 1% of subjects with gout have a history of nephrolithiasis (Mikuls et al., 2005), although kidney stones will form in 10-40% of gout patients (Richette and Bardin, 2010).
Despite the prevalence of chronic kidney disease in the general population, <1% of people progress to end-stage renal disease (White et al, 2005; Coresh et al, 2003). Mortality in subjects with severe acute renal failure is high at approximately 50% (Swartz et al, 2005), although reported rates vary considerably (Bagshaw et al, 2006).
In a survey on US (2007-2008 data), it was estimated that 71% of the 8.3 million gout patients had chronic kidney disease greater than stage 2 (Glomerular Filtration Rate, GFR < 60), almost 20% had chronic kidney disease greater than stage 3 (GFR < 30) and 24% had nephrolithiasis (Zhu et al, 2011). 5% of dialysis patients had gout in the first year but this increased up to 15% in the first 5 years of dislysis (Cohen et al, 2008). From a quantitative point of view it has been estimated that the annual decrease of GFR in healthy adults spans from 0.8 to 1.3 mL/min/1.73m2, whereas in adult hyperuricaemic subjects renal function

declines 2 to 3 fold faster (i.e., mean annual decrease of GFR 2.5 mL/min/1.73m2 (Whelton et al., 2013).
Another retrospective study on the US population (Fuldeore et al., 2011) found that 39% of gout patients had chronic kidney disease and that these patients were older, more likely to be women, had a greater number of co-morbidities, and more likely treated with allopurinol. A higher mortality rate was found in patients with gout and chronic kidney disease as compared to subjects without gout (Teng et al., 2012).
Management of chronic kidney disease includes general health improvement and cardiovascular risk reduction, for example through changes in diet and exercise, as well as control of hypertension. Medications commonly used include angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II antagonists, some of which (e.g., losartan) are mildly uricosuric and may have a beneficial effect on renal function (Choi et al, 2005; Reyes et al, 2003). On the other hand, reported data indicate that ACE inhibitors, which have detrimental effects on renal function, are used by 28.4% of subjects with gout (Riedel et al, 2004).
Furthermore, a role for drugs used for the symptomatic treatment of gout in the development of renal adverse reaction cannot be ruled out. Gout patient with cardiovascular co-morbidities are at high risk of developing a renal reaction to NSAIDs, and NSAIDs are the most commonly prescribed drugs (up to 68%) in gout patients (Roddy et al, 2010). Considering that the association between NSAIDs, ACE inhibitors and diuretics greatly increases the risk of renal failure (Lapi et al, 2013), a certain percentage of renal events collected in the gout population are to be attributed to the co-administration of NSAIDs and cardiovascular drugs.
In conclusion, as for cardiovascular diseases, renal comorbidities are highly represented in the gout population and this is not unexpected when considering that hyperuricaemia is in the vast majority of cases due an impaired renal excretion of uric acid, therefore it is itself a renal disease.

Hepatic comorbidities:

An association between alcohol and liver disease and alcohol and gout is well known. The prevalence of chronic hepatitis was determined to be approximately 5-20% among patients with gout in a retrospective cohort study of patients identified in a Virginia (VA) electronic medical records database (Keenan et al, 2011). Hyperuricemia has been found to be associated with increased risk for development of non-alcoholic fatty liver disease (NAFLD), independently from the presence of other risk diseases such as obesity or diabetes (Lee et al, 2010; Kim et al, 2004). The prevalence of NAFLD was also found to be higher among patients with gout (23.1%) in comparison with patients without gout (10.9%) (Kuo et al, 2010). Uric acid has been directly involved in the genesis of NAFLD (Lanaspa et al., 2012).
In a German cohort of orthopaedic surgery patients a high prevalence (11.3%) of elevated liver enzymes was found in the absence of evidence for viral hepatitis. Patients with elevated liver enzymes had a significantly higher prevalence of hypertension, chronic ischaemic heart disease, hyperlipidaemia and hyperuricaemia. A high prevalence (9%) of elevated liver enzymes still remained even when excluding patients with regular daily alcohol consumption (Lobstein et al, 2008). In this context, hepatic comorbidities can be associated to the use of anti-gout drugs, ie, NSAIDs (Rubenstein et al, 2004), colchicine (Kamath et al, 2008; Miller et al, 2005; Saksena et al, 2003), allopurinol (Zyloric UK SmPC), benzbromarone (Hautekeete et al, 1995; van der Klauw et al, 1994), as well as other herbal drugs (Stickel et al, 2000), all of which are known to induce mild to severe hepatic ADRs.

Neurological and psychiatric comorbidities:

In general, neurological disorders are not commonly associated with gout. However, hyperuricemia has been associated with an increased risk of developing dementia (Ruggiero et al, 2009). Indeed, a decreased cognitive function in hyperuricemia has been attributed with the occurrence of cerebral ischaemia (Vannorsdall et al, 2008). Cognitive impairment and behavioural disturbances are also characteristic of Lesch-Nyhan syndrome that is associated to hyperuricaemia. Another important aspect to consider is the lifestyle of gout patients, where the excessive alcohol consumption can precipitate psychiatric disturbances (e.g., Sharpe 1984).

Haematological and bleeding comorbidities:

Except for rare cases where a mutation in the renin gene which seems to be a predisposing factor for developing anaemia and hyperuricaemia (Zivná et al, 2009) and rare cases of gout patients with eosinophilia (just 1 out of 10 of these patient was treated with allopurinol) (Kargili et al, 2004), haematological and bleeding events are not directly associated with hyperuricemia and / or gout. More often, haematological events are associated with drugs used for gout treatment, mostly, colchicine (No authors listed, 2008) and allopurinol (Kim et al, 2009).
As far as bleeding events are concerned, patients with history of cerebrovascular disease and with higher serum urate levels are also more likely to experience a major vascular event, where 10% of patients had primary intracerebral hemorrhage and 90% had ischemic stroke. This relationship holds true even after correction for the presence of established cardiovascular and cerebrovascular risk factors such as hypertension, diabetes mellitus, and hyperlipidemia (Weir et al., 2003).

Thyroid comorbidities:

A significant prevalence of hypothyroidism has been reported in patients with gout, with rates of 25-40% reported in women and 12-15% reported in men (Erickson et al, 1994).

Indication: Tumor Lysis Syndrome

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

Incidence:

The incidence and the severity of TLS vary widely depending on several risk factors including the cancer mass, the potential for lysis of tumour cells, the characteristics of the patient and the supportive care as summarized in table SI.1.1. (Howard et al., 2011).

Table SI.1.1. Risk Factors for the Tumor Lysis Syndrome

Category of Risk Factor	**Risk Factors**
Cancer mass	Bulky tumor or extensive metastasis
	Organ infiltration by cancer cells
	Bone marrow involvement
	Renal infiltration or outflow-tract obstruction
Cell lysis potential	High rate of proliferation of cancer cells
	Cancer-cell sensitivity to anticancer therapy
	Intensity of initial anticancer therapy
Features on patient presentation	Nephropathy before diagnosis of cancer
	Dehydration or volume depletion
	Acidic urine
	Hypotension
	Exposure to nephrotoxins
Supportive care	Inadequate hydration
	Exogenous potassium
	Exogenous phosphate
	Delayed uric acid removal

Modified from Howard et al., 2011

Moreover the introduction of more aggressive chemotherapy in the management of haematological malignancies, the rare appearance of TLS in some solid tumours and the occurrence of spontaneous TLS, i.e. in absence of cytotoxic therapy, may account for an overall increase in TLS incidence.
Taken together the lack of standard criteria and the variability of patient cohorts in terms of age, disease characteristics and treatments explaine the wide range of reported incidences as shown in table SI.1.2. (Howard SC et al., 2011).

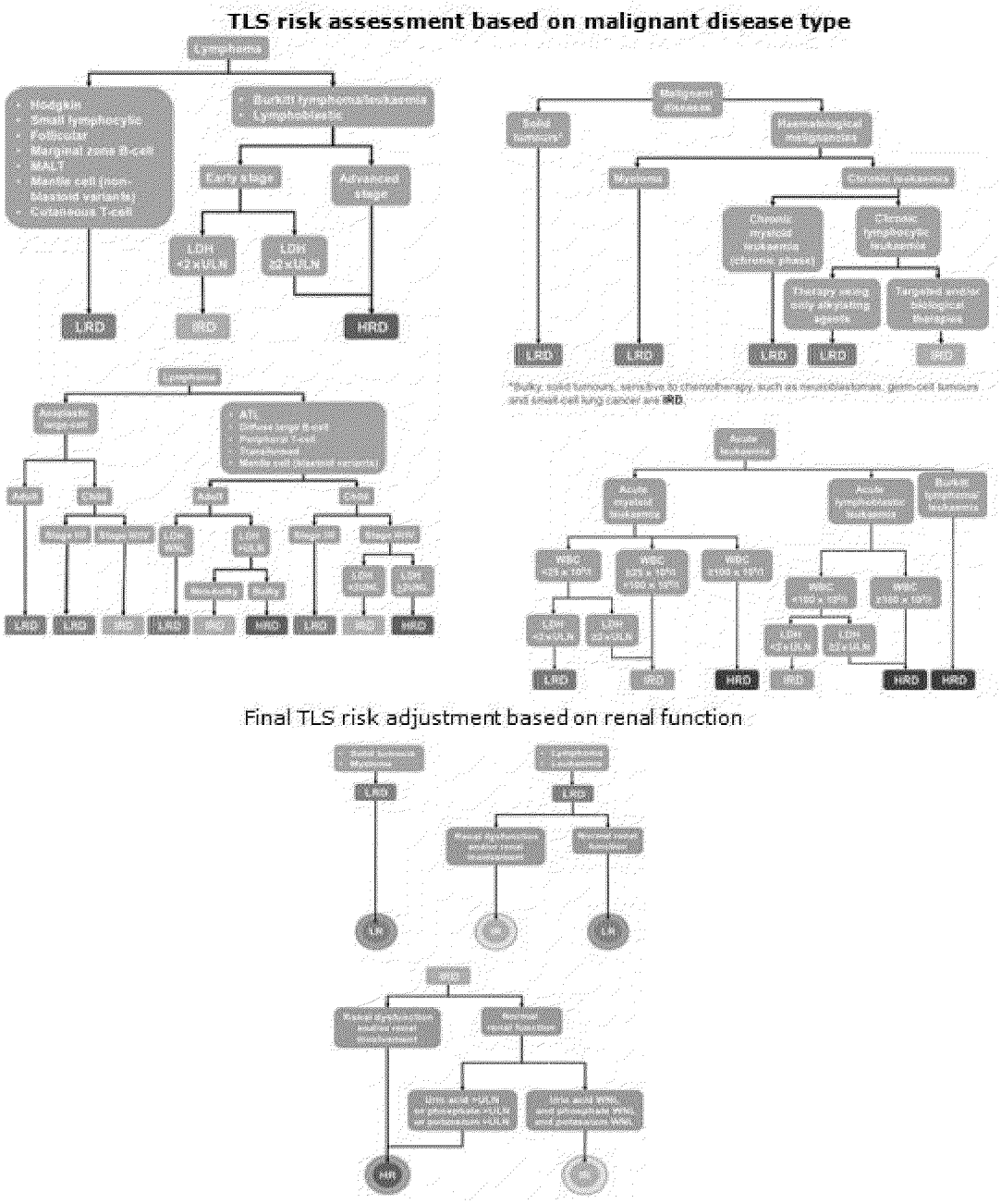
Table SI.1.2. Incidence of Tumor Lysis Syndrome in selected studies with 100 patients or more

Reference	Cancers included	Patients	TLS prevention used in addition to intravenous fluids	Incidence of TLS*	Incidence of dialysis	Death from TLS
Cohorts treated with allopurinol						
Montesinos et al. 2008	Acute myeloid leukemia	772 adults	Allopurinol	17%	0.9%	2.5%
Mato et al. 2006	Acute myeloid leukemia	194 adults	Allopurinol	9.8%	0.5%	0%
Truong et al. 2007	Acute lymphoblastic leukemia	326 children	Allopurinol (rasburicase in 6% of patients)	23%	Not reported	Not reported
Bowman et al. 1996	Advanced-stage B-cell non-Hodgkin lymphoma	133 children	Allopurinol	Not reported	21%	2.2%
Clinical trials in which rasburicase was used in some patients and allopurinol in others						
Cairo et al. 2007	Advanced-stage B-cell non-Hodgkin lymphoma	101 children (USA) 98 children (France)	Allopurinol Rasburicase	26% 9%	15% 3%	0% 0%
Cortes et al. 2010	Hematologic malignancies	91 adults 92 adults 92 adults	Allopurinol Rasburicase Rasburicase plus allopurinol	41% (4% clinical) 21% (3% clinical) 27% (3% clinical)	Not reported	0% 0% 0%
Cohorts treated with rasburicase (or a non-recombinant urate oxidase)						
Patte et al. 2002	Advanced-stage B-cell non-Hodgkin lymphoma	410 children	Non-recombinant urate oxidase	Not reported (8.3% had metabolic problems)	1.7%	0%
Jeha et al. 2005	Mostly hematologic malignancies	1069 adults and children	Rasburicase	Not reported (4.2% had renal insufficiency)	2.8%	0%
Coiffier et al. 2003	Diffuse or bulky lymphoma (mostly diffuse large B-cell histology)	100 adults	Rasburicase	Not reported	0%	0%
Pui et al. 2001	Leukemia or lymphoma	131 children	Rasburicase	Not reported	0%	0%
Bosly et al. 2003	Mostly hematologic malignancies	278 adults and children	Rasburicase	Not reported	1.8%	0.4%
Pui et al. 2001	Mostly hematologic malignancies	245 adults and children	Rasburicase	Not reported	4.1%	0.4%
Pui et al. 1997	Hematologic malignancies	134 children	Rasburicase	Not reported	0%	0%

*Includes both laboratory and clinical TLS. Note that the definition of TLS and clinical TLS differed somewhat in different studies. TLS, tumor lysis syndrome.

Nevertheless TLS is certainly more frequent in malignancies with high proliferating rates, tumor burden and chemosensitivity: the greater is the cancer mass, the greater is the quantity of cellular contents released after administration of effective anticancer therapy (Howard et al., 2011). Therefore hematologic malignancies with large, rapidly growing and chemosensitive cells, such as high-grade acute lymphoblastic leukaemia (ALL), carry the greatest risk. In this regards a TLS expert consensus panel developed guidelines for a medical decision tree to assign a patient at risk of TLS to low, intermediate and high risk level (Cairo et al., 2010) as shown in figure SI.1.1.

Figure SI.1.1. Assessement risk for TLS



ATL: Adult T-cell lymphoma; LDH: lactate dehydrogenase; WNL: Within Normal Limits; ULN: Upper Limit of Normal; WBC: White Blood Cells; LRD: Low Risk Disease; IRD: Intermediate Risk Disease; HRD: High Risk Disease. For chronic lymphoid leukaemia (CLL), IRD is defined not only when treatment targeted and/or biological therapies are used instead of only alkylating agents, but also in the presence of an elevated WBC (≥ 50 x 109/L).
Modified from Cairo et al., 2010.

The risk assessment is based on the combination of histologic diagnosis, extent and bulk of disease, use of specific cytotoxic agents, age at diagnosis, white blood cells count (WBC) and lactate dehydrogenase (LDH) level. Then the resulting risk assessment is adjusted for renal function and metabolic abnormalities (one or more among hyperuricaemia, hyperphosphatemia and hyperkalemia). Thus, lymphomas and leukaemias which are assessed as low risk disease (LRD) or intermediate risk disease (IRD) become IRD and high risk disease (HRD) respectively if a concomitant renal dysfunction or involvement is present.

Furthermore, any IRD must be upgraded to HRD if one or more among serum uric acid (sUA), phosphatemia or kalemia are upper limit of normal (ULN).
The most commonly referenced TLS incidence is from Hande and Garrow's 1993 retrospective analysis of 102 adult patients with high-grade non-Hodgkin's lymphoma (NHL) at intermediated to high risk (Hande and Garrow, 1993). They reported the incidence of TLS identified through serial measurements of laboratory values to be 42%, whereas the incidence of clinically significant TLS was 6% in the same population. Overall the reported incidence varies from sporadic case reports in certain solid malignancies (Baeksgaard et al. 2003) and slow-growing hematologic malignancies (Al-Kali et al., 2009) to the 26.4% incidence described in Burkitt's ALL (B-ALL) (Wössmann et al., 2003). Examples of TLS reported incidence in hematologic malignancies are summarized below.
Data were analyzed from two multicenter studies involving 1791 paediatric patients with NHL. TLS incidence was the highest in the subgroup of patients with B-ALL (26.4%) followed by the subgroup with either Bukitt's lymphoma or B-ALL (8.4%) (Wössmann et al., 2003).
A total of 788 patients (433 adults and 322 children) with acute leukemia and NHL from Belgium, The Netherlands, Spain and UK were screened retrospectively for hyperuricemia and TLS (Annemans et al., 2003). The reported incidence of hyperuricemia and TLS was respectively overall 18.9% and 5%, in NHL 19.6% and 6.1%, in ALL 21.4% and 5.2% and in acute myeloid leukaemia (AML) 14.7% and 3.4%.
Among 328 patients aged ≤ 18 years diagnosed with ALL between 1998 and 2004 at the Hospital for Sick Children in Toronto 23% met criteria for TLS (Truong et al., 2007).
In a study on 772 patients aged ≥13 years with AML treated with chemotherapy, 5% were diagnosed with CTLS and 12% with LTLS (Montesinos et al., 2008). Unlike LTLS, CTLS was associated with a higher rate of death from induction therapy with hemorrhage and renal failure as main causes. TLS was significantly associated with pretreatment WBC >75 vs 25-75 vs ≤25X109/L, LDH >4 vs 1-4 vs ≤1XULN, creatinine >1.4 vs ≤1.4 mg/dL, UA >7.5 vs ≤7.5 mg/dL, FAB subtype M4-M5, and hepatosplenomegaly. In addition CTLS was significantly associated with old age, with 60 years being the most significant cut-off point that resulted significant also for LTLS. Based on these results Montesinos et al. developed and validated a predictive scoring system for CTLS risk.
The incidence of tumor lysis syndrome is unknown. The prevalence varies among different malignancies; bulky, aggressive, treatment-sensitive tumors are associated with higher frequencies of tumor lysis syndrome. In studies of frequency in patients with intermediate-grade or high-grade non-Hodgkin lymphomas, laboratory evidence of tumor lysis syndrome (42%) occurred much more frequently than the symptomatic clinical syndrome (6%). In children with acute leukemia receiving induction chemotherapy, silent laboratory evidence of tumor lysis syndrome occurred in 70% of cases, but clinically significant tumor lysis syndrome occurred in only 3% of cases. As advances are made in cancer treatment and as high-dose regimens become more commonplace, tumor lysis syndrome incidence may increase and the syndrome may emerge in a broader spectrum of malignancies (Medscape, Updated: Apr 22, 2016 Ikeda et al.).

Prevalence:

The true prevalence of Tumor Lysis Syndrome (TLS) is not well established. The lack of definitions universally embraced for its diagnosis made the analysis of the studies examining TLS, either as exposure or outcome, complicated by the high heterogeneity. TLS comprises two components: laboratory TLS (LTLS) and clinical TLS (CTLS), the definition of which

has been standardized by Cairo and Bishop in 2004 (Cairo et al., 2004) based on an earlier definition by Hande and Garrow (Hande and Garrow, 1993) as shown in table SI.1.3.

Table SI.1.3. Comparison of Tumor Lysis Syndrome definition

References	Laboratory TLS	Clinical TLS
Hande and Garrow 1993	≥2 of the following metabolic abnormalities occurring within 4 days of treatment: • 25% increase from baseline in UA • 25% increase from baseline in potassium • 25% increase from baseline in phosphate • 25% decline from baseline in calcium	Laboratory-defined TLS accompanied by any of the following: • Creatinine>221 µmol/L (2.5 mg/dL) • Postassium>6 mmol/L (6 mEq/L) • Calcium <1.5 mmol/L (6 mg/dL) • Development life-threating arrythmia • Sudden death
Cairo and Bishop 2004	≥2 of the following metabolic abnormalities occurring simultaneously within 3 days prior and up to 7 days post-treatment initiation: • UA≥476 µmol/L or 25% increase from baseline • Potassium≥6 mmol/L or 25% increase from baseline • Phosphorous ≥2.1 mmol/L (children) ≥1.45 mmol/L (adults) or 25% increase from baseline • Calcium≤1.75 mmol/L or 25% decrease from baseline	Laboratory-defined TLS accompanied by any of the following: • Creatinine≥1.5 ULN for patients >12 years of age or age adjusted • Seizures • Cardiac dysrhytmia • Death

UA:uric acid; ULN:upper limit of normal. Modified from McBride et al., 2012.

Demographics of the population in the authorised indication and risk factors for the disease:
Males and females of any age or ethnic group can be affected by TLS. However advanced age may increase the risk of developing TLS due to reduced glomerular filtration rate and the higher likelihood of pre-existing serious metabolic, cardiac, renal or multisystemic comorbidities which may predispose to TLS. For instance a patient with nephropathy from hypertension, diabetes or gout has higher risk of acute renal failure and TLS (Howard et al., 2011). The main risk factors are summarized in table SI.1.2.
Although tumor lysis syndrome occurs in all age groups, advanced age leading to impaired renal function may predispose patients to clinically significant tumor lysis syndrome owing to a decreased ability to dispose of tumor lysis byproducts (Medscape, Updated: Apr 22, 2016 Ikeda et al.).

The main existing treatment options:
Appropriate management of TLS should be centered around a) risk assessment of cancer patients, b) preventive treatment where appropriate, c) electrolyte monitoring in patients undergoing cytotoxic therapy, d) and rapid appropriate therapeutic intervention as necessary.

TLS prophylaxis shall be carried out according to TLS risk assessment described in figure SI.1.1. (Cairo et al., 2010). TLS management is quite identical in children and adults, with the exception of an expected higher benefit from a faster control of sUA in pre-adolescent population which is at higher risk of developing crystal-associated ARI due to the age-associated high level of circulating phosphate (Howard et al., 2011).

In general, patients with LRD should be monitored for development of TLS and complications; normal hydration and no prophylaxis for hyperuricaemia should be given except in cases of signs of metabolic changes, bulky and/or advanced disease and/or high proliferative disease, in which case allopurinol should be added.
Patients with IRD should receive increased hydration and allopurinol (100–300 mg/day). Allopurinol is administered at a dose of 100 mg/m2/dose every 8 hours (10 mg/kg/day divided every 8 hours) per os (maximum 800 mg/day) or 200–400 mg/m2/day in 1–3 divided intravenous doses (maximum 600 mg/day) without the need for alkalinization.
In patients with HRD of developing TLS, frequent monitoring should be performed, increased hydration (3000 ml/m2/day), unless evidence of renal insufficiency and oliguria, and rasburicase (0.1–0.2 mg/kg) should be given intravenously as one single dose to be repeated only if clinically necessary. Lastly, patients who develop LTLS after being originally classified as either LRD or IRD, should receive rasburicase unless clinically contraindicated.

With regard to prevention of cardiac dysrhythmias and neuromuscular irritability, hyperkalemia remains the most dangerous component of TLS because it can cause sudden death due to cardiac dysrhythmia. Therefore potassium levels frequent mesurements, continuous cardiac monitoring and the administration of oral sodium polystyrene sulfonate are recommended in patients with TLS and ARI. Hemodialysis and hemofiltration effectively remove potassium. Glucose plus insulin or beta-agonists can be used as temporizing measures, and calcium gluconate may be used to reduce the risk of dysrhythmia while awaiting hemodialysis. Hypocalcemia can also lead to life-threatening dysrhythmias and neuromuscular irritability; controlling the serum phosphorus level may prevent hypocalcemia. Symptomatic hypocalcemia should be treated with calcium at the lowest dose required to relieve symptoms, since the administration of excessive calcium increases the calcium–phosphate product and the rate of calcium phosphate crystallization (Howard et al., 2011).

Urinary alkalinization with sodium bicarbonate has been a standard approach to increase UA excretion. Alkalinization is, however, associated with a reduction in the solubility of calcium phosphate, thus potentially creating the problem in the setting of hyperphosphatemia, a more serious condition than the one it aims to treat. Therefore guidelines for the management of TLS (Coiffier et al., 2008) state that sodium bicarbonate is no longer recommended for TLS management. The rationale for this recommendation is that although alkalinization promotes UA excretion, it has a relatively small impact on xanthine and hypoxanthine solubility.

Reducing the level of UA with the use of a Xanthine Oxidase (XO) inhibitor, such as allopurinol and febuxostat, or the urate oxidase rasburicase can preserve or improve renal function and reduce serum phosphorus levels as a secondary beneficial effect.

Allopurinol is a purine-analogue, non selective inhibitor of XO, which has been used for the prevention and management of hyperuricaemia in leukaemia and lymphoma since over 40 years (Krakoff and Meyer, 1965). Compared to the urate oxidase rasburicase, allopurinol is largely slower in reducing sUA, as it only prevents the new formation of UA but has no action on the existing one. Indeed, in a randomized study for the prevention of TLS in children, allopurinol was significantly less effective than rasburicase in reducing sUA within 4 hours from the drug administration with 86% and 12% reduction of initial sUA for rasburicase and allopurinol respectively (Goldman et al., 2001). Moreover, allopurinol is not effective enough in maintaining the recommended target sUA level ($\leq$ 7.5 mg/dL) in some patients and it is not tolerated in up to 5% of subjects due to hypersensitivity reactions (Schlesinger, 2004; Cortes et al., 2010). Finally, it requires careful dose-adjustments in patients with renal or hepatic

impairment and has important drug interactions. In paediatric patients, allopurinol is administered at a dose of 50 to 100 mg/m2 every 8 hours orally (maximum dose, 300 mg/m2/day) or 10 mg/kg/day divided every 8 hours (maximum dose, 800 mg/day). For patients unable to take allopurinol orally, intavenous administration may be considered, at a dose of 200 to 400 mg/m2/day in one to three divided doses (maximum dose, 600 mg/day). The guidelines for allopurinol dosages and administration for adult patients are the same as those for paediatric patients. Treatment may be started 1 to 2 days before the start of induction chemotherapy and may be continued for up to 3 to 7 days afterwards, based on the ongoing risk of TLS (Coiffier B et al., 2008). As example, the indication in adults and children reported in the SmPC approved in UK and Italy is reported in table SI.1.4.

Table SI.1.4. Approval status of Allopurinol in United Kingdom and Italy

	UNITED KINGDOM	ITALY
ZYLORIC® (Allopurinol) 100 mg tablets ZYLORIC® (Allopurinol) 300 mg tablets ALLOPURINOL 100 mg tablets ALLOPURINOL 300 mg tablets	Reduction of urate/uric acid formation in conditions where urate/uric acid deposition has already occurred or is a predictable clinical risk (e.g. treatment of malignancy potentially leading to acute uric acid nephropathy) Children Use in children is rarely indicated except for malignant conditions (especially leukaemia) and certain enzyme disorders such as Lesch. Nyhan syndrome	Reduction of urate/uric acid formation in conditions where urate/uric acid deposition has already occurred or is a predictable clinical risk (e.g. treatment of malignancy potentially leading to acute uric acid nephropathy Children Use in children is rarely indicated except for malignant conditions (especially leukaemia) and certain enzyme disorders such as Lesch. Nyhan syndrome)

Source: adapted from approved SmPC

Rasburicase is a recombinant form of the urate oxidase, an enzyme present in most mammals but not in humans, which catalyzes the enzymatic oxidation of uric acid into a 5 times more soluble compound called allantoin. In both adults and children rasburicase demonstrated higher efficacy than allopurinol not only in reducing sUA level but also in rapidly achieving sUA control, with a near 7 times smaller time to sUA control in hyperuricaemic patients (Goldman et al., 2001; Cortes et al., 2010). In certain cases, such as in patients experiencing massive tumour lysis, it may be necessary to increase the administration schedule to twice daily. The length of treatment is related to control of plasma uric acid levels, and therefore clinical judgment should be used. Treatment is not necessary when uric acid is extremely low or no longer detectable. Rasburicase is administered as intravenous formulation at a dose of 0.10 to 0.2 mg/kg daily, dependent on whether the intention is prevention or treatment. Potential serious adverse reactions are rare and include anaphylaxis, rash, hemolysis, methemoglobulinemia, fever, neutropenia (with or without fever), respiratory distress, sepsis, and mucositis. Other adverse reactions include vomiting, fever, nausea, headache, and diarrhea. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, in which may cause hemolytic anemia. The approval status of rasburicase in Europe and United States in indicated in table SI.1.5.

Table SI.1.5. Approval status of rasburicase in European Economic Area and in United States

	EEA (European Economic Area)	US (United States)
EEA: FASTURTEC® (Rasburicase) 1.5 mg/ml powder and solvent for solution for infusion. EEA:FASTURTEC® (Rasburicase) 7.5	Treatment and prophylaxis of acute hyperuricaemia, in order to prevent acute renal failure, in patients with haematologic malignancy with a high tumour burden and at risk of a rapid tumour lysis or shrinkage at initiation of chemotherapy	Initial management of plasma uric acid levels in paediatric and adult patients with leukaemia, lymphoma, and solid tumour malignancies who are receiving anti-cancer therapy expected to result in tumour lysis and subsequent elevation

mg/ml powder and solvent for solution for infusion US: ELITEK® (Rasburicase) 1.5 mg powder per single-use vial US: ELITEK® (Rasburicase)7.5 mg powder per single-use vial		of plasma uric acid Limitation of use: Elitek® is indicated only for a single course of treatment Elitek label (FDA): Administer at 0.2 mg/kg as an intravenous infusion over 30 minutes daily for up to 5 days. In Europe, treatment with Fasturtec (Rasburicase) may be prolonged up to 7 days

Source: adapted from EU SmPC and SPC/US

A Variation Application proposed ADENURIC (febuxostat) 120 mg once daily (QD) for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of TLS.
Febuxostat is a novel, potent, non-purine selective inhibitor of XO that inhibits the formation of UA from xanthine. Febuxostat has minimal effect on other enzymes involved in purine and pyrimidine metabolism such as guanine deaminase, hypoxanthine-guanine, phosphoribosyltransferase, orotate phosphoribosyltransferase, orotidine monophosphate decarboxylase, and purine nucleoside phosphorylase (Takano et al., 2005).
Thus, febuxostat is both a more potent and a more selective inhibitor of XO than allopurinol, which is key in the differentiation of febuxostat from allopurinol. Febuxostat does not appear to have the hypersensitivity profile of allopurinol that is not tolerated in up to 5% of patients (Schlesinger et al., 2004). In addition febuxostat does not require dose adjustment in patients with mild/moderate renal impairment that is a frequent condition in TLS patient population.
Rasburicase is certainly superior to XO inhibitors in terms of potency and rapidity of action, and as such it represents the gold standard for patients at high risk of TLS. However it retains some disadvantage such as intravenous administration, possible severe hypersensitivity reactions, and the formation of neutralizing antibodies. These issues, together with cost considerations and pending pharmacoeconomic data, have strongly limited its use in clinical practice.
In this context, febuxostat as orally administrated drug, more effective than allopurinol, less costly than rasburicase and with a favourable safety profile, represent a remarkable improvement in the prevention/treatment of TLS.
Febuxostat was approved through a centralized procedure in the EU in April 2008 for the indication "Treatment of hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis)". Thus, its safety and efficacy profile has been extensively characterized in the above mentioned indication, as reported in detail in the relative EU Marketing Authorization Application (MAA). Therefore the clinical development programme of febuxostat for the prevention and treatment of TLS in adult population affected by haematological malignancies consisted of a single pivotal phase III study as agreed with the Committee for Medicinal Products for Human Use (CHMP) in the SA procedure (procedure no.: EMEA/H/SA/2153/1/2011/II) with the aims:
Primary: to compare the efficacy of febuxostat with allopurinol, in terms of sUA level control and preservation of renal function after seven days of treatment (Day 8) starting from 2 days prior to chemotherapy (Day 1).
Secondary: to compare the efficacy of febuxostat with allopurinol in terms of maintenance of sUA levels $\leq$ 7.5 mg/dL and in terms of occurrence of LTLS and CTLS according to Cairo-Bishop criteria to compare the safety of febuxostat with allopurinol.

A total of 346 patients with median age of 60 years (range 20-87), stratified according to TLS risk (intermediate vs high) and sUA level (≤ 7.5 mg/dL vs >7.5 mg/dL) were randomized 1:1 to either febuxostat or allopurinol starting from 2 days prior chemotherapy and continued for 7-9 days. A total of 339 subjects completed the study. The assigned treatment was blinded whereas the dose level was upon Investigator's choice between low/standard/high dose containing respectively either allopurinol 200/300/600 mg daily dose or febuxostat fixed 120 mg daily dose.
The study results have been extensively described in the Clinical Study Report (Annex 12). Summing up febuxostat showed a clinically relevant and statistically significant benefit over allopurinol in terms of control of sUA level throughout the whole treatment period, starting from two days prior chemotherapy and prolonged for a total of 7 to 9 days. In addition no safety concerns were raised from febuxostat or allopurinol treatments; overall the adverse events reported along the study were in line with those expected for the patient population, namely patients affected by haematologic malignancies and treated with first or following line(s) of chemotherapy.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

TLS mortality is mainly related to acute renal failure, cardiac arrhythmias due to hyperkalaemia and metabolic acidosis. However making inferences about TLS-specific mortality is difficult since TLS is associated with higher tumor burden but also with therapeutic efficacy. The presence of acute renal injury (ARI), even after adjustment for others markers of severity of illness, seems to be a potent predictor of death in TLS. A retrospective study (Darmon et al., 2010) of 63 patients (median age 50 years; range 32-64) with hematologic malignancies and TLS demonstrated that a hospital and 6-month mortality rates were significantly lower in patients without ARI (7% and 21% respectively) than in the group with ARI (51% and 66% respectively). This relationship persisted after multivariable adjustment with ARI independently increasing the odds of higher hospital mortality by 10.41 (95% CI 2.01-19.170; p=0.005) and 6-month mortality by 5.61 (95% CI 1.64-54.66; p=0.006). Overall the study showed that in patients with TLS, ICU management in presence of ARI was associated with higher short- and long-term mortality.

Important co-morbidities:

Comorbidities, whether chronic illnesses present at the initiation of anticancer therapy or acute conditions due to the hematologic malignancies, may promote or amplify the metabolic and electrolyte imbalances caused by TLS. In adults these effects may further weaken an already strained homeostatic regulation and thereby significantly increase the risk of serious clinical complications of TLS. Elderly patients (age ≥ 65 years) are particularly likely to have comorbidities, which may worsen their prognosis in the event of TLS, including baseline chronic renal insufficiency and/or heart disease. TLS risk factors of particular relevance for elderly patients are age-related alterations in heart anatomy and function, obesity, alterations of the cardiovascular and circulatory systems, use of multiple drugs with potential pharmacodynamic interactions, age-related decrease in glomerular filtration rate, tobacco use, excessive alcohol consumption, and unhealthy dietary habits (Pumo et al., 2007). The risk of renal complications is particularly high in elderly patients with baseline renal disease, which may have been caused by diabetes, hypertension, chronic renal diseases, gout or treated malignancies. Furthermore, congestive heart failure, use of thiazide or loop diuretics, obesity,

type II diabetes, renal impairment, hypertriglyceridemia, and peripheral vascular disease are major cardiovascular risk factors associated with hyperuricemia.

According to the model developed by Montesinos et al., high WBC count, pretreatment hyperuricemia, and high baseline serum creatinine and LDH concentrations were significant independent prognostic factors for the development of TLS (Montesinos et al., 2008). In addition to these basic risk categories, other risk factors such as renal function and sUA level at baseline were incorporated into the recommendations for TLS prevention and treatment (Coiffier et al., 2008). For example, the presence of baseline hyperuricemia (defined as sUA level > 7.5 mg/dL) was a modifier of the recommendation of antihyperuricemic therapy for patients at intermediate risk of TLS; in presence of high baseline sUA levels, the drug of choice should not be allopurinol but rather rasburicase. However, these guidelines did not uniformely assess risk depending on renal involvement by the disease or renal function. Consequently, another consensus panel was convened to build upon the 2008 guidelines and produced a medical decision tree for ranking TLS risk adjusted for renal impairment and/or involvement by the disease at the time of TLS diagnosis (Cairo et al., 2010).
The occurence of oncologic emergencies other than TLS may arise at any time during the course of a hematologic malignancy (Lewis et al., 2011) as described below.
Hypercalcemia is experienced in hematologic malignancies by patients with multiple myeloma and adult T-cell leukaemia/lymphoma. A variety of mechanisms can explain elevated calcium in cancer patients: systemic release of parathyroid hormone-related peptide by the tumor, which does not require the presence of bone metastases; local paracrine stimulation of osteoclasts by metastases to bone, leading to osteolytic effects; and systemic secretion of vitamin D analogues by the tumor, which also does not require the presence of bone metastases.
Iatrogenic hyponatremia can be caused by cisplatin, cyclophosphamide, ifosfamide, vinca alkaloids and imatinib. Each of these drugs can cause syndrome of inappropriate antidiuretic hormone (SIADH), but all can also produce hyponatremia through a variety of other mechanisms (eg, platinum-induced salt-wasting nephropathy).
Hypoglycemia due to the anabolic and biosynthetic demands of dividing cells in tumors with high mitotic rates; this is most often seen in aggressive lymphomas (eg, Burkitt lymphoma).
Infectious emergencies may be caused by neutropenia due to cancer's direct interference with hematopoiesis, as in leukemia or metastatic replacement of the bone marrow, or as effect of cytotoxic therapy, such as anthracyclines, taxanes, topoisomerase inhibitors, platinums, gemcitabine, vinorelbine, and certain alkylators like cyclophosphamide and ifosfamide.
Hyperviscosity syndrome (HVS) refers to the clinical sequelae caused by increased blood viscosity. Increased serum viscosity (SV) is a result of excess proteins, usually immunoglobulins, most commonly arising from Waldenstrom macroglobulinemia and multiple myeloma. Increased blood viscosity can result from elevated cellular components seen in hyperproliferative states such as leukaemia and myeloproliferative diseases such as polycythemia vera (PV). When hyperviscosity results from elevated white blood cells, it is referred to as hyperleukocytosis or, if symptomatic, leukostasis. Risk for leukostasis increases with WBC greater than 100x109/L. The incidence ranges from 5% to 13% in patients with AML and 10% to 30% in adult patients with ALL. Other risk factors include younger age (with presentation in infants being most common), ALL with 11q23 rearrangement or the Philadelphia chromosome, and AML subtypes M3, M4, and M5.

As the target population comprises patients with hematologic malignancies at intermediate to high risk of TLS, concomitant intensive cytoreductive chemotherapy, cytolytic andibodies and/or radiation therapy is are usually associated. TLS occurs most often in patients with

acute leukemia with high WBC and in those with high-grade lymphomas in response to aggressive treatment, although occasionally may occur spontaneously, prior to any form of therapy. The more aggressive is the therapy, the higher is the rate of cell lysis and the greater is the TLS risk. For example, some protocols for ALL start with a week of prednisone monotherapy while others begin with a combination of glucocorticoid, vincristine, asparaginase and daunorubicin. A patient treated on a latter protocol would have a greater risk (Howard et al., 2011). TLS also is common in patients receiving chemotherapy for acute adult human T-cell lymphotrophic virus-1–associated T-cell leukemia/lymphoma (ATLL). Fatal TLS occurred in an obese 57-year-old woman with ATLL, in the background of systemic lupus erythematosus, after chemotherapy with high-dose prednisone and adjusted doses of cyclophosphamide and doxorubicin (Fritsch-Stork et al., 2009). Even for hematologic malignancies with a relatively low incidence of TLS, such as chronic lymphocytic leukaemia (CLL), the risk of TLS may increase with the growing use of novel agents that are highly effective inducers of apoptosis. In CLL, WBC count ≥50,000 cells/μL as well as targeted and/or biological therapies (e.g. fludarabine, rituximab) confer intermediate-risk status for TLS, according to 2010 TLS expert panel recommendations for TLS evaluation of risk and prophylaxis (Cairo et al., 2010). A number of case reports have associated imatinib, bortezomib and thalidomide with the development of TLS in adults. Bortezomib and/or thalidomide caused TLS in several patients treated for multiple myeloma, though such disease is at low TLS risk according to the current TLS risk assessment algorythm (Fuente et al., 2004; Sezer et al., 2006; Huston et al., 2006; Chim, 2008; Bereson et al., 2008; Cairo et al., 2010).
Other concomitants medications may result as treatment of preexisting chronic illnesses or metabolic, cardiovascular, infectious, neurologic, hematologic and/or respiratory abnormalities occurring during the course of a hematologic malignancy. It is worth noting that many antihypertensives may increase the risk of hyperkaliemia in patients with renal tubular acidosis (Weir, 1997; Sica, 2006) and treatment with bisphosphonates, anticonvulsivants, cisplatin and the combination of 5-fluorouracil and leucovorin may cause hypocalcemia (Moe, 2008).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

The nonclinical findings within the febuxostat development program had been detailed in Modules 2.4, 2.6 and 4 of the application for registration.
A series of preclinical toxicology studies was conducted with febuxostat that met or exceeded ICH guidelines for chronic use of human drugs.
-Toxicity of febuxostat was assessed following single-dose oral administration in rats and dogs, daily repeated-dose oral administration in mice (4-weeks and 13-weeks), rats (5-weeks, 13-weeks and 26-weeks) and dogs (13-weeks and 52-weeks).
-Two-year carcinogenicity studies have been conducted in mice and rats.
-The potential for effects on fertility and embryonic/fetal development was assessed via oral administration in rats and rabbits. The potential for effects on pre- and postnatal development was assessed following oral administration in rats.
-The potential for antigenicity was assessed in mice and guinea pigs.
-The potential genotoxic effects were assessed in a battery of tests.
-It was reasonable to suppose that in clinical practice it would be likely that patients given febuxostat would include many with pre-existing cardiovascular disorders. Heart attacks and other vascular events are relatively common amongst gout patients because of age and the effect of hyperuricaemia on the kidneys, blood pressure, vascular endothelial cell and platelet function. Accordingly, several special pharmacological studies were done in animal models of appropriate cardiovascular disorders to exclude any deleterious effect of febuxostat on the heart.

Kidney, urinary bladder, thyroid gland and liver were identified as target organs in repeat dose studies of febuxostat. Adverse effects in kidney and urinary bladder in rodents and dogs, including bladder tumour formation in rodents were related to the formation of xanthine crystals and/or calculi in the kidney and/or bladder as a result of xanthine oxidase (XO) inhibition. Data gained from subsequent clinical studies suggested that the xanthine and hypoxanthine crystalluria findings were not relevant to humans. Indeed due to species differences in nucleic acid metabolic turnover, urine volume, urine composition and urinary tract anatomy, adverse effects in kidney and urinary bladder, including bladder tumours, do not occur in humans.

Based on the results from all the toxicology studies, febuxostat is considered to be safe at the dose levels recommended for extended use in humans.

Key safety findings from non-clinical studies and relevance to human dosage:

Toxicity

- **Key issues identified from acute or repeat-dose toxicity studies:**

Lethal dose 50 was between 300 and 600 mg/kg per os in rats and > 2000 mg/kg per os in dogs.
Adverse effects related to thyroid (decreases in T3 and T4, increases in TSH with accompanying follicular cell hyperplasia) were observed in rats during repeated dose toxicology studies (26 weeks duration). Rat thyroid is more sensitive to proliferative lesions caused by chronic TSH stimulation than human thyroid. Even in rats, the most sensitive species, the effects of febuxostat on the thyroid were observed only at a dose with a 31-fold

higher exposure (AUC) compared to the mean exposure (AUC) observed in humans at a dose of 80 mg. Based on this preclinical data, thyroid parameters were monitored in Long Term Extension (LTE) studies.

Relevance to human usage:

Not relevant
The incidence rate of elevated TSH value is expressed as patient-year of exposure because of a substantial imbalance in study drug exposure among the treatment groups in the LTE studies.
The percentages of subjects with at least one increased TSH value based on the annualized rates adjusting for the substantial differences in exposure between the treatment groups in the LTE studies are 2.9%, 3.0%, and 6.4% for febuxostat 80 mg, febuxostat 120 mg, and allopurinol, respectively.
Based on these results, blood thyroid stimulating hormone increased has been inserted in Section 4.8 of the EU-SmPC as uncommon event, a warning on thyroid disorders has been inserted in Section 4.4 and in Section 5.1 a sentence describes the crude incidence (not incidence rate) of these events in phase III studies.

- **Reproductive/developmental toxicity:**

Febuxostat was found to have no effect on fertility and reproductive performance of male and female rats. Reproductive toxicology studies in rats and rabbits indicate that febuxostat is not teratogenic in pregnant animals. The reduction in weaning index and reduced development in F1 offspring observed in the pre- and postnatal study in rats were considered to be secondary effects of kidney injury caused by xanthine crystals and/or calculi.

Relevance to human usage:

Animal studies do not indicate direct or indirect harmful effects on fertility and reproduction but the potential risk in humans is unknown and therefore SmPC and PL report an advice on this matter.

- **Genotoxicity:**

In a chromosomal aberration study using cultured Chinese hamster cells, induction of chromosomal aberration was observed in cultures treated with high doses (422.68 to 632.76 µg/mL) of febuxostat. However, additional chromosomal studies conducted using both *in vitro* (human peripheral blood lymphocytes) and *in vivo* (rat bone marrow) systems showed no chromosomal damage. Moreover, a mouse lymphoma mutagenesis assay conducted in the absence and presence of metabolic activation was also negative. In addition, results of studies of reverse mutation in bacteria, bone marrow micronuclei in mice and *in vivo-in vitro* unscheduled DNA synthesis in rat hepatocytes were all negative. Therefore, there is overwhelming evidence to indicate that febuxostat does not have genotoxicity potential.

Relevance to human usage:

Not relevant. Negative results in animals.

- **Carcinogenicity:**

Xanthine and hypoxanthine crystalluria. In male rats, a statistically significant increase in urinary bladder tumours (transitional cell papilloma and carcinoma) was observed only in association with xanthine calculi in the high dose group, at approximately 11 times human exposure.

Relevance to human usage:

These findings are considered a consequence of species-specific purine metabolism and urine composition and are not relevant to clinical use (Section 5.3, SmPC)

Safety pharmacology

- **Nephrotoxicity:**

Kidney was considered a target organ as results of repeated toxicity studies in animals. Changes in haematological parameters are considered to be secondary effects due to kidney injury and have been observed at total exposures which are 14- to 33-fold higher than those expected at the highest recommended dose in humans (120 mg).

Relevance to human usage:

Not relevant at the doses used in humans. SmPC and PL report that no dose adjustement is necessary in patients with mild or moderate renal impairment.

- **Hepatotoxicity:**

There were some increases in marker enzymes of liver damage but no histological change was seen after high doses of repeated toxicity studies in rats.

Relevance to human usage:

Not relevant at the doses used in humans. SmPC and PL report that no dose adjustement is necessary in patients with hepatic impairment.

- **Cardiovascular Effects:**

Febuxostat up to 500 μM did not block the hERG current. It did produce small changes in the amplitude of the current at certain transmembrane voltages. This effect is not known to have any pathogenetic importance. In the isolated Purkinje fibre test febuxostat up to 1 μM had no effect but at 50 μM it produced some decrease in the rate of depolarisation.
In the experiment in conscious, telemetered dogs dosed with febuxostat 0, 5 or 50 mg/kg/day per os for 14 days there were few transient episodes of hypotension on Days 6 or 7. The scattered nature of these events, the lack of concurrent changes in the ECG or heart rate and the rapid spontaneous recovery despite maintenance of a high plasma drug level do not suggest a drug-related effect. Febuxostat did not have any deleterious effect on animal models of cardiovascular diseases.

Relevance to human usage:

Although there is no preclinical evidence of gross cardiovascular toxicity of febuxostat, the cardiovascular risk is properly addressed in the SmPC and PL, where the increased risk of cardiovascular diseases in patients with pre-existing major CV disease is considered.

- **CNS Effects:**

In an Irwin test in mice febuxostat administered at doses higher than 100 mg/kg showed a slight, short-lived general depressant action not associated with change in locomotion. There was no effect on hexobarbital sleeping time, on the response to chemical convulsants or on the pain response.

Relevance to human usage:

Not applicable

Other toxicity-related information or data

- **Mechanism for drug interactions:**

Febuxostat did not affect the hypotensive effect of nifedipine or the hypoglycaemic effect of glybenclamide. The in vitro and in vivo investigations of febuxostat indicate that it is unlikely to affect the metabolism of other drugs reliant on major Phase I or Phase II pathways nor it will be affected by conventional enzymes inducing or inhibiting agents because its own metabolism uses several CYP450s and UDPGT isoforms in a promiscuous manner.
Febuxostat has no relevant inhibitory action on the CYP450s, nor does it induce them, and it seems unlikely that it would affect the glucuronidation capacity of the liver.
Warfarin, digoxin ibuprofen, captopril, bezafibrate, verapamil and nitrendipine did not affect the protein binding of febuxostat and febuxostat did not alter the binding of warfarin, ibuprofen, nitrendipine and verapamil to human plasma proteins at therapeutically relevant concentrations.
The literature contains substantiated accounts of inhibition of the metabolism of immunosuppressive agents such as 6-mercaptopurine (6-MP) and azathioprine (a pro-drug of 6-MP) by allopurinol. As those effects are considered to be due to inhibition of XO, they may be expected to occur after febuxostat treatment too with a potential overexposure of 6-MP which can lead to haematological toxicities. For these reasons a non-clinical study in rats (study MRPO-2015-PKM005) to investigate drug-drug interaction (DDI) between azathioprine and febuxostat or between azathioprine and allopurinol has been carried out. Either febuxostat or allopurinol increased plasma levels of 6-MP, but, as expected from the different potency in inhibiting XO, febuxostat was more potent than allopurinol. A population PK model for the interaction between febuxostat and 6-mercaptopurine (REP-POPPK-MRPO-2015-PKM005) to be applied in humans was developed based on these preclinical data. The extrapolated PK model for 6-MP in human was qualified by comparing the predicted PK after the administration of azathioprine alone with literature data (Zins et al., 1997; Van et al., 1996). The modeling and simulation framework predicted an azathioprine dose reduction to 20% and 30% of the standard dose when co-administered with febuxostat and allopurinol, respectively.

Relevance to human usage:

Although the risk for inadvertent co-administration of febuxostat and azathioprine is quite small because these drugs are used in different populations, the potential consequences, including neutropenia (due to increased exposure to 6-MP), could be severe or life threatening. Nevertheless, a limited population of patients may benefit of this combination (gout patients with intolerance to allopurinol and inflammatory bowel diseases controlled with azathioprine or 6-MP). The results of the REP-POPPK-MRPO-2015-PKM005 study has reasonably allowed to detect the reduction in dose of azathioprine / 6-MP in case of simultaneous administration with febuxostat. When transferred into the febuxostat SmPC, this information should allow a safer use of azathioprine / 6-MP in patients taking febuxostat and a substantial reductions of toxicities induced by a too high plasma levels of 6-MP. The adequacy of the previously applied modelling and simulation approach to predict the DDI in human (REP-POPPK-MRP-2015-PKM-005) was confirmed by the results of a clinical drug-drug interaction study (FAI-01) in healthy volunteers, receiving azathioprine 100 mg alone and a reduced dose of azathioprine (25 mg) in combination with febuxostat (40 or 120 mg). Thus, the recommended azathioprine dose adjustment when co-administered with febuxostat, i.e. reduction to at least 20% of the usual azathioprine dose, has been confirmed.

- **Immunotoxicity Studies:**

Not antigenicity was found in studies in rats and guinea-pigs.

Relevance to human usage:

Not applicable

Currently, there are no special populations identified that require nonclinical studies.

Febuxostat had almost no other relevant effects in a wide variety of pharmacological and toxicological investigations as the occurrence and consequences of xanthine and hypoxanthine crystalluria are not considered to be a risk in humans. Increased urinary xanthine excretion is an inevitable consequence of therapeutic use of any XO inhibitor but it does not lead to renal damage in humans except in special cases such as in patients with Lesch-Nyhan syndrome (in which the rate of urate formations is greatly increased), as well documented after use of allopurinol. Thyroid hyperplasia has been seen in the rat after high doses. This species is uniquely susceptible to such effects, which are not considered relevant to humans.

Data from the nonclinical program indicate that febuxostat is a potent, selective inhibitor of XO, well suited to the treatment of hyperuricaemia in conditions where urate deposition has already occurred. The interaction with azathioprine was confirmed as identified risk whereas thyroid effects should be considered as potential risk.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Summary information on the clinical trial exposure for the two indications (Gout and Tumor Lysis Syndrome) is provided in the below table SIII.1

Table SIII.1: Duration of exposure

Cumulative for all indications (person-time)		
Duration of exposure	Patients	Person-months
≥1 day	4073	≥ 136
≥7 days	3849	≥ 898
≥1 month	3020	≥ 3020
≥3 months	2745	≥ 8235
≥6 months	2347	≥ 14082
≥9 months	1095	≥ 9855
≥12 months	1039	≥ 12468
≥15 months	940	≥ 14100
≥18 months	902	≥ 16236
≥24 months	832	≥ 19968
≥30 months	769	≥ 23070
≥36 months	582	≥ 20952
≥42 months	308	≥ 12936
≥48 months	197	≥ 9456
≥54 months	60	≥ 3240
≥60 months	60	3600
Total person-months		≥ 172252

Summary information on the clinical trial exposure for the gout indication is provided in the below table SIII.1.1

Table SIII.1.1: Duration of exposure in the gout indication

Gout		
Duration of exposure	Patients	Person-months
≥1 day	4072	≥ 136
≥7 days	3677	≥ 858
≥1 month	3020	≥ 3020
≥3 months	2745	≥ 8235
≥6 months	2347	≥ 14082
≥9 months	1095	≥ 9855
≥12 months	1039	≥ 12468
≥15 months	940	≥ 14100
≥18 months	902	≥ 16236
≥24 months	832	≥ 19968
≥30 months	769	≥ 23070
≥36 months	582	≥ 20952
≥42 months	308	≥ 12936
≥48 months	197	≥ 9456
≥54 months	60	≥ 3240
≥60 months	60	3600
Total person-months		≥ 172212

Phase I studies included: TMX-99-001, TMX-00-002, TMX-00-003, TMX-00-006, TMX-01-008, TMX-01-009, TMX-01-010, TMX-01-012, TMX-01-014, TMX-01-016, TMX-02-017, TMX-02-018, C02-005, C02-006, C02-013, C02-023, C02-033, C02-034, C02-036, C03-040, C03-044, C03-054, C03-057, C03-059, and F-P107-162.
Phase II studies included: TMX-00-004.
Phase III studies included: C02-009 and C02-010, and F-GT06-153.
LTE studies included: TMX-01-005 and C02-021.
Cross-references: Integrated Summary of Safety (ISS), Statistical Table 2.0.1; 2.1.1 and 2.3.1.
Addendum to the Clinical Overview (Mod. 2.5 supplement): Table 5, 8, and 10.

A total of 4072 subjects received at least 1 dose of febuxostat in the Phase I, II, and III studies. Of these subjects, 1039 (26%) received febuxostat for at least 1 year.

Summary information on the clinical trial exposure for the gout indication is provided in the below table SIII.1.2

Table SIII.1.2: Duration of exposure in the Tumor Lysis Syndrome indication

Tumor Lysis Syndrome		
Duration of exposure	Patients	Person-months
6 days	1	0.2
7 days	116	27
8 days	17	5
9 days	39	12
Total person-months		44.2

Mean exposure to study treatment was 7.56 ± 0.92 days for the overall safety population, defined as all patients that received at least one administration of study drug.
Out of the 173 patients exposed to febuxostat, 65 (38 %) were females and 108 (62 %) were males. Regarding ethnicity, 167 (96.53%) patients were Caucasian, 1 (0.58%) was Black and 5 (2.89%) were of other ethnicity. The mean age (±SD) was 59 (±14.26) years, ranging from

20 to 87 years. The mean height (±SD) was 168.76 (±9.643) cm, the mean weight (±SD) was 73.84 (±14.923) kg and the mean BMI (±SD) was 25.77 (±4.726) kg/m2.

Summary information on the clinical trial exposure by age group and gender for all indications is provided in the below table SIII.2

Table SIII.2: Age group and gender

Age group	Patients	Person time
<45	1093	NA
45-<65	2256	NA
≥65	657	NA
Total	4006	NA
Gout*		
Age group	Patients	Person time
<45	1066	NA
45-<65	2171	NA
≥65	596	NA
Total	3833	NA
Tumor Lysis Syndrome		
Age group	Patients	Person time
<45	27	NA
45-<65	85	NA
≥65	61	NA
Total	173	NA

*In the patient treated for gout indication, data includes Phase III studies (C02-009, C02-010 and F-GT06-153) and LTE studies (TMX-01-005 and C02-021 and data collected at entry to the initial studies TMX-00-004, C02-009 and C02-010, from which subjects could subsequently enter the LTE studies.)

Summary information on the clinical trial exposure by dose and for all indications is provided in the below table SIII.3

Table SIII.3: Dose

Gout*		
Dose of exposure (mg QD)	Patients	Person time
10-70b,c	1061	NA
80	2468	NA
90-110	10	NA
120	1079	NA
130-240	164	NA
250-300	52	NA
Total	4072	NA
Tumor Lysis Syndrome (mg QD)		
Dose of exposure	Patients	Person time
120	173	NA
Total	173	NA

QD = once daily

*Patient treated for gout indication include:
Phase I studies included: TMX-99-001, TMX-00-002, TMX-00-003, TMX-00-006, TMX-01-008, TMX-01-009, TMX-01-010, TMX-01-012, TMX-01-014, TMX-01-016, TMX-02-017, TMX-02-018, C02-005, C02-006, C02-013, C02-023, C02-033, C02-034, C02-036, C03-040, C03-044, C03-054, C03-057, C03-059, and F-P107-162.
Phase II studies included: TMX-00-004.
Phase III studies included: C02-009 and C02-010 and F-GT06-153.
LTE studies included: TMX-01-005 and C02-021.
-Daily doses of 40, 80, 120 and 240 mg febuxostat were used in the Phase III studies.
-Daily doses of 40, 80 and 120 mg febuxostat were used in the LTE studies.
-Included 10 mg twice daily (BID) and 30 mg BID doses in Studies TMX-00-003 and TMX-99-001, respectively.
Cross-references: ISS, Statistical Tables 2.0.1, 2.1.1, 2.3.1, 3.12.4

Summary information on the clinical trial exposure by Ethnic origin and for all indications is provided in the below table SIII.4
Other stratifications should be provided where this adds meaningful information for risk management planning purposes (e.g. ethnic origin).

Table SIII.4: Ethnic origin

Ethnic origin	Patients	Person time
Gout*		
Caucasian	3070	NA
Black	381	NA
Asian	114	NA
Other	268	NA
Total	3833	NA

*Data included: Phase III studies (C02-009, C02-010 and F-GT06-153) and LTE studies (TMX-01-005 and C02-021 and data collected at entry to the initial studies TMX-00-004, C02-009 and C02-010, from which subjects could subsequently enter the LTE studies).

Ethnic origin	Patients	Person time
Tumor Lysis Syndrome		
Caucasian	167	NA
Black	1	NA
Other	5	NA
Total	173	NA

Summary information on the clinical trial exposure in special population is provided in the below table SIII.5.

Table SIII.5 Exposure to Febuxostat in Special Populations in the Phase I and Phase II Studies

Special population	Phase I	Phase II (N=115)
	n (%)	n (%)
Renal impairment		
Clcr [a,b,c]		
Normal (≥80 mL/min)	11 (34%)	33 (29%)
Any impairment (<80 mL/min)	21 (66%)	81 (70%)
Mild (50-79 mL/min)e	6 (19%)	60 (52%)
Moderate (30-49 mL/min)	7 (22%)	19 (17%)
Severe (10-29 mL/min)	8 (25%)	2 (2%)
Serum creatinine		
≤1.5 mg/dL	–	95 (90%)
>1.5 mg/dL	–	10 (10%)
Hepatic impairment (Child-Pugh classification)[e]		
Normal	11 (41%)	–
Mild	8 (30%)	–
Moderate	8 (30%)	–
Cardiac impairment/history[f]		
Atherosclerotic disease	–	–
Hypertension	–	24 (21%)
Congestive heart failure	–	4 (3%)

Phase I studies included: TMX-01-008 for renal impairment category; TMX-01-012 for hepatic impairment.
Phase II studies included: TMX-00-004.
Clcr = creatinine clearance (based on the Cockcroft-Gault equation using ideal body weight).
[a] N=32 and N=114 in the Phase I and Phase II studies, respectively.
[b] Units of mL/min/1.73 m2 in Study TMX-01-008.
[c] 50-80 mL/min/1.73 m2 in Study TMX-01-008.
[d] N=105 in Study TMX-00-004.
[e] N=27 in Study TMX-01-012.
[f] History of cardiovascular disease was not summarised for Study TMX-00-004;
Cross-references: data on file.

Summary information on the clinical trial exposure in gout indication in special population in the Phase III and LTE Studies is provided in the below table SIII.6 (in gout).

Table SIII.6 Exposure to Febuxostat in Special Populations in the Phase III and LTE Studies (gout indication)

Special population	Phase III only (N=2690)	LTE onlya (N=1143)
	n (%)	n (%)
Renal impairment		
Clcr [b,c]		
Normal (≥90 mL/min)	1117 (42%)	561 (49%)
Any impairment (<90 mL/min)	1573 (58%)	582 (51%)
Mild (60-89 mL/min)	1145 (43%)	435 (38%)
Moderate (30-59 mL/min)	420 (16%)	141 (12%)
Severe (10-29 mL/min)	8 (<1%)	6 (<1%)
Serum creatinine		
≤1.5 mg/dL	2570 (96%)	1114 (97%)
>1.5 mg/dL	120 (4%)	29 (3%)
Hepatic impairment (Child-Pugh classification)[d]		
Normal	–	–
Mild	–	–
Moderate	–	–
Cardiac impairment/history[e]		
Atherosclerotic disease	320 (12%)	116 (10%)
Hypertension	1332 (50%)	517 (45%)
Congestive heart failure	65 (2%)	24 (2%)

Note that subjects enrolled in the LTE studies had previously been enrolled in Study TMX-00-004 or the pivotal Phase III studies. Baseline data for subjects in the LTE studies were those collected at entry to the previous study.
Clcr = creatinine clearance (based on the Cockcroft-Gault equation using ideal body weight).
a At baseline of the combined Phase III studies.
b N=2690 and N=1143 in the Phase III and LTE studies, respectively.
c Calculated based on age, gender, ideal body weight and serum creatinine value for the combined Phase III studies.
d Subjects with active liver disease or hepatic dysfunction were excluded from the Phase II, Phase III and LTE studies.
e Cardiac history was summarised differently for the Phase II, III and LTE studies: history of cardiovascular disease was not summarised for Study TMX-00-004; history of cardiovascular disease was summarised in more detail (eg, atherosclerotic disease) for the combined Phase III or LTE studies.
Cross-references: ISS, Statistical Table 2.1.4, 2.3.3, and data on file.

Summary information on the clinical trial exposure in TLS indication to Febuxostat 120 mg QD in Special Population is provided in the below table SIII.7

Table SIII.7 Exposure to Febuxostat 120 mg QD in Special Population (n.173) (TLS indication)

Baseline Characteristics		n. subjects (%)
Hematologic malignancies	Acute Leukaemia	34 (19.66%)
	Chronic Lymphoid Leukaemia	80 (46.24%)
	Lymphoma	59 (34.10%)
TLS risk	High	30 (17.34%)
	Intermediate	143 (82.66%)
Serum Creatinine	Mean((±SD)	0.96 (±0,285)
	Median (Min.; Max.)	0.94 (0.31;2.19)
	Normal	130 (75.14%)
	Abnormal NCS	37 (21.39%)
	Abnormal CS	6 (3.47%)
GPT	Mean(±SD)	25.38 (±16.348)
	Median (Min.; Max.)	21 (5;125)
	Normal	147 (86.47%)
	Abnormal NCS	22 (12.94%)
	Abnormal CS	1 (0.59%)
	Not done	3
GOT	Mean(±SD)	26.64(±10.92)
	Median (Min.; Max.)	24 (8;75)
	Normal	147 (85%)
	Abnormal NCS	26 (15%)
	Abnormal CS	0
	N	173
Cardiac disorders history	Overall	41 (23.7%)
	Cardiac failure	2 (1.16%)
	Myocardial ischemia	10 (5.78%)
	Atrial fibrillation	9 (5.2%)
Vascular disorders	Overall	74 (42.78%)
	Arteriosclerosis	2 (1.16%)
	Hypertension	60 (34.68%)
	Essential hypertension	5 (2.89%)

Out of the 173 patients exposed to febuxostat the highest percentage had normal levels of creatinine (75.14%), GPT (86.47%) and GOT (85%) and was at intermediate risk of TLS (82.66%). Out of the 173 patients 23.7% reported in their medical history cardiac disorders and 42.78% suffered from vascular diseases.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

SIV.1.1 GOUT

Hypersensitive to febuxostat or allopurinol or any components of the formulations

Reason for exclusion:
This is a standard exclusion criterion for clinical studies.

Is it considered to be included as missing information? No

Rationale:
The issue "Serious skin/hypersensitivity reactions" is addressed as an important identified risk. Patient which develops hypersensitivity to febuxostat must discontinue the treatment without reintroducing it at any time (see warning on medicinal product allergy/hypersensitivity Section 4.4 of the SmPC).

No further investigation has been deemed necessary.

Patients aged less than 18 years old

Reason for exclusion:
This is a standard exclusion criterion for clinical studies not to be performed in the paediatric population.

Is it considered to be included as missing information?: Yes

Rationale:
Not applicable, the issue "No experience in: Children and adolescents" is addressed as a "missing information"

Patients aged more than 85 year old

Reason for exclusion:
This is a standard exclusion criterion for clinical studies.

Is it considered to be included as missing information?: No

Rationale:
The issue "Limited experience in elderly" has been addressed as missing information till RMP 5.1. In the current RMP version (6.0) it has been removed on the base of data collected in the post marketing experience (see section SVII).
No further investigation has been deemed necessary.

Breast-feeding or pregnant women

Reason for exclusion:
This is a standard exclusion criterion for clinical studies.

Is it considered to be included as missing information?: Yes

Rationale:
Not applicable, the issue "No experience in: pregnancy and lactation" is addressed as a "missing information"

Intolerance to allopurinol

Reason for exclusion:
As allopurinol was used as comparator in clinical trial, patients intolerant to allopurinol could have been allocated to allopurinol with a risk for their health.

Is it considered to be included as missing information?: No

Rationale:
No further investigation has been deemed necessary. A warning has been included in SmPC and PL in order to inform on the experience of "Serious skin/hypersensitivity reactions" in patients intollerant to allopurinol and exposed to febuxostat.

Co-treatment with azathioprine/mercaptopurine

Reason for exclusion:
Febuxostat and allopurinol, as xanthine oxidase inhibitors, may cause increased plasma concentrations of mercaptopurine and azathioprine. As active metabolites azathioprine/mercaptopurine are substrates of xanthine oxidase.

Is it considered to be included as missing information?: No

Rationale:
The issue "Drug-drug interaction with azathioprine or mercaptopurine " is addressed as an important identified risk.

Patients with severe renal impairment

Reason for exclusion:
These patients were excluded from C02-009, C02-010 and F-GT106-153 studies as there is a dose-limitation to 100 mg for allopurinol in these patients and the protocol scheduled a treatment with 300 mg.

Is it considered to be included as missing information?: Yes

Rationale:
Not applicable as the issue "Limited experience in: Severe renal impairment" is addressed as missing information.

Patients with hepatic impairment (active liver disease or hepatic dysfunction)

Reason for exclusion:
These patients were excluded from C02-009, C02-010 and F-GT106-153 studies as there is a dose-limitation to 100 mg for allopurinol in these patients and the protocol scheduled a treatment with 300 mg.

Is it considered to be included as missing information?: Yes

Rationale:
Not applicable as the issues "No experience in : Severe hepatic impairment" and "Limited experience in: Moderate hepatic impairment" are addressed as missing information.

Alcohol abuse within 5 years or current excessive alcohol use

Reason for exclusion:
These patients were excluded from C02-009, C02-010 and F-GT106-153 studies as the liver effects of alcohol may have confounded the liver effects of study treatments.

Is it considered to be included as missing information?: No

Rationale:
No further investigation has been deemed necessary. Gout patients should stop drinking alcohol. Warning on the monitoring of liver function prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment is included in SmPC section 4.4 and the issues the issues "No experience in : Severe hepatic impairment" and "Limited experience in: Moderate hepatic impairment" are addressed as missing information; the issue "Hepatic events" is addressed as important potential risk.

Use of thiazide diuretics

Reason for exclusion:
These patients were excluded from C02-009 and C02-010 studies because thiazide diuretics increase levels of serum uric acid and could have confounded the effect of study treatments

Is it considered to be included as missing information?: No

Rationale:
The analysis of safety and efficacy of febuxostat in the limited population treated with thiazide diuretics (i.e., 2% of the patients enrolled in phase III studies) has not highlighted any additional risk.

Concomitant urate lowering therapy

Reason for exclusion:
These patients were excluded from C02-009, C02-010 and F-GT106-153 studies as the urate lowering therapy could have confounded the effect of study treatments

Is it considered to be included as missing information? No

Rationale:
No further investigation has been deemed necessary.
Urate lowering drugs with different mechanisms of action can be co-administered.

Secondary hyperuricaemia or cancer

Reason for exclusion:
These patients were excluded from C02-009, C02-010 and F-GT106-153 studies to minimise the risk of crystal deposition in the urinary tract.

Is it considered to be included as missing information?: Yes

Rationale:
Not applicable, the issues "No experience in: Subjects in whom the rate of serum urate formation is greatly increased (e.g. Lesch-Nyhan syndrome)" and "Off label use in patients with solid tumors (TLS specific)" and "Interaction with standard therapy of haematological malignancies (TLS specific)" are addressed as missing information.

SIV.1.2 TUMOR LYSYS SYNDROME

Hypersensitive to febuxostat or allopurinol or any components of the formulations

Reason for exclusion:
This is a standard exclusion criterion for clinical studies.

Is it considered to be included as missing information?: No

Rationale:
The issue "Serious skin / hypersensitivity reactions" is addressed as an important identified risk. Patients which develop hypersensitivity to febuxostat must discontinue the treatment without reintroducing it at any time (see warning on Medicinal product allergy/hypersensitivity Section 4.4 of the SmPC).

No further investigation has been deemed necessary

Severe renal insufficiency

Reason for exclusion:
The efficacy and safety have not been fully evaluated in patients with severe renal impairment (creatinine clearance <30 mL/min).

Is it considered to be included as missing information?: Yes

Rationale:
Not applicable as the issue "Limited experience in: Severe renal impairment" is addressed as missing information.

Severe hepatic insufficiency

Reason for exclusion:
No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

Is it considered to be included as missing information?: Yes

Rationale:
Not applicable, as the issues "No experience in: Severe hepatic impairment" is addressed as missing information.

Ischaemic heart disease or congestive heart failure. Amendment n.1 to study protocol clarified that only patients with uncontrolled ischaemic heart disease or uncontrolled congestive heart failure were to be excluded from the study

Reason for exclusion:
In patients with ischemic heart disease or congestive heart failure febuxostat is not recommended based on Phase III trials results showing higher incidence of cardiovascular events in febuxostat arm vs allopurinol arm though not statistical significant and not related to febuxostat.

Is it considered to be included as missing information?: No

Rationale:
The issue "Cardiovascular events" is addressed as "important identified risk".

Mercaptopurine and azathioprine within 14 days prior randomization

Reason for exclusion:
Febuxostat and allopurinol, as xanthine oxidase inhibitors, may cause increased plasma concentrations of mercaptopurine and azathioprine. As active metabolites azathioprine/mercaptopurine are substrates of xanthine oxidase.

Is it considered to be included as missing information?: No

Rationale:
The issue "Drug-drug interaction with azathioprine or mercaptopurine" is addressed as an important identified risk.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

SIV.2.1. Gout

The clinical development programme with a pool of patients exposed to febuxostat (4.072 / 3 = 1,357) allows the detection of rare ADRs (>1/10,000 to <1/1,000). A total of 4.072 patients have been exposed to febuxostat in the clinical trial program. ADRs with a

frequency greater than 1 out of 1.357 could be detected if there is not background incidence for these ADRs.
The upper bound of the 95% confidence interval (CI) of the true probability of an event, if no events were observed, is dependent on the number of subjects observed, as failure to observe events of concern in a particular data set does not exclude the possibility that events are indeed possible. Therefore, If the adverse reaction has never been observed in clinical trials, then the upper limit of the 95% confidence interval is not higher than 3/X, with X representing the total sample size summed up across all relevant clinical trials and studies.

During the clinical development programme the long-term treatment and follow-up should have allowed the detection of ADRs which have a long latency. A total of 1,039 patients have been exposed for 1 year at least, 832 patients for 2 years at least, 582 patients for 3 years at least, 197 patients for 4 years at least. No qualitative or quantitative differences have been observed in the ADRs collected in patients subjected to a long-term treatment as compared to a shorter treatments.

Regarding ADRs due to cumulative effects, PK studies have determined that no accumulation of febuxostat occurs following once daily dosing. No qualitative or quantitative differences have been observed in the ADRs collected in patients subjected to a long-term treatment as compared to a shorter treatments.

No clinical experience has been gained in gout subjects with hepatic impairment in the pre-approval Phase II and III studies, and experience in subjects with severe renal impairment is limited. Phase I studies indicate that dose titration or adjustment is not required in subjects with renal or mild-to-moderate hepatic impairment (Module 2.7.4, Sections 4.5.1.5 and 4.5.1.7, respectively).
No specific studies have been performed in subjects with cardiac impairment. In the Phase II study TMX-00-004, 21% of subjects had a history of cardiovascular disease at baseline. A history of atherosclerotic disease was recorded in 12% of febuxostat-treated subjects in the Phase III studies. In the combined Phase III studies, many subjects were recorded as having relevant risk factors at baseline, including obesity (64% with a BMI ≥30), hypertension (50%), hyperlipidaemia (37%), smoking (19%) and diabetes (11%).
There is very limited experience in pregnant or lactating women (see Module 2.7.4, Section 4.5.4.2).

SIV.2.2. Tumor Lysis Syndrome

The clinical development programme of febuxostat for the prevention and treatment of TLS in adult population affected by haematologic malignancies consists of a single pivotal phase III study as agreed with the CHMP in the SA procedure (procedure no.: EMEA/H/SA/2153/1/2011/II). The Study code is FLO-01. The Study title is "Febuxostat for Tumor Lysis SyndrOme PREvention iN HematologiC MalignanciEs: a Randomized, Double Blind, Phase III Study versus Allopurinol" (FLORENCE).
As far as it specifically concerns the TLS prevention/treatment indication, in the FLORENCE study the duration of treatment was relatively short, namely 7-9 days according to the standard duration of chemotherapy, during which no new safety concern was anticipated for such short-term treatment.
Indeed the safety profile of febuxostat 120 mg QD was extensively studied in clinical trials in more than 1000 subjects (healthy volunteers and gout patients) for a mean duration of treatment of approximately 400 days. Thus during the FLORENCE study no safety concerns

were raised from febuxostat or allopurinol treatments; overall the adverse events reported along the study were in line with those expected for the patient population, namely patients affected by haematologic malignancies and treated with first or following line(s) of chemotherapy. However, due to the limitation of the size of the population exposed (n = 173), only very common, common and uncommon events could be detected (>1/10 to <1/100).

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

SIV.3.1 Gout

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Data on a very limited number of exposed pregnancies have not indicated any adverse effects of febuxostat on pregnancy or on the health of the foetus/new born child. One pregnancy was reported in Study TMX-01-009 in a subject who received both febuxostat 80 mg QD for 9 days and 1 day prior to the estimated time of conception and febuxostat 20 mg QD 6 days and 13 days after the estimated time of conception. The subject had an uneventful pregnancy and delivered a healthy infant. In Study C02-021, pregnancies were reported in female partners of 5 subjects who received febuxostat. All female partners delivered healthy infants.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities: • Patients with hepatic impairment	A Phase 1, parallel-group, open-label, multiple-dose study (TMX-01-012), was performed to assess the safety, PK, and PD of febuxostat in subjects with normal or impaired hepatic function. Subjects were placed into study groups based on the Child-Pugh classification of hepatic function: normal, mildly impaired, or moderately impaired. Of the 27 subjects who received at least 1 dose of febuxostat 80 mg during the study, 8 (30%) subjects had mild and 8 (30%) subjects had moderate hepatic impairment. PK data in subjects with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment revealed that following multiple doses of 80 mg of febuxostat, the maximum plasma concentration (Cmax) or area under the concentration–time curve (AUC) of febuxostat and its metabolites did not change significantly when compared to subjects with no hepatic impairment. No studies have been conducted in subjects with severe hepatic impairment (Child-Pugh Class C). Subjects with acute liver dysfunction (ALT and AST >1.5 × ULN) were excluded from participation in the combined Phase III studies, and were therefore also excluded from the LTE studies. No subjects had a medical history of chronic liver disease.

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with renal impairment	Renal impairment is a common comorbidity with gout. To determine the safety and efficacy of febuxostat in subjects with renal impairment, subjects recruited to the Phase III study C02-009 included those with normal renal function (serum creatinine ≤1.5 mg/dL) and those with mild renal impairment (serum creatinine >1.5 mg/dL and ≤2.0 mg/dL). Subjects with impaired renal function (serum creatinine level >1.5 mg/dL or estimated Clcr <50 mL/min) were excluded from the Phase III study C02-010 and the Phase II study TMX-00-004. Subjects with severe renal impairment, defined as Clcr <20 mL/min in the original protocol and amended in subsequent protocols as Clcr <30 mL/min were excluded from Phase III study F GT06-153. In the Phase III programme, approximately one half of subjects across treatment groups were reported to have renal insufficiency (baseline calculated Clcr <90 mL/min based on ideal body weight). Renal impairment was reported in slightly lower proportion of subject in febuxostat 120 mg (50%) compared to the febuxostat 40 and 80 mg groups (63% and 60%, respectively; ISS Statistical Table 2.3.3). This was due to protocol design of Study F-GT06-153, which enrolled subjects with renal impairment. In addition, a history of renal calculi was recorded in 16% of subjects recruited to Study C02-010, and <1% in Study C02-009, as this was an exclusion criterion for the study. In the Phase III RCT studies, 14 subjects had severe renal impairment based on calculated Clcr <30 mL/min at baseline. This included 7 febuxostat 80 mg subjects, 1 febuxostat 240 mg, 1 placebo subject, and 5 allopurinol subjects. Of the 8 febuxostat-treated subjects with severe renal impairment, 5 subjects (all febuxostat 80 mg) were exposed for at least 6 months, with one subject exposed to febuxostat 80 mg for ≥24 months (including the LTE). Two subjects were exposed to febuxostat 80 mg for 5 and 94 days, respectively and 1 subject was exposed to febuxostat 240 mg for 47 days. In addition, 4 allopurinol subjects and 1 placebo subject with severe renal impairment in the Phase III studies continued to the LTE studies, where they received either allopurinol or febuxostat 80 mg or 120 mg for up to 3 years.
Patients with relevant comorbidities: • Patients with cardiovascular impairment	In the combined Phase III studies, 320 (12%) febuxostat-treated subjects had concurrent atherosclerotic disease and 65 (2%) had congestive heart failure. In addition, many febuxostat-treated subjects in the Phase III studies had multiple cardiovascular risk factors at baseline. These risk factors included obesity (1715 [64%] subjects with a BMI ≥30), hypertension (1332 [50%] subjects), hyperlipidaemia (1007 [37%] subjects), smoking (501 [19%] subjects) and diabetes (296 [11%] subjects). Further analyses of the association between known cardiovascular risk factors and adjudicated APTC events for all subjects (N=4101, including comparator arms) in the Phase III studies have been performed. As expected, a number of established cardiovascular risk factors were found to have a significant or nearly significant association with APTC events, supporting the hypothesis that many of the APTC events observed during the clinical studies are associated with known cardiovascular risk factors. Established risk factors with a significant association with APTC events were: medical history of atherosclerotic disease, medical history of myocardial infarction and baseline congestive heart failure and age >60 years at baseline.
Patients with relevant comorbidities: • Subjects in whom the rate of serum urate formation is greatly increased	In the phase III studies subjects were excluded if they had a history of cancer (other than basal cell carcinoma of the skin) or had received systemic cancer chemotherapy both within 5 years prior to screening.

Type of special population	Exposure
Patients with relevant comorbidities: • Subjects with disease severity different from inclusion criteria in clinical trials	Subjects recruited to the clinical programme were representative of the patient population for which febuxostat use is intended, ie, the management of hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis). Subjects recruited to the 6 Phase II and III efficacy studies had hyperuricaemia (serum urate ≥8 mg/dL) and a history or presence of gout, as defined by the preliminary criteria of the ARA for the classification of the acute arthritis of primary gout. These criteria are comparable to the criteria used in clinical practice in the EU. A large proportion of subjects in the Phase III studies had a serum urate level ≥10.0 mg/dL (37% and 34% for febuxostat and allopurinol, respectively) and a history or presence of a tophus (23% and 22% for febuxostat and allopurinol, respectively) at baseline (ISS Statistical Table 2.3.3). Thus, these subjects represent the more severe end of the disease spectrum. In the LTE studies, 39% and 42% of subjects in the febuxostat total and allopurinol groups, respectively, had a baseline serum urate level ≥10.0 mg/dL, and 25% and 24%, respectively, had a history or presence of a tophus
Population with relevant different ethnic origin	The 6 Phase II and III efficacy studies included in this RMP were conducted in the US and Canada. Although 80% of febuxostat-treated subjects in the combined Phase III studies were Caucasian, subjects of other ethnic origins such as Black (11%), and Asian (3%) were also represented (see Table SIII.2.3). A clinical program has been carried out exposing Japanese hyperuricaemic and gout patients to febuxostat at 10 to 60 mg/day, according the Japanese guideline for the treatment of these diseases. No substantial differences in the safety and efficacy profile of febuxostat have been noted as compared to that emerging from the north American studies.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other	
Children and adolescents	Not included in the clinical development program. All subjects recruited to the clinical studies were >18 years of age. Gout is rare in paediatric subjects. As there has been no experience of the use of febuxostat in children and adolescents, its use is not recommended.
Elderly	Of the 2,690 subjects treated with febuxostat in the combined Phase III studies, 436 (16%) of subjects were aged ≥65 years.
Females	Of the 2,690 subjects who received at least one dose of febuxostat in the combined Phase III studies, only 139 (5%) were female.

SIV.3.2 Tumor Lysis Syndrome

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment	Only subjects with severe hepatic insufficiency were excluded from the FLORENCE study participation.
Patients with relevant comorbidities: • Patients with renal impairment	Not included in the clinical development program.
Patients with relevant comorbidities: • Patients with cardiovascular impairment	Baseline data of the FLORENCE study were analyzed. Not clinically significant ECG abnormalities were detected in 135 (39.5%) patients with a higher percentage in allopurinol arm compared to febuxostat arm (43.9% vs 35.1%). On the other hand, clinically significant ECG abnormalities at baseline were detected in 11 (3.2%) patients with a higher percentage in febuxostat arm compared to allopurinol arm (4.7% vs 1.8%). Cardiac disorders were reported in the medical history of 69 (19.9%) patients, occurring in a slightly higher percentage of patients in febuxostat arm compared to allopurinol arm: overall 23.7% vs 16.2%, atrial fibrillation 5.2% vs 1.7% myocardial ischemia 5.8% vs 2.3%. Consistently the use of concomitant medication of the cardiovascular system before the first study drug intake was higher in febuxostat arm compared to allopurinol arm: 46.2 % vs 37.6%.
Patients with relevant comorbidities: • Patients with solid tumors	Patients with solid tumors have not been included in the FLORENCE study because these patients are at low risk of TLS and they do not generally require pharmacological prophilaxis for TLS; indeed the Florence study, as per inclusion criteria, included only patients at intermediate/highly risk for TLS.
Population with relevant different ethnic origin	Not included in the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other	
Children and adolescents	Not included in the clinical development program.
Elderly	61 patients aged ≥65.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

For febuxostat, the methodology used to calculate the exposure was from data on the quantity of tablets shipped.
Based on the approved defined daily dose (DDD) of one tablet (any dose), the estimated exposure was calculated as follows:
Patient-Years of Exposure = Tablet count/ (1 tablet per day x 365.25 days per year).

SV.1.2 Exposure

Based on the above assumption, the patient exposure can be estimated to be 9 billion DDDs, corresponding to approximately 24.60 million patient-years of treatment cumulatively. It is not possible to stratify exposure by different indications (gout/hyperuricemia vs TLS) separately.
The estimated patient exposure for febuxostat is presented in table SV.1.

Table SV.1: Exposure table by region and dosage

Strength	Patient-years					
	North America (a)			EU, Oceania and CIS (b)	Asia and Middle East (c)	Worldwide
	USA	Canada	Mexico			
10 mg					8,449,687	8,449,687
20 mg					7,998,391	7,998,391
40 mg	[redacted]				[redacted]	2,296,541
80 mg	[redacted]	[redacted]		3,962,843	964,957	5,496,008
120 mg				358,795	3,237	362,032
Cumulative (d)	[redacted]			*4,321,639*	[redacted]	*24,602,659*

Data sources:
(a) Shipment data from Corporate Finance & Controlling Department of Takeda Pharmaceutical Company Ltd.
(b) Shipment data provided by Menarini.
(c) Shipment data provided by Teijin.
(d) Date ranges used: US: 13 February 2009 to 28 February 2021; Canada: 01 September 2010 to 28 February 2021; Mexico: 01 March 2016 to 28 February 2021; EU: 01 March 2010 to 28 February 2021; Asia: 01 May 2011 to 28 February 2021.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Based on the pharmacological properties of febuxostat, no specific risks of abuse or misuse for illegal purposes are expected and no potential for dependence has been identified in the post-marketing experience.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Important identified risks:	None
Important potential risks:	• Cardiovascular effects • Hepatic effects • Renal effects • Neurological effects • Haematological effects • Severe rash/hypersensitivity reactions • Thyroid effects
Important missing information:	**No experience in:** • Children and adolescents • Subjects in whom the rate of serum urate formation is greatly increased (e.g. 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

The data presented at the time of the approval of initial RMP were taken from the Integrated Summary of Safety (ISS), the subsequent safety updates (4 and 16 months), Module 2.7.4 and published literature.
In the pivotal Phase III studies, the most commonly reported ADRs (investigator assessment) were liver function abnormalities (3.5%), diarrhoea (2.7%), headache (1.8%), nausea (1.7%) and rash (1.5%). There were no statistically significant differences between the febuxostat 80 mg, 120 mg, and allopurinol 300/100 mg treatment groups for the most common, treatment-related high-level terms. Overall, a similar profile was observed for the febuxostat total group in the LTE studies.
No important identified risks associated with febuxostat treatment were reported.
Potential risks were based on epidemiological considerations (cardiovascular, hepatic, renal) or the limited size of the database and thus the ability to detect rare events (neurological, haematological, thyroid and severe rash/hypersensitivity reactions).
The important potential risks at the time of the approval of initial RMP were the following:
• Cardiovascular effects
• Hepatic effects
• Renal effects
• Neurological effects
• Haematological effects
• Severe rash/hypersensitivity reactions
• Thyroid effects

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

The risks that were not considered important and that were not included in the safety concerns list were those not associated to a relevant risk or they were associated with a low frequency during the clinical development. There are also risks considered as class effect but not considered important for the inclusion among the safety concerns.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):
- Diarrhoea and nausea: These adverse reaction were mostly mild or moderate in severity. In relation to the severity of the indication treated were not included in the list of safety concerns

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
- Eye disorders: Blurred vision
- Metabolism and nutrition disorders: Diabetes mellitus, hyperlipidemia, weight decrease, increase appetite, anorexia
- Psychiatric disorders: Nervousness
- Ear and labyrinth disorders: Tinnitus
- Respiratory system disorders: Dyspnoea, bronchitis, upper respiratory tract infection, cough
- Gastrointestinal disorders: Pancreatitis, abdominal pain, abdominal distension, gastro-oesophageal reflux disease, mouth ulceration
- Musculoskeletal and connective tissue disorders: Joint stiffness, muskoskeletal stiffness, arthralgia, arthritis, myalgia, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis
- Reproductive system and breast disorder: Erectile dysfunction
- General disorders and administration site conditions: Chest pain, chest discomfort, thirst
- Investigations: Blood glucose increase, blood triglycerides increase, blood cholesterol increase,

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. action being part of standard clinical practice in each EU Member state where the product is authorised):
- Gout flares: it is a class effect. As with other antihyperuricaemic agents, gout flares may occur during treatment initiation due to changing serum uric acid levels resulting in mobilisation of urate from tissue deposits. This is a disease-specific risk and appropriate recommendations were provided in Section 4.4 of the SmPC on gout flare prophylaxis with an NSAID or colchicine. There was no additional risk of gout flares specifically associated with febuxostat.

Known risks that do not impact the risk-benefit profile:
None.

Other reasons for considering the risks not important:

Uncommon adverse reactions with minimal impact on patients:

- Metabolism and nutrition disorders: Decrease appetite, weight increase
- Psychiatric disorders: Libido decreased, insomnia
- Gastrointestinal disorders: Vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort
- General disorders and administration site conditions: Fatigue

Class effect. Non-serious skin reactions

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

The data presented in this section are referring to the initial RMP (module 1.8.2 version 2.0 , dated 19-Feb-2008) and they are coherent with the ISS (Integrated Summary of Safety), the subsequent safety updates (4 and 16 months), Module 2.7.4 and published literature.

Important Identified Risks:
Not applicable: there are no important identified risks.

Risk-benefit impact:
Not applicable

Important Potential Risk:

Cardiovascular effects

Cardiovascular events are relatively common in subjects with gout. At the time of the initial approved RMP, data suggest that any additional risk associated with febuxostat treatment was unlikely. A numerically greater incidence of investigator reported cardiovascular events was observed in the febuxostat total group compared to the allopurinol group in the pivotal Phase III (1.3 vs 0.3 events per 100 PYs) and longterm extension studies (1.4 vs 0.7 events per 100 PYs), although no statistically significant differences were found and no causal relationship with febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure.

Risk-benefit impact:
Cardiovascular events, may have significant morbidity and mortality and their occurrence should be carefully monitored. Cardiovascular disorders are frequent comorbidities in subjects with gout, with frequencies of 24.9%, 15.5% and 10.5% reported for coronary artery disease *[Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR Jr, Saag KG. Gout epidemiology: results from the UK General Practice Research Database, 1990-1999. Ann Rheum Dis 2005; 64(2): 267-72.*], coronary atherosclerosis and cardiac arrhythmias[*Riedel AA, Nelson M, Wallace K, Joseph-Ridge N, Cleary M, Fam AG. Prevalence of comorbid conditions and prescription medication use among patients with gout and hyperuricemia in a managed care setting. J Clin Rheumatol 2004; 10(6): 308-14*], respectively. In the pivotal Phase III studies, 13% of febuxostat-treated subjects had a history of atherosclerotic disease, and 2% of febuxostat treated subjects had a history of congestive heart failure at baseline. No specific cardiovascular risk factors were identified as being associated with febuxostat treatment. Although many subjects had cardiovascular risk factors at baseline, only 28

subjects experienced adjudicated primary APTC (Antiplatelet Trialists' Collaboration) events in the Phase III and LTE studies.
Based on these information, cardiovascular effects had been classified as important potential risk.

Hepatic effects
During the phase 3 clinical studies, mild liver function test were observed in patients treated with febuxostat (3.5%).

Risk-benefit impact:
In the pivotal Phase III studies, an increased incidence of mild LFT elevations was noted in subjects with elevated baseline ALT/AST and in alcohol-consuming subjects. The magnitude of the increase was generally similar across all treatment groups, including allopurinol, and no dose-relationship was noted in the febuxostat treatment groups.
Based on these information, hepatic effects had been classified as important potential risk.

Renal effects
Renal effects have been observed during clinical trials, in particular, few renal adverse events in the pivotal Phase III studies were considered treatment-related (<1-3% across treatment groups). In the LTE studies, the incidence of treatment-related events was also low (approximately 1%) across all treatment groups except the febuxostat 40 mg group (17%), in which the higher incidence was probably due to the low number of subjects in the group (N = 12). There have been some reports of raised serum creatinine, just over half of which were considered related to study drug. Factors that may contribute to renal impairment, however, such as pre-existing renal dysfunction, hypertension or concomitant medications, were often recorded in the study population.

Risk-benefit impact:
In the pivotal Phase III studies, febuxostat-treated subjects experienced serious adverse events of renal failure acute, renal impairment, and renal insufficiency (1 subject each), one of which (renal impairment) was considered related to treatment. In febuxostat-treated subjects in the LTE studies, serious adverse events of renal failure acute, renal failure and nephrolithiasis (1 subject each) were recorded, none of which were considered treatment related. The majority of renal adverse events experienced by febuxostat-treated subjects in both the pivotal Phase III and LTE studies were mild or moderate in severity. Severe renal events recorded in more than one subject included renal lithiasis (5 [<1%] and 9 [1%] in the pivotal Phase III and LTE studies, respectively) and renal failure and impairment (2 [<1%] in the LTE studies). No severe renal adverse events were reported in Study TMX-00-004.
Based on these information, renal effect had been classified as important potential risk.

Neurological effects
As with other XO inhibitors, adverse reactions such as somnolence, dizziness and paraesthesia have been reported in patients receiving febuxostat. There is no evidence to suggest that febuxostat treatment increases the risk of these events. It is recommended that 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.

Risk-benefit impact:
The large heterogeneity of neuropsychiatric events under exam does not allow to draw conclusions on the impact of neuropsychiatric events on individual patients, as these events could span from headache or dizziness to Guillain-Barrè syndrome or toxic encephalopathy.
The vast majority of neuropsychiatric events was not serious. For the most concerning events, only isolated cases have been collected, so that the overall public health impact does not seem to be important
The overall incidence of treatment-emergent neurological adverse events was comparable (10-16%) among each of the febuxostat, allopurinol and placebo treatment groups in the pivotal Phase III studies. Disturbances in consciousness NEC, headaches NEC, neurological signs and symptoms NEC, and paraesthesias and dysaesthesias were the only specific MedDRA HLTs reported by ≥1% and at least 2 subjects in any treatment group.
In the LTE studies, the incidence of treatment-emergent neurological events per 100 PY was similar in the febuxostat total (9.4 subjects) and allopurinol (10.5 subjects) groups. The most common neurological events per 100 PY in the febuxostat total and allopurinol groups were headache (3.9 and 4.5 subjects, respectively), dizziness (1.5 subjects, both groups), and paraesthesia (1.4 and 1.5 subjects, respectively). No clinically relevant differences were observed between the treatment groups and there was no evidence of a dose response.
In general, neurological disorders are not commonly associated with gout.
Based on these data, neurological effects had been classified as important potential risk.

Haematological effects
Haematological effects have been observed during clinical trials. In the pivotal Phase III studies, treatment-emergent haematological adverse events were experienced by low proportions of subjects, and the incidence was comparable across treatment groups (<1-3%).
For the LTE studies, analysis of haematological adverse events adjusted for exposure revealed a greater incidence in the febuxostat 80 mg and 120 mg groups (2.1 and 1.6 subjects per 100 PY) compared with the allopurinol group (0.8 subjects per 100 PY). This difference may be a reflection of the greater number of laboratory assessments performed for subjects treated with febuxostat compared with allopurinol.

Risk-benefit impact:
The impact of haematological events on patients' life can vary depending on the kind of event. Anaemia can be even asymptomatic, whereas other events such as pancytopenia or neutropenia can cause a significant disability in the patients' daily activity.
If cerebrovascular accidents are excluded, none of the Haematological/Bleeding events had a fatal outcome, although they can be life threatening and about the half required hospitalisation.
Haematological and bleeding events are not directly associated with gout.
The majority of haematological events experienced by febuxostat-treated subjects in the LTE and pivotal Phase III studies were of mild or moderate intensity.
Based on these information, haematological effects had been classified as important potential risk.

Severe rash/hypersensitivity reactions
Severe rash/hypersensitivity reactions have been observed during clinical trials. PTs that occurred in the febuxostat groups of the pivotal Phase III studies were: dermatitis contact and rash papular [drug hypersensitivity]. PTs that occurred in the febuxostat groups of the LTE, but not the pivotal Phase III studies were: pruritus, psoriasis, purpura, rash, rash macular and urticaria.

Risk-benefit impact:
Serious rash / hypersensitivity reactions have a significant impact in the patient's quality of life.
Serious skin / hypersensitivity reactions have an important impact on public health as they can be fatal, life threatening or their management requires hospitalisation or intervention.
During the pivotal Phase III studies, 3 subjects treated with febuxostat 80 mg, 2 subjects treated with allopurinol and 1 subject treated with febuxostat 120 mg experienced rash/hypersensitivity reactions that were reported as severe. No subjects treated with febuxostat 240 mg or placebo experienced rash/hypersensitivity reactions that were reported as severe.
During the LTE studies, 5 subjects treated with febuxostat 80 mg and 4 subjects treated with febuxostat 120 mg experienced rash/hypersensitivity reactions that were reported as severe. No subjects treated with febuxostat 40 mg or allopurinol experienced rash/hypersensitivity reactions that were reported as severe.
Rash does not appear to have a direct association with gout. A mechanism by which febuxostat could cause severe rash/hypersensitivity reactions had not been identified.
Based on these information, severe rash/hypersensitivity reactions had been classified as important potential risk.

Thyroid effects
Increased TSH values (>5.5 µIU/ml) were observed in patients on long-term treatment with febuxostat (5.0%) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function.

Risk-benefit impact:
In the absence of effects on thyroxine T3 and T4, increase in blood levels of TSH is asymptomatic.
No febuxostat patient with TSH above ULN showed altered T4 or clinical symptoms of thyroid dysfunction (Perez-Ruiz et al, 2012).
In the pivotal Phase III studies, the incidence of treatment-emergent thyroid events was low, with similar proportions of subjects experiencing at least one thyroid event across the treatment groups (<1% in the placebo, febuxostat 80 mg, febuxostat 120 mg and allopurinol groups, respectively, and 0% in the febuxostat 240 mg group).
Similarly, in the LTE studies, the proportion of patients experiencing at least one thyroid event was low at ≤2% in all treatment groups, and overall incidence rates per 100 PY were similar in the febuxostat total (1.0 subjects per 100 PY) and allopurinol (0.8 subjects per 100 PY) groups.

Missing information:

No experience in:

-Children and adolescent

Risk-benefit impact:
All subjects recruited to the clinical studies were >18 years of age. Gout is rare in paediatric subjects. As there has been no experience of the use of febuxostat in children and adolescents, its use is not recommended.

Based on these lack of information, children and adolescent have been included in missing information.

-Subjects in whom the rate of serum urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome)

Risk-benefit impact:
In the pivotal studies subjects have been excluded if they had a history of cancer (other than basal cell carcinoma of the skin) or had received systemic cancer chemotherapy both within 5 years prior to Screening.
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.
Based on these, subjects in whom the rate of serum urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) had been included in missing information.

-Organ transplantation

Risk-benefit impact:
Information on the efficacy and safety of febuxostat is missing in subjects who have experienced organ transplantation as these subjects were excluded in the clinical development program.
As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended.
Based on these lack of information, subjects with organ transplantation have been included in missing information

-Severe hepatic impairment

Risk-benefit impact:
The recommended dosage in patients with mild hepatic impairment is 80 mg. Limited information is available in patients with moderate hepatic impairment. During the Phase III clinical studies, mild liver function test abnormalities were observed in subjects treated with febuxostat (3.5%). The efficacy and safety of febuxostat has not been studied in patients with severe hepatic impairment (Child Pugh Class C).
Based on the lack of information, severe hepatic impairment has been classified as missing information.

-Pregnancy and lactation

Risk-benefit impact:
Data on a very limited number of exposed pregnancies have not indicated any adverse effects 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. However, the potential risk for humans is unknown; therefore, febuxostat should not be used during pregnancy.
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; therefore, febuxostat should not be used while breast-feeding.
Based on the lack of information, the use of febuxostat during pregnancy and lactation has been classified as missing information.

Limited experience in:

-Female patients

Risk-benefit impact:
Women rarely experience attacks of gout before the menopause. Oestrogen exerts a uricosuric effect and may protect females from hyperuricaemia before the menopause.
Of the 1177 subjects who received at least one dose of febuxostat in the pivotal phase III studies, only 58 (5%) were female.
Based on the limited information, female patients were included in missing information.

-Elderly patients

Risk-benefit impact:
Although considered to be primarily a male disease, the sex distribution of gout is closer among elderly subjects.
Of the 1177 subjects treated with febuxostat in the pivotal Phase III studies, 677 (58%) were 45-65 years of age. A further 160 (14%) of subjects were aged >65 years.
Based on the limited information, elderly patients were included in missing information.

-Severe renal impairment

Risk-benefit impact:
Renal impairment is a common comorbidity with gout.The safety of febuxostat have not been fully evaluated in patients with severe renal impairment (Clcr <30 mL/min).
Based on the limited information, patients with severe renal impairments were included in missing information.

-Moderate hepatic impairment

Risk-benefit impact:
Limited information is available in patients with moderate hepatic impairment. During the Phase III clinical studies, mild liver function test abnormalities were observed in subjects treated with febuxostat (3.5%).
Based on the limited information, patients with moderate hepatic impairment were included in missing information.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The safety concerns of the initial RMP (module 1.8.2 ver 2.0 dated 19-Feb-2008) are those reported in the previous section SVII.1.
Here we report the new safety concerns and reclassification with the submissions of the updated RMPs occurred overtime, coherently with the data reported at Annex 8 "Summary of changes to the risk management plan over time".

RMP ver 3.0 vs 2.0
No changes to the safety issues have been implemented; the update was concerning the inclusion of final data of clinical studies and data from post-marketing surveillance

RMP ver 3.1 vs 3.0
This RMP has been revised to specify that the potential risk of "Neurological events" also included psychiatric events.
The risk of "Serious skin / hypersensitivity events" was updated to include ADRs collected in the post-marketing surveillance such as: "Generalised rash" and "Drug hypersensitivity".
No other changes were concerning the safety issues whose denomination did not change vs previous 3.0 version.

RMP ver 3.2 vs 3.1
In the 3.2 version of the RMP the important potential risk "Serious rash / hypersensitivity events" has been upgraded to important identified risk and renamed as "Serious rash / hypersensitivity reactions", according to data collected during the postmarketing surveillance.
Data from a study showing the lack of interaction between febuxostat and rosiglitazone were also included.

RMP ver 3.3 vs 3.2
The 3.3 version of the RMP included the description of risk minimisation measures for the identified safety issue "Serious skin / hypersensitivity reactions" (SmPC wording and a Direct Healthcare Professional Communication) and a method to improve the quality of data collected on this safety issue.
The important identified risk "Serious skin / hypersensitivity reactions" was updated to include ADRs collected in the post-marketing surveillance such as: "Anaphylactic reaction", "Stevens-Johnson Syndrome", "Rash pruritic" and to upgrade the frequency of "Rash" from uncommon to common.
The important potential risk "Haematological / bleeding events" was updated to include ADRs collected in the post-marketing surveillance such as: "Thrombocytopenia".
The important potential risk "Renal events" was updated to include ADRs collected in the post-marketing surveillance such as: "Tubulointerstitial nephritis".

RMP ver 3.4 vs 3.3
The RMP was updated to include the commitment to perform a drug-drug interaction study between febuxostat and azathioprine.
The safety issue of "Hepatic events" was updated to include hepatitis and jaundice.
This version has not been accepted by EMA because of the too extensive revisions.

RMP ver 3.5 vs 3.4
At the end of the procedure for the renewal of the Marketing Authorisation this updated 3.5 version (replacing v. 3.4 and 3.3) was a less extensive revision to include the commitment to perform a drug-drug interaction study between febuxostat and azathioprine.
The safety issue of "Hepatic events" was updated to include hepatitis and jaundice.

RMP ver 4.0 vs 3.5
"Rhabdomyolysis" and "Interaction with azatihioprine/mercaptopurine" were added as important identified risks.
The identified risk of "Serious skin / hypersensitivity – allergic reactions" was updated to include angioedema. Data from postmarketing surveillance were updated including 3 years post- marketing experience.

The RMP was also adapted to the new format detailed by the Good Pharmacovigilance Practices (GVP) Module V.

RMP ver 4.1 vs 4.0
The RMP was revised in order to take into account the comments on the previous version and to adhere to the revised format of part IV issued on 25-Jul-2013 (EMA/465929/2012 Rev. 1).
The safety concerns are the same of the previous version.

RMP ver 4.2 vs 4.1
The RMP was updated to include the proposed indication for prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS).
No changes to the safety concerns were proposed.

RMP ver 5.0 vs 4.2
The RMP was revised to take into account new potential risks and missing information arising from the proposed indication for prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome (TLS) following the Assessor recommendations (EMA/PRAC/672228/2014).
"Off label use in patients with solid tumours (TLS specific)" and "Off label use in the paediatric population (TLS specific)" were included as new important potential risks.
"Interaction with standard therapy of haematological malignancies (TLS specific)" was included as new missing information.

RMP ver 5.1 vs 5.0
"Off label use in patients with solid tumors (TLS specific)", previously classified as important potential risk was reclassified as missing information.

RMP ver 6.0 vs 5.1
The missing information "Subjects in whom the rate of serum urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) has been renamed in "Subjects in whom the rate of serum urate formation is greatly increased (e.g. Lesch-Nyhan syndrome) in order to remove the reference to the use in patient affected by malignant disese: information concerning the use in patients with hematologic malignancies have been adquired overtime (studies supporting the indication in prevention TLS syndrome

in patients with hematological malignancies) and the missing information concerning use in patients with solid tumors already exists (see below).

"Limited experience in female patients "and "Limited experience in elderly patients" previously classified as missing information have been removed from the list of safety concerns because, during the post marketing experience, information was collected and it evidenced a safety profile similar to that of the overall exposed population. Safety data collected during the post-marketing experience that justify the removal of this missing information are reported below:

- Females

As of 20 April 2017, of those patients with a known gender (8,287), 2,173 were females from all post-marketing sources (including spontaneous, literature, literature clinical, regulatory authority, and post-marketing survey).
The most frequently reported AEs in female patients were rashes, gout, pruritus, diarrhea, and nausea. The most frequently reported serious events in this population were PTs within the HLTs of Renal failure and impairment; Heart failures NEC; Ischemic coronary artery disorders; Rashes, eruptions and exanthemas NEC and, Death and sudden death.
Overall, the safety profile is similar to that of the overall exposed population.

- Elderly

As of 20 April 2017, of those patients with a known age, 3,596 were elderly patients among cases from all post-marketing sources. The most frequently reported AEs in elderly patients were gout, rashes, pruritus, diarrhea, nausea, blood creatinine increased and dizziness. The most frequent serious events reported in the elderly population included PTs within HLTs of Renal failure and impairment, Heart failures NEC, Ischemic coronary disorders, Rashes, eruptions and exanthemas NEC, and Central nervous system haemorrhages and cerebrovascular accidents.
Overall, the safety profile is similar to that of the overall exposed population.

Additionally on the base of the safety data emerged from a preclinical study (MRPO-2015-PKM005) and the results of a related pharmacokinetic model (REP-POPPK-MRPO-2015-PKM005), a change to the PI is proposed in order to minimize the risk of drug interaction with azathiprine/mercaptopurine; the clinical study MIOL/13/FEB+AZADDI/001 has been removed from the pharmacovigilance plan.

The milestones of the study FAST (MEA 005) have been updated in order to state the ones currently agreed with the EMA, according to the request of the EMA's Product Manager.

The new RMP template (EMA/PRAC/613102/2015 rev 2), according with the revised GVP V (rev 2.0) has been adopted.

RMP ver 6.1 vs 6.0
No changes to the safety issues have been implemented.

In accordance with the Request for Supplementary Information received in the frame of the Type II variation n. C.I.4 (procedure n. EMEA/H/C/000777/II/0047), an update has been performed and the following changes have been included:
- The category that identifies the study "Febuxostat versus Allopurinol Streamlined Trial" (FAST, MEA 005) has been corrected from category 1 to category 3;

- An Interventional study (code: tbd) to assess the effect of multiple-dose of febuxostat on the PK profile of 6-MP following single-dose of azathioprine, on healthy volunteers, has been included in the RMP as additional pharmacovigilance activity (to be handled as category 3 study, MEA); the study is required in order to confirm the results of the Pop-PK (REP-POPPK-MRP-2015-PKM-005) modelling study performed to explore the "Drug-drug interaction with azathioprine or mercaptopurine".
- An updated product information is proposed according to the provisions of the aforesaid Request for Supplementary Information.

RMP ver 7.0 vs 6.1
- "Cardiovascular events" previously classified as Important Potential Risk has been reclassified as Important Identified Risk, according to PRAC assessment (PSUSA procedure number EMEA/H/C/PSUSA/00001353/201804 related to the submitted PSUR with covered period 21-Apr-2017_20-Apr-2018) and to the 4th Request for Supplementary Information issued by the Committee for Medicinal Products for Human Use (CHMP) on 29th May 2019 concerning the Type II variation (Procedure No. EMEA/H/C/000777/II/0051). The reason for the reclassification was the safety result of the completed study (CARES study), in which a significantly higher number of patients with cardiovascular death in the febuxostat arm compared to the allopurinol arm were reported.
- An update of the product information has been performed (as requested) according to the impact of the CARES study (TMX-67_301) and submitted with the Type II variation (Procedure No. EMEA/H/C/000777/II/0051).

RMP ver 7.1 vs 7.0
No change to the safety concerns list has been performed.

The RMP has been updated by modifying the milestone related to the submission of the FAST (Febuxostat versus Allopurinol Streamlined Trial) Clinical Study Report, as requested by the EMA in the Final Assessment Report on the FAST study 8th Interim Report (MEA 005.13), dated 30th April 2020.

RMP ver 7.2 vs 7.1
No change to the safety concerns list has been performed.

The RMP has been updated to include the milestones First subject in and Last subject out of the FAI-01 clinical study (MEA 029) agreed with the EMA in the frame of the procedure EMEA/H/C/000777/MEA 029, intended to assesss the final version of the relevant clinical study protocol (CHMP positive opinion adopted on 29 May 2019), and to include the updated milestone related to the submission of the FAI-01 Clinical Study Report. Other information on this clinical study have been aligned with those reported in the approved protocol.

RMP ver 8.0 vs 7.2
No change to the safety concerns list has been performed.

The RMP has been updated to include safety data from the FAST (Febuxostat versus Allopurinol Streamlined Trial) Clinical Study Report.

RMP ver 8.1 (under evaluation) vs 8.0
No change to the safety concerns list has been performed.

Information about the DHPC letter distributed in EU countries in 2019, after the CARES study, has been reincluded below the paragraph "Preventability" of the important identified risk "Cardiovascular events".

RMP ver 9.0 vs 7.2
No change to the safety concerns list has been performed.

The RMP has been updated to include safety data from the FAI-01 Clinical Study Report.

RMP ver 9.1 vs 9.0
No change to the safety concerns list has been performed.
Information about the DHPC letter distributed in EU countries in 2019, after the CARES study, has been reincluded below the paragraph "Preventability" of the important identified risk "Cardiovascular events".

RMP ver 10.0 (current) vs 9.1
No change to the safety concerns list has been performed.

Safety data from the FAST (Febuxostat versus Allopurinol Streamlined Trial) Clinical Study Report have been included in the important identified risk "Cardiovascular events".

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: "Serious skin / hypersensitivity reactions"

Potential mechanisms:
A mechanism by which febuxostat could cause Serious skin / hypersensitivity reactions has not been identified. A form to collect follow-up information on these cases that could help the investigation of the mechanism(s) underlying serious skin / hypersensitivity reactions related to febuxostat has been developed (see Annex 4A).

Evidence source(s) and strength of evidence:
The potential of febuxostat to induce serious skin/hypersensitivity reactions was already postulated at the time of the approval due to the fact that the other xanthine oxidase inhibitor, allopurinol, was known to precipitate such ADRs. However, no treatment-related serious skin/hypersensitivity events were collected in clinical trials; therefore, this risk was initially classified as a potential one. During the post-marketing experience, serious skin/hypersensitivity events causally related to febuxostat had been collected, so this risk was upgraded to an identified one (RMP version 3.2 and later). Several patients experiencing serious skin/hypersensitivity to febuxostat had history of a previous similar reaction to allopurinol and/or renal impairment. As febuxostat is an elective drug for these patients, it is uncertain whether prior hypersensitivity to allopurinol and/or renal impairment are actual risk factors for developing serious skin/hypersensitivity to febuxostat or rather it is due to a high percentage of these patients being exposed to febuxostat because of a lack of therapeutic alternatives.

Characterisation of the risk:
The search strategy was based on serious ADRs belonging to the SOCs "Skin and subcutaneous tissue disorders" and "Immune system disorders."

Clinical studies
No serious skin events had been collected in pre-authorization clinical trials (including CONFIRMS) in patients exposed to febuxostat, allopurinol, or placebo. Two serious events included in the SOC "Immune system disorders" were collected in 2 patients treated with febuxostat (n = 2,690) in phase III trials (anaphylactic reaction caused by a fire ant sting and an event of drug hypersensitivity). One serious event (drug hypersensitivity) was recorded in a patient treated with allopurinol (n = 1,277), whereas no event was collected in the placebo group. Therefore the risk frequency is 0.074% (95% CI 0.009 - 0.268%) for febuxostat and 0.078% (95% CI 0.002-0.436%) for allopurinol.
In the phase III studies, the overall incidence of treatment-emergent rash adverse events was 5.2% (95% CI 2.1-10.5%) in the placebo, 6.4% (95% CI 5.5-7.4%) in the total febuxostat, and 7.6% (95% CI 6.2-9.2%) the allopurinol groups. The most common rash events (preferred terms ≥ 1%) were dermatitis contact (1.5% placebo, 1.4% total febuxostat, and 2.0% allopurinol groups), and rash erythematous (0.7% placebo, 0.7% total febuxostat, and 1.3% allopurinol groups).
In the long term extension (LTE) studies, the overall incidence of subjects per 100 patient years (PY) with treatment-emergent rash adverse events was 6.0 subjects (95% CI 5.1-7.0) in the total febuxostat group, and 5.8 subjects (95% CI 2.8-10.7) in the allopurinol group. The

most common rash events (preferred terms ≥ 1 subject per 100 patient-years) were dermatitis contact (1.8 subjects in the total febuxostat and 1.2 subjects in the allopurinol groups), rash erythematous (0.6 subjects in the total febuxostat and 1.2 subjects in the allopurinol groups), rash macular (0.5 subjects in the total febuxostat and 1.7 subjects in the allopurinol groups), and urticaria (0.3 subjects in the total febuxostat and 1.2 subjects in the allopurinol groups). The vast majority of serious skin/hypersensitivity events collected in post-authorisation ongoing clinical trials are still blinded. One unblinded event of SJS occurred in a patient treated with allopurinol in TMX-67_301 CV safety study.

Cumulatively, a total of 29 serious cases describing 30 SAEs have been received with febuxostat. Of these 21 unblinded cases were reported in a post approval clinical trial versus allopurinol (TMX-67_301). Of these 21 events, 1 event (anaphylactic reaction) was considered as related to the febuxostat.

One case had a fatal outcome (anaphylactic reaction caused by a fire ant sting); one event was not resolved, 5 events resolved with sequelae, 1 was resolving and the remaining events were resolved.
The intensity of SAEs reported in clinical trials was defined of grade3 (n=1), mild (n=1), moderate (n=10), severe (n=13) and unknown in the remaining 5 events.
As far as the nature of the risk is concerned, the most commonly reported serious events reported in the clinical trials were: Skin ulcer n = 6 (unlisted), Diabetic foot n = 5 (unlisted), Angioedema (unlisted) and Drug hypersensitivity (listed) (n = 3 each), Anaphylactic reaction (listed) and Diabetic ulcer (unlisted) (n = 2 each). All the other serious events had in only 1 occurrence.

Post-marketing experience
By searching ICSRs describing skin/hypersensitivity events reported in the post-marketing experience (spontaneous reports or solicited reports from non-interventional studies or post-marketing surveys) included in the SOCs "Skin and subcutaneous tissue disorders" and "Immune system disorders," 2,561 ICSRs (476 serious) were collected cumulatively. A total of 3,126 ADRs (553 serious and 2,573 non-serious) identified in the post-marketing surveillance (2,967, of which 497 serious, in the SOC "Skin and subcutaneous tissue disorders" and 159,56 of which reported as serious, in the SOC "Immune system disorders"). Among these, 6 serious ICSRs [redacted] and [redacted] with 7 serious ADRs, were identified from non interventional post-marketing studies.
The overall reporting rate was 19.35 serious ICSRs describing skin/hypersensitivity events per million patient-years (476 serious ICSRs/ 24.60 million patient-years).
The outcome of serious events collected in the post-marketing experience is indicated at the event level: fatal (n = 23), not recovered (n = 49), recovered (n = 246), resolved with sequelae (n = 3), resolving (n = 105), unknown (n = 122) and not reported (n = 5).
As far as the nature of the risk is concerned, the most commonly reported serious events identified in the post-marketing experience were: "Rash" n = 87 (including 3 serious related from non-interventional PMS).

<u>Risk factors and risk groups:</u>
Several patients experiencing serious skin/hypersensitivity to febuxostat had history of a previous similar reaction to allopurinol and/or renal impairment. As febuxostat is an elective drug for these patients, it is uncertain whether prior hypersensitivity to allopurinol and/or renal impairment are actual risk factors for developing serious skin/hypersensitivity to

febuxostat or rather it is due to a high percentage of these patients being exposed to febuxostat because of a lack of therapeutic alternatives.
Whether previous allopurinol hypersensitivity and/or renal impairment is an actual risk factor for the development of serious skin/ hypersensitivity reactions related to febuxostat is to be determined yet. In fact these patients are the first candidates to be treated with febuxostat because of the previous allopurinol intolerance and/or the dose limitations of allopurinol in renally impaired patients which could not achieve an optimal control of serum uric acid levels. Based on this, it can be hypothesized that a relatively large percentage of patients with allopurinol hypersensitivity and/or renal impairment will be exposed to febuxostat.

Preventability:
Whereas it is still uncertain whether previous allopurinol hypersensitivity and/or renal impairment represent true risk factors for the development of serious skin/hypersensitivity reactions to febuxostat, the prognosis of these reactions can be mitigated by the early identification of signs and symptoms and the prompt withdrawal of the treatment. This has been addressed in Section 4.4 and in Section 4.8 of the SmPC.
A Direct Healthcare Professional Communication (DHPC) on the risk of serious skin/hypersensitivity was distributed in EU countries in 2012 as additional risk minimization measure. In particular, the DHPC was aimed to alert prescribers and patients associations that the occurrence of Serious skin / hypersensitivity - allergic reactions was higher during the first 2 months of treatment with febuxostat.
The DHPC was also aimed to highlight the main signs and symptoms characterising Serious skin / hypersensitivity - allergic reactions and to identify putative subpopulations (such as patients which had already previously suffered from similar reactions under allopurinol treatment and patients with renal function impaired, which could be at higher risk to develop Serious skin / hypersensitivity reactions). The DHPC was also aimed to instruct prescribers and patients to stop the treatment with febuxostat upon the identification if first signs and symptoms characterising Serious skin / hypersensitivity reactions to decrease their morbidity and improve the outcome and to don't re-introduce the drug in patients who have had these reactions in the past.

Impact on the risk-benefit balance of the product:
Serious skin / hypersensitivity reactions have a significant impact in the patient's quality of life and could be life threatening. The actual impact of the risk is calculated in a reporting rate of 19.35 serious ICSRs describing skin/hypersensitivity events per million patient-years (476serious ICSRs over a total exposure of 24.60 million patient-years).

Public health impact:
Serious skin / hypersensitivity reactions have an important impact on public health as they can be fatal, life threatening or their management requires hospitalisation or intervention.

Important Identified Risk: "Rhabdomyolysis"

Potential mechanisms:
The mechanism(s) through which febuxostat induces rhabdomyolysis alone or in association with other drugs is unknown. In fact febuxostat does not interfere with enzymes involved in the metabolism of colchicine or statins.

Evidence source(s) and strength of evidence:
Events of rhabdomyolysis did not occur in clinical trials, but, although in some cases collected in the post-marketing experience the role of co-suspect/concomitant drugs was likely, in other cases the relationship with febuxostat was possible. This prompted the insertion of this term in Section 4.8 of the SmPC and, given the severity of this risk, this safety issue has been considered as an important identified risk.

Characterisation of the risk:
The search strategy to retrieve suspected cases of rhabdomyolysis is the following:
Rhabdomyolysis/myopathy (SMQ-narrow)
In addition to the above SMQ, the search strategy also considers the following PT: Blood creatine phosphokinase increased.

Clinical studies
Three events of CPK increase were recorded in the febuxostat groups (one event at 40, 80 and 120 mg, n = 2,690) in phase III studies, whereas none of these events were recorded in placebo (n = 134) or allopurinol (n = 1,277) groups. Just one of these events was considered as treatment-related.
Seven events of CPK increase occurred in febuxostat groups (4 events at 80 mg and 3 events at 120 mg) in the LTE studies (n = 1,143 patients corresponding to 2,661 patient-years), whereas no such events occurred in the allopurinol group (n = 178 patients corresponding to 172 patient-years).
The frequency of CPK increase in phase III studies was 0.111% (95% CI 0.023 – 0.326%).
The events of Blood CPK increased collected in the LTE studies were mild (n = 3) or moderate (n = 4), whereas those collected in phase III studies were mild (n = 1) or moderate (n = 2).

Cumulatively, 5 serious events of "Rhabdomyolysis" have been collected in a post approval clinical trial versus allopurinol (TMX-67_301) and 1 serious event of "Blood creatine phosphokinase increased" had been collected from study Febuxostat XR-1011.

These 6 events have been considered not related to the treatment and reported with seriousness criteria of hospitalization in clinical trials.

One case of blood creatine phosphokinase increased and 5 cases describing rhabdomyolysis in study TMX 67_301 reported with seriousness criteria of hospitalization in clinical trials.

The events of Rhabdomyolysis in study TMX-67_301 were moderate (n=2) and severe (n=3).

Post-marketing experience
Cumulatively, by searching ICSRs describing rhabdomyolysis reported in the post-marketing experience (spontaneous reports or solicited reports from non-interventional studies) 224 ICSRs (91 serious) were collected from healthcare professionals or consumers, reporting 230 ADRs (95 serious and 135 non-serious). Among these, 2 serious ICSRs ([redacted] and [redacted]) with 2 serious ADRs was identified from non-interventional post-marketing studies.
The overall reporting rate of rhabdomyolysis or blood CPK increased was 9.11 ICSRs per million patient-years (224 ICSRs/24.60 million patient-years) and 3.70 serious ICSRs per million patient-years (91 serious ICSRs/24.60 million patient-years).

In the post-marketing experience a total of 95 serious ADRs describing rhabdomyolysis, myoglobin blood increased, myopathy or blood CPK increased met the seriousness criteria (the worst for each event): life-threatening (n = 4), hospitalization (n= 48), significant disability (n = 4), important medical event (include medically significant and requiring intervention, n = 74).
None of these events had a fatal outcome.
The outcome of these all ADRs is reported as resolved (n = 110), resolving (n = 40), not resolved (n = 13), unknown (n = 66), not reported (n=1).
The events intensity is mostly unknown, severe for 2 ADRs, moderate for 1 ADR and mild for 1 ADR.
Overall only ADRs of "Rhabdomyolysis" (n = 79, 76 of which serious), "Myopathy" (n = 7, 5 of which serious), "Myoglobin blood increased" (n = 2, both seirous) and "Blood CPK increased" (n =142, 12 of which serious) have been collected.

Risk factors and risk groups:
Beyond the male gender, lifestyle habits, the use of the above mentioned drugs (e.g., statins and colchicine), other risk factors include renal impairment (which is also a complication of rhabdomyolysis). Renal impairment was a pre-existing condition in several cases collected in post-marketing experience.

Preventability:
Latency, provided in 16 of the 31 cases (including those describing non-serious events), ranged from 10 to 198 days. The majority occurred within approximately 1 month of initiating febuxostat therapy. "Rhabdomyolysis" and "Blood creatine phosphokinase increase"are included at SmPC section 4.8.

Impact on the risk-benefit balance of the product:
The actual impact of the risk is calculated in a reporting rate of of 9.11 ICSRs of rhabdomyolysis or blood CPK increased per million patient-years (224 ICSRs over 24.60 million patient-years) and 3.70 serious ICSRs per million patient-years (91 serious ICSRs/24.60 million patient-years).
Due to the very low incidence, additional risk minimisation measures are not considered necessary.

Public health impact:
Although rare, drug-induced rhabdomyolysis has a significant impact on public health: a study on FDA AERs database exploring years 2004 – 2009 identified 8,610 cases of drug-induced rhabdomyolysis, 10.8% had a fatal outcome (Oshima, 2011).

Important Identified Risk: "Drug-drug interaction with azathioprine or mercaptopurine"

Potential mechanisms:
The inhibition of Xanthine Oxidase (XO) by febuxostat is likely to significantly increase serum concentrations of azathioprine or mercaptopurine active metabolites leading to increased toxicity. In fact, XO is responsible for the metabolism of 6-thioguanine nucleotides which are azathioprine / mercaptopurine metabolites.

Evidence source(s) and strength of evidence:
Based on the mechanism of action of xanthine oxidase inhibition, co-administration of febuxostat with azathioprine or mercaptopurine was not recommended. Although the potential for inadvertent co-administration is very small because these drugs are used in different populations, the potential consequences, including neutropenia, could be severe or life threatening. Following a preclinical study and a pharmacokinetic analysis to predict the dose reduction of azathioprine/mercaptopurine to be used when co-administered with febuxostat in humans, a study (FAI-01) to assess the PK profile of 6-mercaptopurine (6-MP) following coadministration of two doses febuxostat and azathioprine in healthy subjects has been completed.

Characterisation of the risk:
The search strategy is based on the identification of cases where azathioprine or mercaptopurine is co-suspect/concomitant medication.

Clinical studies
No cases of interaction between febuxostat and azathioprine (or mercaptopurine) have been collected in completed clinical trials. One serious unblinded case reported 2 events (Pneumonia and Sepsis) with febuxostat in the TMX-67_301 study. This case was fatal and did not report any drug-drug interaction, but had AZA reported as a concomitant drug and assessed as not related to study drug. In the FAI-01 study, a total of 11 Treatment Emergent Adverse Events (TEAEs) occurred in 9 participants. No death or serious adverse events were registered, all TEAEs were considered mild or moderate in terms of intensity.
The most commonly reported TEAE was headache experienced by 4 subjects overall. The only two Adverse Drug Reactions (ADRs), one event of headache and one of nausea, both mild and spontaneously resolved, were considered by the Investigator related to febuxostat 120 mg.

Post-marketing experience
Cumulatively, 68 ICSRs (47 serious and 21 non-serious) have been collected in the post-marketing experience from spontaneous sources, describing 177 ADRs (118 serious). Among these, 1 serious ICSR [redacted] with 2 serious ADRs was identified from non-interventional post-marketing studies.The outcome of these ADRs is reported as fatal (n = 2), resolved (n = 63), resolving (n = 53), not resolved (n = 7) and unknown (n = 52).
The severity of most post-marketing events is mostly unknown.
The overall reporting rate of serious cases involving this interaction was 2.76 ICSRs per million patient-years (68 ICSRs/ 24.60 million patient-years) and 1.91 serious ICSRs per million patient-years (47 serious ICSRs/ 24.60 million patient-years).

Risk factors and risk groups:
The populations at risk for this interaction is that which benefit from azathioprine treatment; these populations include patients with Inflammatory Bowel Diseases (Crohn's disease and ulcerative cholitis), with lupus erythematosus, and transplanted patients.

Preventability:
This issue of the interaction between febuxostat and azathioprine has been addressed in Section 4.4 and in Section 4.5 of the SmPC. A dose reduction to the 20 % of the usual azathiorprine dose when coadministered with febuxostat is recommended.

Impact on the risk-benefit balance of the product:
The actual impact of the risk is calculated in a reporting rate of 2.76 ICSRs per million patient-years (68 ICSRs/ 24.60 million patient-years) and 1.91 serious ICSRs per million patient-years (47 serious ICSRs/ 24.60 million patient-years).
Due to the very low incidence, additional risk minimisation measures are not considered necessary.
The interaction between febuxostat and azathioprine could have an important impact on the patient's life as azathioprine toxicity could be potentially fatal/life threatening.

Public health impact:
Although the absolute number of cases concerning the interaction between febuxostat and azathioprine is quite limited, the consequences of this interaction can be fatal, life-threatening and involve the patients' hospitalisation.

Important Identified Risk: "Cardiovascular events"

Potential mechanisms:
A mechanism by which febuxostat would cause cardiovascular events has not been identified; rather there is evidence that lowering serum uric acid through urate lowering therapy (ULT) would decrease the risk of cardiovascular events in gout patients.

Evidence source(s) and strength of evidence:
Multiple cardiovascular co-morbidities are present in gout patients, therefore a background of cardiovascular events is expected in patients treated with febuxostat, rendering difficult the detection of eventual specific cardiovascular issue related to the treatment.
Furthermore, in pre-registration studies the number of adjudicated APTC events was greater in patients treated with febuxostat than in patients treated with allopurinol. Because of this, two clinical trials (TMX-67_301 in US and FAST in EU) have been implemented to investigate this issue specifically, although the number of APTC events under febuxostat was not statistically significantly greater than in patients treated with allopurinol.

In the Phase IV CARES (Cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular comorbidities) study (TMX-67_301) performed in the US, Canada and Mexico, the CV safety of febuxostat and allopurinol in subjects with gout and major cardiovascular comorbidities has been evaluated. More than 6,000 patients were recruited to compare CV outcomes with febuxostat versus allopurinol. The primary endpoint in CARES study was time to first occurrence of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction (MI), non-fatal stroke, CV death and unstable angina with urgent coronary revascularization. The endpoints (primary and secondary) were analysed according to the intention-to-treat (ITT) analysis including all subjects who were randomized and received at least one dose of double-blind study medication.
Overall 56.6% of patients discontinued trial treatment prematurely and 45% of patients did not complete all trial visits. In total, 6,190 patients were followed for a median of 32 months and the median duration of exposure was 728 days for patients in febuxostat group (n=3,098) and 719 days in allopurinol group (n=3,092).
The primary MACE endpoint occurred at similar rates in the febuxostat and allopurinol treatment groups (10.8% vs. 10.4% of patients, respectively; hazard ratio [HR] 1.03; two-sided repeated 95% confidence interval [CI] 0.87-1.23).
In the analysis of the individual components of MACE (secondary endpoint), the rate of CV deaths was significantly higher with febuxostat than allopurinol (4.3% vs. 3.2% of patients;

HR 1.34; 95% CI 1.03-1.73). The rates of the other MACE events were similar in the febuxostat and allopurinol groups, i.e. non-fatal MI (3.6% vs. 3.8% of patients; HR 0.93; 95% CI 0.72-1.21), non-fatal stroke (2.3% vs. 2.3% of patients; HR 1.01; 95% CI 0.73-1.41) and urgent revascularization due to unstable angina (1.6% vs. 1.8% of patients; HR 0.86; 95% CI 0.59-1.26). The rate of all-cause mortality was also significantly higher with febuxostat than allopurinol (7.8% vs. 6.4% of patients; HR 1.22; 95% CI 1.01-1.47), which was mainly driven by the higher rate of CV deaths in that group.

In the Phase IV FAST study, the CV safety of febuxostat versus allopurinol in 6128 patients with gout, aged over 60 years and with at least one additional CV risk factor, who were already treated with allopurinol, has been evaluated. Eligible patients received allopurinol treatment prior to randomization, and dose adjustments were required when needed, according to clinical judgement, EULAR recommendations and the approved posology. At the end of the allopurinol lead-in phase, patients with a sUA level of <0.36 mmol/L (<6 mg/dL) or receiving the maximum tolerated dose or the maximum licensed dose of allopurinol were randomised in a 1:1 ratio to receive either febuxostat or allopurinol treatment. Randomisation was stratified according to whether or not the patients had a history of the following CV events: myocardial infarction (MI), stroke or hospitalisation for congestive heart failure (CHF) or peripheral vascular disease (PVD). The study was planned to be terminated after patients had been followed up for an average of at least 3 years and until it was predicted that at least 456 patients had experienced a first primary event on-treatment (OT). The duration of treatment for each subject varied due to the event driven study design. The primary endpoint of the study FAST was the time from randomization to the first occurrence of any event included in the Antiplatelet Trialists' Collaborative (APTC) composite endpoint, which included: i) hospitalisation for non-fatal MI/biomarker positive acute coronary syndrome (ACS); ii) non-fatal stroke; iii) death due to a CV event. The primary analysis was based on the on-treatment (OT) approach, i.e. covering the period patients remained on randomised therapy.

In summary, febuxostat 80 mg to 120 mg was non-inferior to allopurinol 100 mg to 900 mg with respect to its impact on adverse CV events. In contrast to the previous CARES study (TMX-67_301), there was no signal of increased all-cause or CV mortality with febuxostat. Furthermore, there were no unexpected safety signals of concern and the superior uric acid lowering effect of febuxostat was evident. Notably, no increased risk of adverse CV events was found neither in the overall safety population nor in the subgroup of patients with prior myocardial infarction (MI), stroke or acute coronary syndrome (ACS) (33.4%) who were very similar to the patients included in the CARES study.

Characterisation of the risk:
CV events occurring during febuxostat treatment have been retrieved from the Global Safety Database by searching the PTs included in the following SMQs:
Ischaemic heart disease (SMQ) – broad
Arrhythmia related investigations, signs and symptoms (SMQ) – broad
Cardiac arrhythmia terms (incl. bradyarrhythmias and tachyarrhythmias) (SMQ) – broad
Embolic and thrombotic events (SMQ)-broad
Cardiac failure (SMQ)-broad
Cardiomyopathy (SMQ) – broad
Pulmonary hypertension (SMQ) – broad
Ischaemic central nervous system vascular conditions (SMQ) - narrow
Haemorrhagic central nervous system vascular conditions (SMQ) - narrow

Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic - (SMQ) – narrow
In addition the search strategy also contained the following PTs not included in the above mentioned SMQs:
Aortic aneurysm
Aortic valve stenosis
Arteriosclerosis
Arteritis coronary
Carotid bruit
Cardiac murmur
Cerebrovascular arteriovenous malformation
Coronary artery aneurysm
Coronary artery dilation
Coronary artery perforation
Diastolic dysfunction
Electrocardiogram QT interval abnormal
Electrocardiogram ST-T change
Femoral artery aneurysm
Ischaemia
Peripheral artery aneurysm
Peripheral vascular disorder

Clinical studies
All cardiovascular events
In the phase III studies, similar proportions of subjects experienced treatment-emergent CV events across the treatment groups (5.2%, 6.3%, 6.3%, 6.0% and 6.0% in the febuxostat 40 mg, 80 mg, 120 mg, 240 mg and allopurinol groups, respectively) compared to 3.0% in the placebo group.
In the LTE studies, the incidences of CV events per 100 patient-years were similar across treatment groups (5.3, 6.6, 7.2 and 6.6 subjects for the febuxostat 40 mg, 80 mg, 120 mg and febuxostat total groups, respectively, and 8.1 subjects for the allopurinol group). These incidences were lower than those reported in the Phase III studies per 100 patient-years (12.4, 10.8 and 11.5 subjects in the febuxostat 80 mg, 120 mg and allopurinol groups, respectively).
In the phase III studies, the incidence of CV events in subjects treated with febuxostat was 5.9% (95% CI 5.1-6.9%) whereas the incidence in subjects treated with allopurinol was 6.0% (95% CI 4.8-7.5%) and in subjects treated with placebo was 3.0% (95% CI 0.8-7.5%).
In the LTE studies, the incidence of CV events in subjects treated with febuxostat was 6.6 per 100 patient-years (95% CI 5.6-7.6) whereas the incidence in subjects treated with allopurinol was 8.1 (95% CI 4.4-13.6).
In the phase III studies, a total of 47 serious adverse events, CV in nature, were reported by 41 febuxostat-treated subjects.
In the LTE studies, a total of 95 serious CV events were reported by 67 febuxostat-treated subjects.

The outcomes of the SAEs are summarized below.

Outcome	Number of serious adverse events			
	Phase III		LTE	
	Events	Subjects	Events	Subjects
Death	1	1	3	3
Resolved	43	37	88	60

Ongoing	3	3	3	3
Unknown	0	0	1	1

The most commonly reported serious events in phase III studies were: cardiac failure congestive (8 events in 6 subjects), myocardial infarction (5 events in 5 subjects), atrial fibrillation (5 events in 4 subjects), chest pain, coronary artery disease and transient ischemic attack (TIA) (3 events in 3 subjects each), and angina pectoris, angina unstable, atrioventricular block, and cardiac arrest (2 events in 2 subjects each). Single events of atrial fibrillation and TIA were considered possibly related to febuxostat. All other serious CV events in the phase III studies were considered to be unlikely or not related to febuxostat.
The most commonly reported serious CV events in the LTE studies were: coronary artery disease (17 events in 16 subjects), myocardial infarction (15 events in 14 subjects), atrial fibrillation (9 events in 8 subjects), cerebrovascular accident (7 events in 7 subjects), cardiac failure congestive (8 events in 6 subjects), acute myocardial infarction (5 events in 4 subjects), chest pain (3 events in 3 subjects) and angina pectoris, carotid artery stenosis, and coronary artery occlusion (2 events in 2 subjects each). Single events of hemiparesis, lacunar infarction and cerebrovascular accident were considered possibly related to febuxostat. All other serious CV events in the LTE studies were considered to be unlikely or not related to febuxostat.

In the phase III studies, events that led to discontinuation of febuxostat were atrial fibrillation and dyspnea (3 subjects each); palpitations, cardiac failure congestive, and myocardial infarction (2 subjects each); chest pain, chest discomfort, coronary artery disease, ventricular extrasystoles, angina unstable, angina pectoris, atrioventricular block, acute coronary syndrome, brain edema, carotid artery stenosis, cerebrovascular accident, ruptured cerebral aneurysm, and Wolff-Parkinson-White syndrome (1 subject each).

In the LTE studies, febuxostat was discontinued due to events of cerebrovascular accident, acute myocardial infarction and myocardial infarction (2 subjects each), cardiomyopathy alcoholic, chest discomfort, chest pain and dyspnea (1 subject each).
No subjects in the phase II study TMX-00-004 discontinued febuxostat due to CV adverse events.
In the phase III studies, the majority of CV events experienced by febuxostat-treated subjects were of mild or moderate intensity.
Severe events (i.e., those that caused considerable interference with the subject's normal activities and may have been incapacitating or life-threatening) reported included the preferred terms in ≥ 2 subjects: cardiac failure congestive (5 subjects), myocardial infarction (4 subjects) and chest pain, coronary artery disease, angina unstable, and atrioventricular block (2 subjects each).
In the LTE studies, over half of the subjects who reported treatment-emergent adverse events in the cardiac disorders SOC experienced mild or moderate events. The most frequently reported (≥ 2 subjects) severe events were: coronary artery disease (16 subjects), myocardial infarction (12 subjects), atrial fibrillation (5 subjects); chest pain, angina pectoris, cardiac failure congestive, bradycardia, acute myocardial infarction (4 subjects each); dyspnea and cerebrovascular accident (3 subjects each); and coronary artery occlusion (2 subjects).

Adjudicated APTC events
In the phase III studies, the proportions of subjects with treatment-emergent adjudicated APTC events were 0.5%, and 0.6% in the febuxostat 80 mg and 120 mg groups, respectively, and 0.3% in the placebo and allopurinol groups, respectively. No subjects in the placebo,

febuxostat 40 mg or febuxostat 240 mg groups experienced an adjudicated APTC event in the phase III studies.
In the LTE studies, the overall incidences of adjudicated APTC events were 1.0, 1.0 and 0.6 events per 100 patient-years of exposure in the febuxostat 80 mg and 120 mg groups and allopurinol group, respectively. One subject experienced an adjudicated APTC event while receiving febuxostat 40 mg (rate=2.7 per 100 PY based on only N=12 subjects).
In the phase III studies, the incidence of APTC events in subjects treated with febuxostat was 0.4% (95% CI 0.2-0.7%) whereas the incidence in subjects treated with allopurinol was 0.3% (95% CI 0.1-0.8%) and in subjects treated with placebo was 0.0% (95% CI 0.0-2.7%).
In the LTE studies, the incidence of APTC events in subjects treated with febuxostat was 1.0 per 100 patient-years (95% CI 0.7-1.5) whereas the incidence in subjects treated with allopurinol was 0.6 (95% CI <0.1-3.2).
In the Phase III studies, as well as in the LTE studies, the incidence of adjudicated APTC events was low across treatment groups. The 95% confidence intervals for the event rates overlapped and there were no statistically significant differences between treatment groups for the incidence of adjudicated events.
All the adjudicated APTC events in the phase III and LTE studies were reported as serious.
A total of 10 febuxostat-treated subjects in the phase III and 27 febuxostat-treated subjects in the LTE studies experienced at least one adjudicated APTC event, as outlined below.

	Number of subjects	
APTC Criterion	Phase III studies (N=2690)	LTE studies (N=1143)
All Adjudicated APTC Events	10	27
CV death	3	7
Nonfatal myocardial infarction	5	11
Nonfatal stroke	2	9

In the Phase III studies, all the nonfatal adjudicated APTC events summarized above resolved except for a nonfatal stroke (PT ruptured cerebral aneurysm). Of the nonfatal adjudicated APTC events in the LTE studies, 1 nonfatal stroke (PT cerebrovascular accident) and 1 myocardial infarction remained ongoing at the time of data cut-off.
In the phase III studies, adjudicated APTC events in the febuxostat groups led to discontinuation in 5 subjects (1 nonfatal stroke, 1 nonfatal myocardial infarction, 3 CV death).
In the LTE studies, adjudicated APTC events led to discontinuation in 12 subjects (4 nonfatal stroke, 1 nonfatal myocardial infarction, 7 CV death).

Two post-approval safety studies to assess the CV safety of febuxostat versus allopurinol in patients at risk for developing CV events (TMX-67_301 in US and FAST in EU) have been completed.
Cumulatively, 1,619 serious events (1,301 cases) were reported in patients exposed to febuxostat of which 1,404 serious events (1,113 cases) were reported from unblinded TMX-67_301 study (CARES) cases. Of the 1,619 SAEs, 32 events were assessed as related to febuxostat.
The outcome of these events was fatal (n = 154), not resolved (n = 133), resolved with sequelae (n = 70), resolved (n = 1,204), resolving (n = 48) and unknown (n = 10).
The severity of the events reported in study tmx-67_301 was mild (n = 85), moderate (n = 454) and severe (n = 907) and not reported in the remaining 173 events.

In the FAST study, the summaries of AEs are presented for two periods: during the study (randomisation up to date of death or end of study plus 28 days) and during treatment period

(randomisation up to date of death or end of study investigational medicinal product (IMP) plus 28 days, whichever came first).
During the study period, 493/6051 (8.2%) patients included in the safety population died: 226/3001 (7.5%) patients in the febuxostat group and 267/3050 (8.8%) patients in the allopurinol group. The proportion of patients who died during the treatment period was lower in the febuxostat group (4.9%) than in the allopurinol group (7.3%).
During the study period, at least one SAE was reported by 3532/6051 (58.4%) patients: 1720 (57.3%) in the febuxostat group and 1812 (59.4%) in the allopurinol group. The proportion of patients who experienced at least one SAE during the treatment period was lower in the febuxostat group (50.9%) than in the allopurinol group (58.1%), consistent with a shorter OT duration.
During the study period, 24 patients (0.4%) had at least one SAE considered treatment-related, 19 patients (0.63%) in the febuxostat group and 5 patients (0.16%) in the allopurinol group. All patients with related SAEs experienced these during the treatment period except for one patient in the febuxostat group.
Treatment with febuxostat was not associated with an increase in CV death or all-cause death, overall or in the subgroup of patients with a baseline history of MI, stroke or ACS. Overall, there were fewer deaths in the febuxostat group (2.02% CV deaths and 3.53% all-cause deaths), than in the allopurinol group (2.68% CV deaths and 5.68% all-cause deaths). These differences were statistically significant (p-value: 0.018 for CV deaths and <0.001 for all-cause deaths).
Rates of patients with CV adjudicated cause of death (by a blinded independent committee) were 3.8% patients in the febuxostat group and 4.0% in the allopurinol group. A higher proportion of patients died from non-cardiovascular deaths in the allopurinol group (4.6% patients) compared to the febuxostat group (3.4% patients).
There was a greater reduction in uric acid levels on febuxostat treatment compared to allopurinol treatment.

Post-marketing experience
All CV events
A total of 1,372 ICSRs (710 serious) were identified from post-marketing sources by performing the mentioned search strategy. These 1,372 ICSRs reported 1,673 ADRs (931 serious and 742 non-serious).
The most commonly reported serious CV PTs collected in the post-marketing experience were: “Myocardial infarction” (n = 84, including 7 from non-interventional post-marketing surveys), “Cardiac failure” (n = 70, including 9 from non-interventional post-marketing surveys), “Acute myocardial infarction” (n = 67, including 3 from non-interventional post-marketing surveys), “Dyspnoea” (n = 53), “Cerebrovascular accident” (n =50, including 1 from non-interventional post-marketing surveys), “Cardiac failure congestive” (n = 44, including 7 from post-marketing surveys), “Atrial fibrillation” (n = 40, including 2 from non-interventional post-marketing surveys), “Chest pain” (n = 30, including 1 from post-marketing study), “Coronary artery disease” (n = 25), “Angina pectoris” (n = 20, including 1 from non-interventional post-marketing surveys), “Palpitations” (n=20), “Arrhythmia” (n = 18), “Syncope” (n = 18, including 1 from non-interventional post-marketing surveys), “Oedema peripheral” (n = 15), “Bradycardia” (n = 14, including 2 from non-interventional post-marketing surveys), “Cardiac arrest” (n = 14, including 2 from non-interventional post-marketing surveys), “Pulmonary embolism” (n = 14), “Tachycardia” (n = 14), “Blood creatine phosphokinase increased” (n = 12), “Loss of consciousness” (n = 12), “Acute coronary syndrome” (n=11), “Cerebral haemorrhage” (n = 11, including 1 from non-interventional post-marketing surveys). “Cerebral infarction” (n = 10, including 6 from non-interventional

post-marketing surveys), "Deep vein thrombosis" (n = 10, including 1 from non-interventional post-marketing surveys), "Transient ischaemic attack" (n = 10, including 2 from non-interventional post-marketing surveys).
All the other represented CV terms accounted for 9 or fewer serious events each.
The outcome of these serious CV events is summarized as follow: fatal (n =131), not resolved (n =109), resolved with sequelae (n =25), resolved (n =246), resolving (n =115) and unknown (n =305).
The severity of most post-marketing events was unknown.
The overall reporting rate was 55.77 ICSRs per million patient-years (1,372 ICSRs/24.60 million patient-years) and of 28.86 serious ICSRs per million patient-years (710 serious ICSRs over 24.60 million patient-years).

Risk factors and risk groups:
In the pre-registration clinical studies, no specific cardiovascular risk factors were identified as being associated with febuxostat treatment. In these studies, patients' heart failure and ischemic heart diseases were found to be at higher risk to develop APTC events. In the post-registrational TMX-67_301 study (CARES), patients with gout and a history of major CV disease including MI, hospitalization for unstable angina, coronary or cerebral revascularization procedure, stroke, hospitalized transient ischemic attack, peripheral vascular disease, or diabetes mellitus with evidence of microvascular or macrovascular disease were studied to compare CV outcomes with febuxostat versus allopurinol.
In the post-registrational FAST study, patients with clinically diagnosed symptomatic hyperuricaemia who were 60 years of age or older, with at least one additional CV risk factor, and who were currently prescribed allopurinol for chronic hyperuricaemia in conditions where urate deposition had already occurred were studied.
Even if the FAST study showed no difference in CV and all-cause mortality rate with febuxostat compared to allopurinol, taking into consideration the results of CARES study (TMX-67_301), the MAH considers that caution should be exercised in patients with pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke or unstable angina) when administering febuxostat (see *Preventability* below).

Preventability:
Cardiovascular risk has been addressed in Section 4.4, 4.8 and 5.1 of the SmPC.
A Direct Healthcare Professional Communication (DHPC) letter was distributed in EU countries in 2019, as additional risk minimization measure, to the concerned Specialists, General Practitioners and Pharmacists, as well as relevant Patients and HCP associations, to notify the risk of cardiovascular events in patients with pre-existing major CV disease (e.g. myocardial infarction, stroke or unstable angina) and to communicate on the TMX-67_301 (CARES) study results and the SmPC changes.

Impact on the risk-benefit balance of the product:
The actual impact of the risk is calculated in a reporting rate of 55.77 ICSRs per million patient-years (1,372 ICSRs over 24.60 million patient-years) and of 28.86 serious ICSRs per million patient-years (710 serious ICSRs over 24.60 million patient-years).

Public health impact:
Cardiovascular disease imposes a huge burden in terms of mortality, morbidity, and healthcare costs (Yazdanyar and Newman, 2009).
Cardiovascular disease is the second leading cause of disability among older adults (after arthritis), and it is an important cause of a decline in self-reported health. Furthermore, both

clinical and subclinical cardiovascular diseases, contribute to dementia and functional decline, manifested by loss of independence and the ability to perform routine activities of daily living. (Yazdanyar and Newman, 2009).

Important Potential Risk: "Hepatic events"

Potential mechanisms:
A mechanism by which febuxostat could induce hepatic events has not been identified. In a limited percentage of cases hepatic adverse reactions are associated with serious skin / hypersensitivity ADRs (see SmPC Sections 4.4 and 4.8).

Evidence source(s) and strength of evidence:
Hepatic events, namely an increase in liver function tests, were among the more common events and ADRs collected in the clinical program on febuxostat.
The association between gout and hepatic events may be due to factors such as obesity, alcohol consumption and the metabolic syndrome which are linked to hepatic disease and are also common in the gout population (Luk et al 2005, Brunt et al 2004). Accordingly, the prevalence of chronic hepatitis was approximately 5-20% among patients with gout (Keenan eet al 2011). However other more specific mechanisms for this association is likely to exist as hyperuricemia has been found to be associated with increased risk for development of NAFLD, independently from the presence of other risk diseases such as obesity or diabetes (Lee et al 2010, Kim et al 2004). The prevalence of NAFLD was also found to be higher among patients with gout (23.1%) in comparison with patients without gout (10.9%) (Kuo et al 2010).

Characterisation of the risk:
Hepatic events have been retrieved from the Company global safety database by searching the PTs included in the following SMQs:
Biliary system related investigations, signs and symptoms (SMQ) – broad
Cholestasis and jaundice of hepatic origin (SMQ) – broad
Hepatic disorders specifically reported as alcohol-related (SMQ) – broad
Gallstone related disorders (SMQ) - narrow
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) – broad
Hepatitis, non-infectious (SMQ) – broad
Liver related investigations, signs and symptoms (SMQ) - broad

Clinical studies
In the phase III studies, the overall incidence of treatment-emergent hepatic adverse events was 2.2% (95% CI 0.5-6.4%) in the placebo, 7.0% (95% CI 6.1-8.0%) in the total febuxostat and 6.8% (95% CI 5.5-8.3%) the allopurinol groups.
In the LTE studies, the overall incidence of subjects per 100 patient-years with treatment-emergent hepatic adverse events was 3.8 subjects (95% CI 3.1-4.6) in the total febuxostat group, and 3.5 subjects (95% CI 1.3-7.6) in the allopurinol group. The most common (preferred terms $\geq$ 1 subject per 100 patient-years) hepatic event was hepatic enzyme increased (1.1 subjects in the total febuxostat and 1.2 in the allopurinol groups).
No febuxostat-treated subjects in the phase III studies or Study TMX-00-004 reported serious hepatic adverse events.

In the LTE studies, a total of 13 serious hepatic adverse events were reported in 11 febuxostat-treated subjects. Two of these events were considered related to study drug: cholelithiasis and cholecystitis.

The outcomes of the serious hepatic adverse events are summarized below.

Outcome	Number of serious adverse events			
	Phase III		LTE	
	Events	Subjects	Events	Subjects
Death	0	0	1	1
Resolved	0	0	11	9
Ongoing	0	0	1	1
Unknown	0	0	0	0

In phase III studies, the most common (preferred terms ≥ 1%) hepatic events were ALT increased (0.7% placebo, 2.3% total febuxostat and 1.6% allopurinol groups), AST increased (0% placebo, 1.6% total febuxostat and 1.6% allopurinol groups), hepatic enzyme increased (0.7% placebo, 2.0% total febuxostat and 2.3% allopurinol group) and liver function test (LFT) abnormal (0.7% placebo, 1.8% total febuxostat and 1.5% allopurinol group). Although reports of ALT ≥ 5 times the upper limit of normal (ULN) were rare (2% in the febuxostat 240 mg group and < 1% in the other treatment groups), all episodes resolved spontaneously. The majority of hepatic events concerned liver function analyses and subjects with mild transaminase elevations who continued on febuxostat treatment remained stable or improved, indicating that elevations were often only transient.
In the LTE studies the most common (preferred terms ≥ 1 subject per 100 PY) hepatic event was hepatic enzyme increased (1.1 subjects in the total febuxostat and 1.2 in the allopurinol groups).
As far as serious events are concerned, the following were collected in the LTE studies: cholecystitis (7 events in 7 subjects), cholelithiasis (4 events in 4 subjects) and bile duct cancer and hepatitis acute (1 event in 1 subject each).

Cumulatively 47 SAEs from 41 cases were reported from studies C02-021 (n=5), TMX-67_203, TMX-67_204, MEIN/11/FEB-GOU/001 and FEB-XR_201, FLO-01 (1 event for each) and TMX-67_301 (n=34) and TMX-67-11 (n=2) in patients treated with febuxostat.
Outcome was reported as: fatal (n = 3), not recovered (n = 7), recovered/resolved (n = 36), recovering (n = 1).
Severity was assessed as mild (n = 3), moderate (n = 16) and severe (n = 19). For the remaining events the intensity was not reported.
Only for 6 SAEs the causality was determined as related to febuxostat.

Post-marketing experience
A total of 1,137 ICSRs (299 serious) were identified from post-marketing sources by adopting the mentioned search strategy. These ICSRs reported 1,331ADRs (338 serious and 993 non-serious).
The most commonly reported serious PTs for hepatic events collected in the post-marketing experience were: “Drug-induced liver injury” (n =32), “Hepatic function abnormal” (n =30, including 1 from non-interventional PMS), “Hepatic enzyme increased” (n = 27), “Liver disorder” (n =23, including 1 from non-interventional PMS), “Jaundice” (n =22, including 1 from non-interventional PMS), “Liver function test abnormal” (n =21), “Alanine aminotransferase increased” (n =15, including 3 from non-interventional PMS), “Hepatocellular injury” (n =15), “Aspartate aminotransferase increased” (n = 14, including 3

from non-interventional PMS), "Transaminases increased" (n =14), "Hepatic failure" (n =13, including 2 from non-interventional PMS), "Liver function test increased" (n =12), "Gamma-glutamyltransferase increased" (n =12, including 2 from non-interventional PMS), "Cholestasis" (n = 9), "Hepatitis" (n =9). All the other represented PTs accounted for 8 or fewer events each.
The outcome of these serious events was the following: fatal (n = 19), not resolved (n = 28), resolved with sequelae (n = 3), resolved (n = 116), resolving (n = 99), not reported (n=1) and unknown (n = 72).
The severity of most post-marketing events is unknown.
The overall reporting rate of cases was 46.22 ICSRs per million patient-years (1,137 ICSRs/24.60 million patient-years) and of 12.15 serious ICSRs per million patient-years (299 serious ICSRs over 24.60 million patient-years).

Risk factors and risk groups:
No particular risk factor favouring the development of hepatic events was identified in clinical trials. In the post-marketing experience, beyond the very common co-morbidities which are associated with gout (e.g., hypertension, chronic kidney disease and diabetes), there were more specific co-morbidities that are linked to hepatic events such as chronic alcohol consumption and liver insufficiency. However, as the percentage of patients exposed to febuxostat with chronic alcohol consumption and liver insufficiency is unknown, it is doubtful if these conditions actually represent risk factors for the development of hepatic events. A study (Perez-Ruiz et al., 2013) has determined that treatment of patients with high basal level of liver enzymes (a cohort of 79 patients including 1 Child –A liver cirrhosis, 1 liver transplant, and 1 liver adenomatosis) with febuxostat for 12 months did not worsen these levels, rather there was an improvement of gamma-glutamyl transferase after 3 and 6 months of treatment.

Preventability:
The periodic monitoring of liver enzymes and the interruption of treatment when clinically significant increases are noted, may prevent the development of serious hepatic reactions. Therefore a specific warning has been inserted in Section 4.4 of the SmPC.

Impact on the risk-benefit balance of the product:
The actual impact of the risk is calculated in a reporting rate of 46.22 ICSRs per million patient-years (1,137 ICSRs/24.60 million patient-years) and of 12.15 serious ICSRs per million patient-years (299 serious ICSRs over 24.60 million patient-years).
Due to the very low incidence, additional risk minimisation measures are not considered necessary.

Public health impact:
Either acute or chronic liver diseases can have a fatal outcome, be life-threatening, or lead to important medical intervention such as liver transplant.

Important Potential Risk: "Renal events"

Potential mechanisms:
Renal toxicity in gout patients is thought to result primarily from the precipitation of uric acid, xanthine, and calcium phosphate in the renal tubules. In a small percentage of patients, renal toxicity is associated with the development of serious skin / hypersensitivity reactions to allopurinol or febuxostat.

Evidence source(s) and strength of evidence:
Renal diseases are one of the most important co-morbidity of gout (actually gout itself is a renal disease since in about 90% of cases, it consists in a deficiency in the renal excretion of uric acid), but also one of the target organs where signs of serious skin/hypersensitivity adverse reactions to febuxostat and a possible risk factor for the development of these reactions.
Impairment of renal function is both a major risk factor for developing gout and a common co-morbidity in patients with the condition (Perez-Ruiz et al 1999, Luk et al 2005). Indeed, hyperuricemia is caused by underexcretion of urate in approximately 90% of cases (Luk et al 2005, Choi et al 2005). Accordingly, the age standardized prevalence of gout in the 2009-2010 cycle of the US national health and Nutrition Examination Surveys was 2.9% in patients with normal GFR and 24% in patients with GFR<60 mL/min/1.73m2 (Krishnan 2012). Published studies of patients with gout/hyperuricemia have reported some degree of renal impairment in approximately 33% of patients (Akkasilpa et al 2004), although renal failure is less common (1-17%) (Mikuls et al 2005, Koh et al 1998). Approximately 1% of subjects with gout have a history of nephrolithiasis (Mikuls et al 2005), although kidney stones will form in 10-40% of gout patients (Richette et al 2010). Patients with gout have also a higher risk to develop end stage renal disease than non-gout patients (incidence rates: 1.73 vs. 0.41 per 1000 patient-years, respectively) (Yu et al 2012).

Characterisation of the risk:
The search strategy for renal events was based on the following SMQs:
Acute renal failure (SMQ) – broad
Haemodynamic oedema, effusions and fluid overload (SMQ) - narrow
Hypertension (SMQ) - narrow
Renovascular disorders (SMQ) – broad
And also includes the following additional Preferred Terms:
Arteriogram renal
Renal cyst
Blood urea nitrogen/creatinine ratio decreased
Renal mass
Blood creatine increased
Chronic kidney disease
Blood urine present
Urogram abnormal
Calculus bladder
Ultrasound kidney abnormal
Crystal urine
Urinary system x-ray abnormal
Crystal urine present
Urine oxalate increased
Glomerulonephritis acute
Urine protein/creatinine ratio abnormal
Glomerulonephritis chronic
Urine protein/creatinine ratio decreased
Haemoglobin urine present
Urine protein/creatinine ratio increased
Haematuria
Vasopressin challenge test abnormal
Nephrotic syndrome

White blood cells urine positive
Nephrolithiasis.

Clinical studies
In the phase III studies, the overall incidence of treatment-emergent renal adverse events was 6.0% (95% CI 2.6-11.4%) in the placebo group, 5.7% (95% CI 4.9-6.7%) in the total febuxostat, and 6.1% (95% CI 4.9-7.6%) the allopurinol group.
In the LTE studies, the overall incidence of subjects per 100 PY with treatment-emergent renal adverse events was 6.5 subjects (95% CI 5.5-7.5) in the total febuxostat group, and 5/.8 subjects (95% CI 2.8-10.7) in the allopurinol group.
The vast majority of serious renal event collected in the ongoing post-registration studies is still blinded.
The results of a post-registration study investigating the safety and efficacy of febuxostat in patients with moderate to severe renal failure (TMX-67_203) are available: Renal failure or related events (Renal failure acute, Renal failure chronic, Renal impairment) were more often (Fisher exact test: p = 0.03) observed in the placebo group (9 events over 32 patients), than in the febuxostat (30 mg BID or 40/80 mg QD) (5 events over 64 patients), indicating that febuxostat might have a protective effect on the renal function of these patients.
In the phase III studies, a total of 4 serious renal adverse events were reported in 4 febuxostat-treated subjects and included the following: renal failure acute (2 events in 2 subjects), and renal failure and renal impairment (1 subject each). Single events of renal failure and renal failure acute were considered related to study drug.
In febuxostat-treated subjects in the LTE studies, a total of 6 serious renal adverse events were reported in 5 febuxostat-treated subjects and included the following: renal failure and renal failure acute (2 events in 2 subjects each) and nephrolithiasis and renal cell carcinoma stage unspecified (1 events in 1 subject each). None of these events were considered treatment related. No renal adverse events were considered serious in the phase II study TMX-00-004.

The outcomes of the serious renal adverse events are summarized below.

Outcome	Number of serious adverse events			
	Phase III		LTE	
	Events	Subjects	Events	Subjects
Death	0	0	0	0
Resolved	4	4	6	5
Ongoing	0	0	0	0
Unknown	0	0	0	0

The most common (preferred terms ≥ 1%) renal events in phase III studies were edema peripheral (0.7% placebo, 2.2% total febuxostat and 2.2% allopurinol groups) and nephrolithiasis (0.7% placebo, 0.9% total febuxostat and 1.1% allopurinol groups).
In the LTE studies, the most common (preferred terms ≥ 1 subject per 100 patient-years) renal events were oedema peripheral (2.6 subjects in the total febuxostat group and 1.7 subjects in the allopurinol group), nephrolithiasis (1.4 subjects in the total febuxostat group and 1.7 subjects in the allopurinol group), renal cyst (0.2 subjects in the total febuxostat group and 1.7 subjects in the allopurinol group), blood creatinine increased (0.6 subjects in the total febuxostat group and 1.2 subjects in the allopurinol group).

Cumulatively, 360 serious renal events coincident with febuxostat (all doses) were reported in patients treated with febuxostat. Most of the events were reported from study TMX-67_301 (n=325). The outcomes of all the events were fatal (n=19), not recovered (n=46), recovered (n=279), resolved with sequelae (n=4) and resolving (n=12).

The severity of the events reported in clinical trials was mild (n=31), moderate (n=131), severe (n=181) and unknown in remaining 17 events. The most commonly reported renal events were acute kidney injury (n=217), followed by renal failure (n=26).

Post-marketing experience
A total of 1,344 (520 serious and 824 non-serious) ICSRs were received reporting 1,478 ADRs (555 serious and 923 non-serious).
The overall reporting rate was 54.63 ICSRs per million patient-years (1,344 ICSRs/24.60 million patient-years) and of 21.14 serious ICSRs per million patient-years (520 serious ICSRs over 24.60 million patient-years).
The outcome of serious events was the following: fatal (n = 29), not resolved (n = 66), resolved with sequelae (n = 7), resolved (n = 181), resolving (n = 93) and unknown (n = 179).
The severity of most post-marketing events is unknown.
The most commonly reported serious PTs for renal events collected in the post-marketing experience were: "Acute kidney injury" n = 159 (including 9 from non-interventional PMS), "Renal failure" n = 103 (including 14 from non-interventional PMS), "Renal impairment" n = 56 (including 4 from non-interventional PMS), "Blood creatinine increased" n = 29 (including 3 from non-interventional PMS),"Chronic kidney disease" n = 20 (including 4 from non-interventional PMS), "Tubulointerstitial nephritis" n = 17, "Oedema peripheral" n = 15 and "Blood pressure increased" n=10 (including 1 from non-interventional PMS).
All the other represented PTs accounted fewer than 9 events each.

Risk factors and risk groups:
Although gout has traditionally been considered to represent a significant risk for renal disease (Nickeleit et al, 1997; Talbott et al, 1960), such complications are usually attributable to alternative factors such as age, hypertension, vascular disease, and pre-existing renal conditions (Nickeleit et al, 1997; Berger et al, 1975; Yu et al, 1982). However, uric acid and hyperuricaemia have also been linked to progression of renal disease (Kang et al, 2002; Kang et al, 2005), and chronic use of NSAIDs may cause or worsen renal impairment (Henry et al, 1997).
From a quantitative point of view it has been estimated that the annual decrease of GFR in healthy adults spans from 0.8 to 1.3 mL/min/1.73m2, whereas in adult hyperuricaemic subjects renal function declines 2 to 3 fold faster (i.e., mean annual decrease of GFR 2.5 mL/min/1.73m2 (Whelton et al., 2013).

As compared with gout patients without chronic kidney disease, gout patients with chronic kidney disease are more likely to be older, women, had a greater number of co-morbidities, and more likely treated with allopurinol (Fuldeore et al., 2011).
Common co-morbidities of patients developing renal events in post-marketing experience included arterial hypertension, CKD not otherwise specified, diabetes mellitus, ischemic heart disease, cardiac failure. As these are the usual co-morbidities found in the gout population, these co-morbidities cannot be considered specific risk factors for the development of renal events.

Preventability:
As uric acid is suspected to be primarily the cause of renal toxicity (Avram et al, 2008), the administration of urate lowering therapy could reduce the risk to develop renal events.
Renal and urinary disorders are listed in febuxostat product information.

Impact on the risk-benefit balance of the product:
The actual impact of the risk is calculated in a reporting rate of 54.63 ICSRs per million patient-years (1,344 ICSRs/24.60 million patient-years) and of 21.14 serious ICSRs per million patient-years (520 serious ICSRs over 24.60 million patient-years).
Due to the very low incidence, additional risk minimisation measures are not considered necessary.

Public health impact:
Patients with chronic kidney disease associated to cardiovascular diseases are at major risk to develop cardiovascular complications. Population studies have found symptomatic kidney stone formers to be at increased risk for chronic kidney disease (Rule et al., 2011).

Important Potential Risk: "Neuropsychiatric events"

Potential mechanisms:
A mechanism by which febuxostat could cause neurological effects has not been identified. Hyperuricaemia can be associated to cerebral ischaemia.

Evidence source(s) and strength of evidence:
A single confounded case of Guillain-Barré syndrome was reported in Study TMX-00-004 (Subject [redacted]) and was considered possibly related to study drug by the investigator. The study sponsor assessed the report as not related to febuxostat (Council for International Organizations of Medical Sciences [CIOMS] report, study report TMX-00-004 [Module 5.3.5.1]); however, the occurrence of this event further prompted the analysis of neurological effects. In general, neurological disorders are not commonly associated with gout. Hyperuricemia has been associated with an increased risk to develop dementia (Ruggiero et al. 2009). Indeed, a decreased cognitive function in hyperuricemia has been attributed with the occurrence of cerebral ischemia (Vannorsdall et al., 2008). Cognitive impairment and behavioral disturbances are also characteristic of Lesch-Nyhan syndrome that is associated to hyperuricemia. Another important aspect to consider is the lifestyle of gout patients where the excessive alcohol consumption can precipitate psychiatric disturbances.

Characterisation of the risk:
Neurological and psychiatric events have been retrieved from the Company global safety database according to the search strategy below:
Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ) – broad
Convulsions (SMQ)
Guillain-Barré syndrome (SMQ) – broad
Hostility/aggression (SMQ) – broad
Lens disorders (SMQ) – broad
Noninfectious encephalopathy/delirium (SMQ) – broad
Noninfectious meningitis (SMQ) – broad
Optic nerve disorders (SMQ)
Peripheral neuropathy (SMQ) – broad
Suicide/self-injury (SMQ)
Taste and smell disorders (SMQ) – narrow
Vestibular disorders (SMQ) – broad
Aphonia (PT)
Cluster headache (PT)

Diplopia (PT)
Headache (PT)
Migraine (PT)
Migraine with aura (PT)
Sinus headache (PT)
Sleep apnoea syndrome (PT)
Syncope (PT)
Tension headache (PT)
Trigeminal neuralgia (PT)

Clinical studies
The overall incidence of treatment-emergent neurological adverse events was comparable among the total febuxostat, allopurinol and placebo groups in the phase III studies (9.7% [95% CI 5.3-16.0%] for placebo, 9.9% [95% CI 8.8-11.1%] for total febuxostat, and 9.9% [95% CI 8.3-11.6%] for allopurinol). The most common (preferred terms ≥ 1%) neurological AEs reported were headaches (5.2% for placebo, 4.4% for total febuxostat, and 4.5% for allopurinol) and dizziness (1.5% for placebo, 2.6% for total febuxostat and 1.5% for allopurinol).
In the LTE studies, the incidence of treatment emergent neurological events per 100 patient-years was similar in the febuxostat total (8.7 subjects; 95% CI 7.6-9.9) and allopurinol (11.6 subjects; 95% CI 7.1-17.9) groups. No clinically relevant differences were observed between the treatment groups and there was no evidence of a dose response.
In the phase III studies, a total of 4 serious neurological adverse events were reported in 4 febuxostat-treated subjects and included the following: syncope, anoxic encephalopathy, convulsion and vertigo positional (1 event in 1 subject each).
In febuxostat-treated subjects in the LTE studies, a total of 5 serious neurological adverse events were reported in 5 febuxostat-treated subjects and included the following: syncope (4 events in 4 subjects) and lumbar spinal stenosis (1 subject). None of the serious adverse events were considered related to febuxostat.
The outcomes of the serious neurological adverse events are summarized below.

Outcome	Number of serious adverse events			
	Phase III		LTE	
	Events	Subjects	Events	Subjects
Death	1	1	0	0
Resolved	3	3	5	5
Ongoing	0	0	0	0
Unknown	0	0	0	0

The most common (preferred terms ≥ 1 subject per 100 patient-years) neurological events per 100 patient-years in the febuxostat total and allopurinol groups were headache (3.3 and 4.1 subjects, respectively), dizziness (1.4 and 2.9 subjects, respectively), paraesthesia (1.3 and 2.3 subjects, respectively) and hypoesthesia (1.4 and 1.2 subjects, respectively).
In both the LTE and phase III studies, most neurological events experienced by febuxostat-treated subjects were mild or moderate in severity. In the phase III studies, following neurological events were reported as severe: headache (6 subjects), dizziness (4 subjects), syncope (3 subjects), and sciatica, neuropathy peripheral, nerve compression, anoxic encephalopathy, cluster headache, convulsion, loss of consciousness, optic neuritis, and vertigo positional (1 subject each). In the LTE studies, following neurological events were reported as severe: syncope (4 subjects), headache and dizziness (2 subjects), and par aesthesia, somnolence and lumbar radiculopathy (1 subject each).

In Study TMX-00-004, events of delirium tremens and suicide attempt led to discontinuation of febuxostat in 1 subject each. Febuxostat-treated subjects experienced severe events of delirium tremens and Guillain-Barré syndrome (1 subject) and headache (1 subject) in Study TMX-00-004.

Cumulatively in clinical trials 221 SAEs were collected in 201 ICSRs for this risk in febuxostat treated subjects.
Outcome was reported as: fatal (n = 28), not recovered (n = 18), recovered/ resolved with sequelae (n = 8), recovered/resolved (n = 162), recovering (n = 4) and unknown (n = 1).
Severity was assessed mild (n = 14), moderate (n = 63) and severe (n = 115). For the remaining the event intensity was not reported.
The most commonly reported events were syncope (n = 44), respiratory failure (n = 34), seizure (n = 12), mental status changes (n = 9), hepatic encephalopathy (n = 8), vertigo (n = 8), dizziness (n = 7), asthenia (n = 7) and encephalopathy (n = 7).
The causality was determined as related to febuxostat for 4 SAE.

Post-marketing experience
A total of 1,296 (313 serious) ICSRs were identified, reporting a total of 1,652ADRs (369 serious and 1,283 non-serious).
The outcome of these serious events was the following: fatal (n = 21), not resolved (n = 57), resolved (n = 147), recovered with sequelae (n = 4), resolving (n = 56) and unknown (n = 84).
The severity of most post-marketing events is unknown.
The most commonly reported serious PTs for neuropsychiatric events collected in the postmarketing experience were: “Dizziness” n = 46 (including 2 from non-interventional PMS), “Headache” n = 27 “Asthenia” n = 24 (including 1 from non-interventional PMS), , “Syncope” n = 18 (including 1 from non-interventional PMS), “Somnolence” n = 13, “Loss of consciousness” n = 12, “Hypoaesthesia” n = 12 (including 1 from non-interventional PMS), “Respiratory failure” n = 11 (including 2 from non-interventional PMS) “Muscular weakness” n = 10 and “Confusional state” n = 10 (including 1 from non-interventional PMS).
All the other represented PTs accounted for 9 or fewer events each.
The overall reporting rate was 52.68 ICSRs per million patient-years (1,296 ICSRs/24.60 million patient-years) and of 12.72 serious ICSRs per million patient-years (313 serious ICSRs over 24.60 million patient-years).

Risk factors and risk groups:
No specific risk groups or risk factors for neurological events were identified. Patients consuming an excessive quantity of alcohol may be at higher risk to develop psychiatric events.
Co-morbidities of patients developing neuropsychiatric events in post-marketing experience include: arterial hypertension, renal insufficiency, diabetes, hypercholesterolemia or hyperlipidemia or other cardiac conditions (including Atrial fibrillation). As these are the usual co-morbidities found in the gout population, these co-morbidities cannot be considered specific risk factors for the development of neuropsychiatric events.

Preventability:
In the absence of any identifiable risk, it is not possible to provide preventative measures.

Impact on the risk-benefit balance of the product:
The actual impact of the risk is calculated in a reporting rate of 52.68 ICSRs per million patient-years (1,296 ICSRs/24.60 million patient-years) and of 12.72 serious ICSRs per million patient-years (313serious ICSRs over 24.60 million patient-years).
Due to the very low incidence, additional risk minimisation measures are not considered necessary.
The large heterogeneity of neuropsychiatric events under exam does not allow to draw conclusions on the impact of neuropsychiatric events on individual patients, as these events could span from headache or dizziness to Guillain-Barrè syndrome or toxic encephalopathy.

Public health impact:
For the most concerning events, only isolated cases have been collected, so that the overall public health impact does not seem to be important.

Important Potential Risk: "Hematological/bleeding events"

Potential mechanisms:
A mechanism by which febuxostat could cause haematological effects has not been identified, however it should be considered that several of these events could have been precipitated by concomitant colchicine, warfarin (and fluindione) and azathioprine administration.

Evidence source(s) and strength of evidence:
Some reports have been collect in clinical development experience (see the below section Characterisation of the risk). Hematological and hemostasis disturbances have not traditionally linked to gout or hyperuricemia, although renal impairment, which is a significant co-morbidity of the gout population, may predispose to these conditions. Anemia has been identified as co-morbidity associated to about 2% of gout population (Primatesta et al., 2011). More importantly, beyond being a side effect of anti-gout treatments such as allopurinol and colchicine, hematological/bleeding ADRs are common of anticoagulant treatment taken by a significant proportion of gout patient which are at risk of thrombotic events, such as acetylsalicylic acid, clopidogrel or warfarin.

Characterisation of the risk:
Hematological/Bleeding events which occurred in the post-marketing surveillance have been retrieved from the Company global safety database according to the search strategy below:
Haemotopoietic cytopenias affecting more than one type of blood cell (SMQ)-broad
Haematopoietic erythropenia (SMQ)-broad
Haemolytic disorders (SMQ)- narrow
Haemorrhagic central nervous system vascular conditions (SMQ)- broad
Haemorrhage terms (excl. laboratory terms) (SMQ) - broad
Haemorrhage laboratory terms (SMQ) - broad
Haematopoietic leukopenia (SMQ) - broad
Haematopoietic thrombocytopenia (SMQ) - broad
Immune thrombocytopenic purpura (PT)
Leukocytosis (PT)
White blood cell count increased (PT)

Clinical studies
In the phase III studies, the overall incidence of treatment-emergent hematological adverse events was 1.5% (95% CI 0.2-5.3%) in the placebo, 2.2% (95% CI 1.6-2.8%) in the total

febuxostat, and 1.1% (95% CI 0.6-1.8%) the allopurinol groups. The incidence rate of any event by preferred term was <1.0% in the placebo, febuxostat total and allopurinol group.
In the LTE studies, the overall incidence of subjects per 100 patient-years with treatment-emergent hematological adverse events was 1.9 subjects (95% CI 1.4-2.5) in the total febuxostat group, and 1.7 subjects (95% CI 0.4-5.1) in the allopurinol group. The incidence rate of any event by preferred term was <1.0 subject per 100 patient-years in the febuxostat total and allopurinol groups.
In the phase III studies, a total of 4 serious hematological adverse events were reported in 3 febuxostat-treated subjects and included the following: anemia, thrombocytopenia, international normalized ratio increased and leukocytosis (1 event in 1 subject each). Single events of thrombocytopenia and leukocytosis were considered to be related to study drug. In febuxostat-treated subjects in the LTE studies, a total of 4 serious hematological adverse events were reported in 4 febuxostat-treated subjects and included the following: B-cell lymphoma (2 events in two subjects) and iron deficiency anemia and idiopathic thrombocytopenic purpura (ITP) (1 event in 1 subject each). The event of ITP was considered related to febuxostat.
The outcomes of the serious hematological adverse events are summarized below.

Outcome	Number of serious adverse events			
	Phase III		LTE	
	Events	Subjects	Events	Subjects
Death	0	0	0	0
Resolved	4	3	2	2
Ongoing	0	0	2	2
Unknown	0	0	0	0

In the phase III studies, 7 febuxostat-treated subjects discontinued the studies because of 1 or more of the following hematological events: platelet count decreased, thrombocytopenia, and pancytopenia (2 subjects each), and anemia, splenomegaly, hemolytic anemia, leukocytosis and myelodysplastic syndrome (1 subject each). In the LTE studies, 4 febuxostat-treated subjects discontinued the studies because of 1 or more of the following hematological events: B-cell lymphoma (2 subjects) and anemia and ITP (1 subject each).
The majority of hematological events experienced by febuxostat-treated subjects in the LTE and phase III studies were of mild or moderate severity. In the phase III studies, following hematological events were reported as severe: anemia and thrombocytopenia (2 subjects each), and leukopenia, pancytopenia, and leukocytosis (1 subject each).
In the LTE studies, the following hematological events were reported as severe: lymphadenopathy, white blood cell count decreased, thrombocytopenia, iron deficiency anemia, B-cell lymphoma and ITP (1 subject each).

Cumulatively, in clinical trials 240 SAEs were collected in 206 ICSRs for this risk in febuxostat treated subjects.
Outcome was reported as: fatal (n = 14), not recovered (n = 18), recovered with sequelae (n = 25), recovered (n = 172), recovering (n = 9) and unknown (2). Severity was assessed Grade 3 (n = 1), mild (n = 16), moderate (n = 56), not mentioned (n = 1) and severe (n = 124). For the remaining the event intensity was not reported.
The most commonly reported serious events were cerebrovascular accident (n=76), anaemia (n=24), gastrointestinal haemorrhage (n=21), upper gastrointestinal haemorrhage (n=8), haematoma (n=7) and thrombocytopenia (n = 6). All the other represented PTs accounted for 5 or fewer events each.
Only for 9 SAEs the causality was determined as related to febuxostat.

Post-marketing experience
A total of 718 (392 serious and 326 non-serious) ICSRs reporting 860 ADRs (478 serious and 382 non-serious) have been collected.
The outcome of these serious events was the following: fatal (n = 40), not resolved (n = 54), resolved with sequelae (n = 8), resolved (n = 177), resolving (n = 101), unknown (n = 97) and not reported (n = 1).
The severity of most post-marketing events is unknown.
The most commonly reported serious PTs for Hematological/Bleeding events collected in the post-marketing experience were: "Cerebrovascular accident" (n = 50, including 1 from non-interventional PMS), "Thrombocytopenia" (n =48), "Pancytopenia" (n = 44, including 1 from non-interventional PMS), "Anaemia" (n = 36, including 3 from non-interventional PMS), "Platelet count decreased" (n = 31), "Agranulocytosis" (n = 22), "Leukopenia" (n = 19), "White blood cell count decreased" (n = 15, including 1 from non-interventional PMS), "Neutropenia" (n = 13), "Cerebral haemorrhage" (n = 11, including 1 from non-interventional PMS) and "Purpura" (n = 11) . All the other represented PTs accounted for 9 or fewer events each.
The overall reporting rate is 29.19 ICSRs per million patient-years (718ICSRs/24.60 million patient-years) and of 15.93 serious ICSRs per million patient-years (392 serious ICSRs over 24.60 million patient-years).

Risk factors and risk groups:
The most common co-morbidities of patients having experienced hematological/bleeding events in post-marketing experience with febuxostat are the following: arterial hypertension, renal insufficiency, other cardiac conditions (including atrial fibrillation), diabetes, malignancies or hyperplasias, ischemic heart disease, hypercholesterolemia or hyperlipidemia, cardiac failure, allopurinol allergy, overweight.
Beyond the well-known gout co-morbidities, there were groups of patients such as those with malignancies or hyperplasias and allopurinol intolerance that appears susceptible to develop hematological/bleeding events under febuxostat therapy. Actually a quite large percentage of patients with history of malignancies or hyperplasias were concomitantly treated with colchicine or warfarin or fluindione, so it cannot be excluded that these drugs could be the cause of hematological/bleeding events.

Preventability:
About 50% of these events have occurred within the first month of treatment."Blood and limphatic system dysorders" and "Investigation" side effect are mentioned in the product information concerned section.

Impact on the risk-benefit balance of the product:
The actual impact of the risk is calculated in a reporting rate of 29.19 ICSRs per million patient-years (718ICSRs/24.60 million patient-years) and of 15.93 serious ICSRs per million patient-years (392serious ICSRs over 24.60 million patient-years).
Due to the very low incidence, additional risk minimisation measures are not considered necessary.

Public health impact:
If cerebrovascular accidents are excluded, none of the haematological/bleeding events had a fatal outcome, although they can be life threatening and about the half required hospitalisation.

Important Potential Risk: "Thyroid events"

Potential mechanisms:
A mechanism by which febuxostat could cause thyroid effects has not been identified.

Evidence source(s) and strength of evidence:
Adverse effects related to thyroid (decreases in T3 and T4, increases in TSH with accompanying follicular cell hyperplasia) were observed in rats during repeated dose toxicology studies. Rat thyroid is more sensitive to proliferative lesions caused by chronic TSH stimulation than human thyroid. Even in rats, the most sensitive species, the effects of febuxostat on the thyroid were observed only at a dose with a 31- fold higher exposure (AUC) compared to the mean exposure (AUC) observed in humans at a dose of 80 mg. Based on this preclinical data, thyroid parameters were monitored in LTE studies. Some cases of TSH increase have been collected during clinical development (see the below section characterisation of the risk). Significantly increased ($p < 0.05$) prevalence rates of hypothyroidism have been reported in patients with gout, with rates of 25% to 40% reported in women and 12% to 15% reported in men (Erickson et al., 1994). In patients with hypothyroidism, a significantly increased prevalence of hyperuricemia and gout has been reported compared to prevalence rates reported in the general population. While no significantly increased prevalence of gout was observed in hyperthyroid patients, a significantly increased prevalence of hyperuricemia was reported (Giordano et al., 2001).

Characterisation of the risk:
Thyroid effects have been retrieved from the Global Safety Database by searching the PTs included in the following SMQs:
Hyperthyroidism (SMQ) – broad
Hypothyroidism (SMQ) - broad

Clinical studies
In the phase III studies, the overall incidence of treatment-emergent thyroid adverse events was 0.7% (95% CI < 0.1-4.1%) in the placebo, 0.4% (95% CI 0.2-0.7%) in the total febuxostat, and 0.5% (95% CI 0.2-1.0%) the allopurinol groups. The incidence rate of any event by preferred term was < 1.0% in the placebo, febuxostat total, and allopurinol group.
In LTE studies, the overall incidence of subjects per 100 patient-years with treatment-emergent thyroid adverse events was 1.1 subjects (95% CI 0.7-1.6) in the total febuxostat group, and 0.6 subjects (95% CI < 0.1-3.2) in the allopurinol group.
The percentages of subjects with at least one increased TSH value based on the annualized rates adjusting for the substantial differences in exposure between the treatment groups in the LTE studies are 2.9%, 3.0%, and 6.4% for febuxostat 80 mg, febuxostat 120 mg and allopurinol, respectively.
No febuxostat-treated subjects in the phase III or LTE studies reported serious thyroid AEs.
MedDRA PTs that occurred in the febuxostat groups of the phase III studies: benign neoplasm of thyroid gland, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, hypothyroidism, thyroid cyst.
All thyroid events in both the phase III and LTE studies were mild to moderate in severity.

Cumulatively 2 SAEs ("Goitre" and "Hyperthyroidism") were collected in 2 ICSRs in post-registration clinical trial TMX-67_301 with febuxostat.
Outcome was reported recovered for both, severity was assessed mild and moderate.

Both SAEs were determined as not related to febuxostat.

Post-marketing experience
Cumulatively, a total of 61 ICSRs (9 serious) were identified. These ICSRs reported 68 ADRs (7 serious and 61 non-serious). Among these, 1 serious ICSR ([redacted]) with 2 ADRs ("Blood thyroid stimulating hormone abnormal" and "Tri-iodothyronine free abnormal") was identified from non interventional post-marketing studies.
The overall reporting rate is 2.48 ICSRs per million patient-years (61 ICSRs/24.60 million patient-years) and of 0.37 serious ICSRs per million patient-years (9 serious ICSRs over 24.60 million patient-years).
The outcome of the serious ADRs was the following: resolved (n = 3), not resolved (n = 1), resolving (n = 1) and unknown (n = 2).
The severity of most post-marketing events is unknown.
Seven serious PTs for thyroid events were collected in the post-marketing experience: "Blood thyroid stimulating hormone increased" (n = 3), "Basedow's disease" (n = 1), "Blood thyroid stimulating hormone abnormal" (n = 1, from non-interventional PMS), "Hyperthyroidism" (n = 1) and "Tri-iodothyronine free abnormal" (n = 1, from non-interventional PMS).

Risk factors and risk groups:
Thyroid effects could be linked to the dose of febuxostat but a mechanism by which febuxostat could cause thyroid effects has not been identified. In a study involving 68 normothyroid patients (Perez-Ruiz et al, 2012), TSH levels were measured before and 6 months after febuxostat treatment. Febuxostat was started 80 mg every other day for the first month, then all patients escalated to 80 mg every day until the 3-month visit, then adjusted according sUA levels up to a maximum of 120 mg/day. Multivariate analysis indicated that baseline TSH and dose of febuxostat at the 6th month were independently associated with TSH levels at the 6th month.
A significant prevalence of hypothyroidism has been reported in patients with gout, with rates of 25-40% reported in women and 12-15% reported in men (Erickson et al, 1994).

Preventability:
Caution is required when febuxostat is used in patients with alteration of thyroid function . A warning has been included in SmPC Section 4.4 and 5.1; SmPC section 4.8 includes "Blood thyroid stimulating hormone increased" among side effects.

Impact on the risk-benefit balance of the product:
The actual impact of the risk is calculated in a reporting rate of 2.48 ICSRs per million patient-years (61 ICSRs/24.60 million patient-years) and of 0.37 serious ICSRs per million patient-years (9 serious ICSRs over 24.60 million patient-years).
Due to the very low incidence, additional risk minimisation measures are not considered necessary.

Public health impact:
No relevant impact on public health as expected due to the low incidence rate of the issue.

Important Potential Risk: "Off label use in the paediatric population (TLS specific)"

Potential mechanisms:
Allopurinol is used to treat TLS in the paediatric population (Tazi et al., 2001) [76], therefore it is possible that febuxostat may be used as well.

Evidence source(s) and strength of evidence:
The pivotal phase III FLORENCE study has determined the safety and efficacy of febuxostat in adult patients affected by hematological malignancies, but no information is available in the pediatric population.
Aggressive Non-Hodgkin's Lymphoma and B and T Acute Lymphoblastic Leukaemia are most commonly associated with hyperuricemia and TLS: in these conditions TLS occurred in percentages between 26% (B Acute Lymphoblastic Leukaemia) and 4.4% (Non-Hodgkin's Lymphoma) of children.
No safety concerns are anticipated for an off label use in adolescents, whereas the lack of a suitable formulation could have had an impact for an off label use in children. Nevertheless, as in adults no outstanding safety issues have been highlighted for exposure up to 2.5 folds the dose recommended for TLS, an eventual overdose in exposed children should not involve major safety issues.

Characterisation of the risk:
Off label use in the paediatric population (TSL specific) have been retrieved from the Global Safety Database by searching the PTs: Off-label use, Drug administered to patient of inappropriate age.

Clinical studies
No clinical studies have been performed in the past to determine the safety and efficacy of febuxostat in the prevention of TLS in pediatric patients. The FLORET study (FLO-02) was conducted to compare the PK, PD and safety of Febuxostat between paediatric population (6-18 years of age) and adults. Up to the DLP, 30 patients have been enrolled. However, no information on the effect of febuxostat in this population is available from other sources.

Post-marketing experience
Cumulatively, a total of 10 non-serious ICSRs ([redacted] and [redacted]) reported off label use in patients with tumour lysis syndrome indication but only 5 of them involved pediatric patients. These 10 ICSRs were received from spontaneous post-marketing source with no associated ADRs. Five ICSRs reported the PT "Off-label use" and the other 5 ICSRs reported the PT "Product administered to patient of inappropriate age".
The outcome of these PTs was reported as unknown (n=9) and not recovered (n=1).
Cumulatively, considering only the ICSRs involving pediatric patients, the reporting rate (rr) of this risk was 0.20 ICSRs per million patient/year (5 ICSRs/24.60 million patient/year).

Risk factors and risk groups:
Children affected by malignancies at risk of TLS developing are at risk to be exposed to this off label use.

Preventability:
The febuxostat TLS indication is concerning only adult patients. The 4.2 SmPC section informs on the absence of data concerning paediatric population.

Impact on the risk-benefit balance of the product:
Considering only the ICSRs involving pediatric patients, the actual impact of the risk is calculated in a reporting rate of 0.20 ICSRs per million patient-years (5 ICSRs/24.60 million patient-years).
Due to the very low incidence, additional risk minimisation measures are not considered necessary.

Public health impact:
Hematological malignancy increases markedly with age: the median age at diagnosis being 70.6 years, however the precursor B-cell and T-cell lymphoblastic leukemias tend to occur at the youngest ages, the medians being 12.7 years and 18.5 years, respectively. However the rates of these leukemias is quite low, being one or less than one case per 100,000 (Smith et al., 2011). Furthermore, no outstanding safety issues can be anticipated from an eventual off-label use.

SVII.3.2. Presentation of the missing information

No experience in:

- Children and adolescents:

Evidence source:
No children or adolescents have been treated with febuxostat in clinical studies, therefore no information on the safety of this treatment is available in these patients.

Population in need of further characterisation:
Cases of children and adolescent are searched considering 18 or <18 years of age.

- Subjects in whom the rate of serum urate formation is greatly increased (e.g. Lesch-Nyhan syndrome):

Evidence source:
In patients in whom the rate of urate formation is greatly increased (e.g. 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 (except for patient affected by haematologic malignancies that have used the product to prevent TLS).

Population in need of further characterisation:
Patient with increased rate of urate formation (e.g. Lesch-Nyhan patients).

- Organ transplantation:

Evidence source:
No information on the safety of febuxostat is available in patients who had received a transplanted organ. These patients should be carefully monitored in case they need to be treated with febuxostat. As there has been no experience in organ transplant recipients, the use of febuxostat in such patients is not recommended.

Population in need of further characterisation:
Patients with history of organ transplant.

- Severe hepatic impairment:

Evidence source:
No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

Population in need of further characterisation:
Patients with severe hepatic impairment.

- Pregnancy and lactation:

Evidence source:
Data on a very limited number of exposed pregnancies have not indicated any adverse effects 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. Febuxostat should not be used during pregnancy (see Section 4.6 of the SmPC).
One pregnancy was reported in Study TMX-01-009 in a subject who received both febuxostat 80 mg QD for 9 days and 1 day prior to the estimated time of conception and febuxostat 20 mg QD 6 days and 13 days after the estimated time of conception. The subject had an uneventful pregnancy and delivered a healthy infant. In Study C02-021, pregnancies were reported in female partners of 5 subjects who received febuxostat. All female partners delivered healthy infants

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. Febuxostat should not be used while breastfeeding.

Population in need of further characterisation:
Pregnant and breastfeeding women.

- Off label use in patients with solid tumors (TLS specific):

Evidence source:
No studies have been performed on the effect of febuxostat on prevention and treatment of TLS in solid tumours that are ranked as low risk diseases for TLS except for neuroblastoma, germ cell tumours and small cell lung cancer or other bulky or advance stage disease that may be classified as intermediate risk diseases.

Population in need of further characterisation:
Patients with solid tumors.

- Interaction with standard therapy of haematological malignancies (TLS specific):

Evidence source:
No drug-drug interaction (DDI) studies between febuxostat and chemotherapic drugs for haematological malignancies have been carried out; such an interaction can be reasonably excluded on the basis of the metabolic characteristics of these drugs when compared with febuxostat and by the safety profile observed in the FLORENCE study.

Population in need of further characterisation:
Patients treated with standard therapy for haematological malignancies

Limited experience in:

- Severe renal impairment:

Evidence source:
Although there is limited experience on febuxostat in patients with severe renal impairment, PK studies have indicated that there is no change of the PK of febuxostat in this population as compared to healthy subjects.

Population in need of further characterisation:
Patients with severe renal impairment.

- Moderate hepatic impairment:

Evidence source:
Although febuxostat is mainly metabolised into the liver and excreted through the bile, PK studies have indicated that there is no change of the PK of febuxostat in mild to moderate hepatic impairment, even though the dose should not exceed 80 mg daily.

Population in need of further characterisation:
Patients with moderate hepatic impairment.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

The below table summarises the febuxostat safety concerns identified so far.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	- Serious skin / hypersensitivity reactions - Rhabdomyolysis - Drug-drug interaction with azathioprine or mercaptopurine - Cardiovascular events
Important potential risks	- 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 (e.g Lesch-Nyhan syndrome) - Organ transplantation - Severe hepatic impairment - Pregnancy and lactation - Off label use in patients with solid tumors (TLS specific) - Interaction with standard therapy of hematological malignancies (TLS specific) Limited experience in: - Severe renal impairment - Moderate hepatic impairment

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

All the safety concerns reported in this document (see Module II, part SVIII) are subjected to routine pharmacovigilance.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for "Serious skin/hypersensitivity reactions" (important identified risk) and "Hepatic events " (important potential risk):

The aim of these questionnaires is to collect additional structured information about clinical features of patients experiencing "Serious skin/hypersensitivity reactions" to febuxostat and "Hepatic events".
The forms are provided in Annex 4 of this RMP.

- Other forms of routine pharmacovigilance activities for "Interaction with standard therapy of haematological malignancies (TLS)" (missing information):

Possible interactions of febuxostat with cytotoxic chemotherapy will be closely monitored in future PSURs (all cases including possible interactions will be reviewed and discussed).
The objective of this routine pharmacovigilance activity is monitoring the interaction with standard therapy of haematological malignancies and the patient safety.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

No additional pharmacovigilance activities are planned for the safety concerns identified in the safety specification.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 3 - Required additional pharmacovigilance activities				
None	Not applicable	Not applicable	Not applicable	Not applicable

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable: no post-authorisation efficacy study has been mandated by Regulatory Authorities or have been proposed by the MAH.
Registration and post-registration studies (80% Caucasian, 11% Black, 3% Asian, 6% of other ethnicities in the phase III studies) have indicated that febuxostat at 80 or 120 mg is more effective than allopurinol in reducing serum uric acid, this profile has been confirmed in the post-marketing setting and the efficacy found in clinical trials has been confirmed in the daily practice through the observational study FORTE.
Efficacy has been confirmed in Japanese patients in both clinical studies and post-marketing experience.
No evidence indicates that febuxostat is not effective in any sub-population of gout patients.
As there are no uncertainties about efficacy of febuxostat, no post-authorisation efficacy study has been mandated by Regulatory Authorities or have been proposed by the MAH.

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due Date**
Efficacy studies which are conditions of the marketing authorisation				
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. ROUTINE RISK MINIMISATION MEASURES

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk: Serious skin / hypersensitivity reactions	Routine risk communication: SmPC Section 4.4 and corresponding PL section SmPC Section 4.8 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations on signs and symptoms and actions to be taken in case of allergic/Hypersensitivity reactions are included in SmPC sections 4.4 and corresponding PL section Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription
Important identified risk: Rhabdomyolysis	Routine risk communication: SmPC Section 4.8 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription
Important identified risk: Drug-drug interaction with azathioprine or mercaptopurine	Routine risk communication: SmPC Section 4.4 and corresponding PL section SmPC Section 4.5 and corresponding PL section SmPC Section 5.3 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation is reported in proposed SmPC sections 4.4 and 4.5 about dose reduction of mercaptopurine or azathioprine in order to avoid possible haematological effects where the combination with febuxostat cannot be avoided. Patients taking concomitantly febuxostat and mercaptopurine or azathioprine should be closely monitored. Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription

Safety concern	Routine risk minimisation activities
Important identified risk: Cardiovascular events	Routine risk communication: SmPC Section 4.4 and corresponding PL section SmPC Section 4.8 and corresponding PL section SmPC Section 5.1 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 recommends caution to use febuxostat in patients with pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke or unstable angina). Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription
Important potential risk: Hepatic events	Routine risk communication: SmPC Section 4.2 and corresponding PL section SmPC Section 4.4 and corresponding PL section SmPC Section 4.8 and corresponding PL section SmPC Section 5.1 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: Dose recommendation in patients with mild hepatic impairment is reported in SmPC Section 4.2 Recommendation regarding the performing of liver function test prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription
Important potential risk: Renal events	Routine risk communication: SmPC Section 4.2 and corresponding PL section SmPC Section 4.8 and corresponding PL section SmPC Section 5.2 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: No dose adjustment is necessary in patients with mild or moderate renal impairment (SmPC section 4.2) Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription

Safety concern	Routine risk minimisation activities
Important potential risk: Neuropsychiatric events	Routine risk communication: SmPC Section 4.8 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription
Important potential risk: Haematological / Bleeding events	Routine risk communication: SmPC Section 4.8 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription
Important potential risk: Thyroid events	Routine risk communication: SmPC Section 4.4 and corresponding PL section SmPC Section 4.8 and corresponding PL section SmPC Section 5.1 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 recommends caution when febuxostat is used in patients with alteration of thyroid function. Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription
Important potential risk: Off label use in paediatric patients (TLS specific)	Routine risk communication: SmPC Section 4.1 and corresponding PL section SmPC Section 4.2 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: As reported in the SmPC sections 4.1 and 4.2, Febuxostat is indicated in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of Tumor Lysis Syndrome. Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription

Safety concern	Routine risk minimisation activities
Missing information: No experience in: Children and adolescents	Routine risk communication: SmPC Section 4.2 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: As reported in the SmPC, section 4.2., the safety and the efficacy of febuxostat in children aged below the age of 18 years have not been established. No data are available. Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription
Missing information: No experience in: Subjects in whom the rate of serum urate formation is greatly increased (e.g. Lesch-Nyhan syndrome)	Routine risk communication: SmPC Section 4.4 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: There has been no experience with febuxostat, its use in these populations is not recommended (SmPC Section 4.4 and corresponding PL section). Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription
Missing information: No experience in: Organ transplantation	Routine risk communication: SmPC Section 4.4 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to not use febuxostat in organ transplant recipients is included in SmPC, section 4.4., as there has been no experience in such patients (SmPC Section 4.4 and corresponding PL section). Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription
Missing information: No experience in: Severe hepatic impairment	Routine risk communication: SmPC Section 4.2 and corresponding PL section SmPC Section 5.2 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C) (SmPC Section 4.2 and 5.2). Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription

Safety concern	Routine risk minimisation activities
Missing information: No experience in: Pregnancy and lactation	Routine risk communication: SmPC Section 4.6 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: The potential risk for pregnant women is unknown. It is unknown whether febuxostat is excreted in human breast milk. Febuxostat should not be used during pregnancy and breastfeeding (SmPC Section 4.6). Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription
Missing information: No experience in: Off label use in patients with solid tumors (TLS specific)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription
Missing information: No experience in: Interaction with standard therapy of haematological malignancies (TLS specific)	Routine risk communication: SmPC Section 4.8 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: A summary of available information on the safety profile of febuxostat in patients undergoing chemotherapy for haematologic malignancies is provided in SmPC Section 4.8 and corresponding PL section. Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription
Missing information: Limited experience in: Severe renal impairment	Routine risk communication: SmPC Section 4.2 and corresponding PL section SmPC Section 5.2 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: The efficacy and safety have not been fully evaluated in patients with severe renal impairment (SmPC Section 4.2). Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription

Safety concern	Routine risk minimisation activities
Missing information: Limited experience in: Moderate hepatic impairment	Routine risk communication: SmPC Section 4.2 and corresponding PL section SmPC Section 5.2 and corresponding PL section Routine risk minimisation activities recommending specific clinical measures to address the risk: Limited information is available in patients with moderate hepatic impairment (SmPC Section 4.2). Other routine risk minimisation measures beyond the Product Information: Legal status: Medical prescription

V.2. ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Serious skin / hypersensitivity reactions	Routine risk minimisation measures: SmPC Section 4.4 and corresponding PL section SmPC Section 4.8 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None
Important identified risk: Rhabdomyolysis	Routine risk minimisation measures: SmPC Section 4.8 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important identified risk: Drug-drug interaction with azathioprine or mercaptopurine	Routine risk minimisation measures: SmPC Section 4.4 and corresponding PL section SmPC Section 4.5 and corresponding PL section SmPC Section 5.3 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important identified risk: Cardiovascular events	Routine risk minimisation measures: SmPC Section 4.4 and corresponding PL section SmPC Section 4.8 and corresponding PL section SmPC Section 5.1 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk: Hepatic events	Routine risk minimisation measures: SmPC Section 4.2 and corresponding PL section SmPC Section 4.4 and corresponding PL section SmPC Section 4.8 and corresponding PL section SmPC Section 5.1 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None
Important potential risk: Renal events	Routine risk minimisation measures: SmPC Section 4.2 and corresponding PL section SmPC Section 4.8 and corresponding PL section SmPC Section 5.2 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important potential risk: Neuropsychiatric events	Routine risk minimisation measures: SmPC Section 4.8 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important potential risk: Haematological / Bleeding events	Routine risk minimisation measures: SmPC Section 4.8 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important potential risk: Thyroid events	Routine risk minimisation measures: SmPC Section 4.4 and corresponding PL section SmPC Section 4.8 and corresponding PL section SmPC Section 5.1 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk: Off label use in paediatric patients (TLS specific)	Routine risk minimisation measures: SmPC Section 4.1 and corresponding PL section SmPC Section 4.2 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information: No experience in: Children and adolescents	Routine risk minimisation measures: SmPC Section 4.2 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information: No experience in: Subjects in whom the rate of serum urate formation is greatly increased (e.g. Lesch-Nyhan syndrome)	Routine risk minimisation measures: SmPC Section 4.4 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information: No experience in: Organ transplantation	Routine risk minimisation measures: SmPC Section 4.4 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information: No experience in: Severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 and corresponding PL section SmPC Section 5.2 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information: No experience in: Pregnancy and lactation	Routine risk minimisation measures: SmPC Section 4.6 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information: No experience in: Off label use in patients with solid tumors (TLS specific)	Routine risk minimisation measures: None Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information: No experience in: Interaction with standard therapy of haematological malignancies (TLS specific)	Routine risk minimisation measures: SmPC Section 4.8 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Possible interactions of febuxostat with cytotoxic chemotherapy will be closely monitored in future PSURs (all cases including possible interactions will be reviewed and discussed). Additional pharmacovigilance activities: None
Missing information: Limited experience in: Severe renal impairment	Routine risk minimisation measures: SmPC Section 4.2 and corresponding PL section SmPC Section 5.2 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information: Limited experience in: Moderate hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 and corresponding PL section SmPC Section 5.2 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ADENURIC (FEBUXOSTAT)

This is a summary of the risk management plan (RMP) for Adenuric. The RMP details important risks of Adenuric, how these risks can be minimised, and how more information will be obtained about Adenuric's risks and uncertainties (missing information).
Adenuric's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Adenuric should be used.
This summary of the RMP for Adenuric should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates of Adenuric 's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Adenuric is authorised for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis) and 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) (see SmPC for the full indication). It contains febuxostat as the active substance and it is given by oral formulations (80 mg film-coated tablets and 120 mg film-coated tablets).
Further information about the evaluation of Adenuric's benefits can be found in Adenuric 's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000777/human_med_000627.jsp&mid=WC0b01ac058001d124.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Adenuric, together with measures to minimise such risks and the proposed studies for learning more about Adenuric's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Adenuric is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Adenuric are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Adenuric. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected;

List of important risks and missing information	
Important identified risks	- Serious skin / hypersensitivity reactions - Rhabdomyolysis - Drug-drug interaction with azathioprine or mercaptopurine - Cardiovascular events
Important potential risks	- 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 (e.g. Lesch-Nyhan syndrome) - Organ transplantation - Severe hepatic impairment - Pregnancy and lactation - Off label use in patients with solid tumors (TLS specific) - Interaction with standard therapy of hematological malignancies (TLS specific) Limited experience in: - Severe renal impairment - Moderate hepatic impairment

II.B Summary of important risks

Important identified risk: Serious skin/hypersensitivity reactions	
Evidence for linking the risk to the medicine	The potential of febuxostat to induce serious skin/hypersensitivity (allergic) reactions was already postulated at the time of the approval due to the fact that the other drugs used to lower acid uric levels (xanthine oxidase inhibitor, allopurinol) was known to precipitate such ADRs. However, no treatment-related serious skin/hypersensitivity (allergic) events were collected in clinical trials; therefore, this risk was initially classified as a potential one. In the first stages of the post-marketing experience, serious skin/hypersensitivity events causally related to febuxostat had been collected, so this risk was upgraded to an identified risk. Several patients experiencing serious skin/hypersensitivity (allergic) to febuxostat had history of a previous similar reaction to allopurinol and/or renal impairment. As febuxostat is an elective drug for these patients, it is uncertain whether prior hypersensitivity to allopurinol and/or renal impairment are actual risk factors for developing serious skin/hypersensitivity to febuxostat or rather it is due to a high percentage of these patients being exposed to febuxostat because of a lack of therapeutic alternatives.

Risk factors and risk groups	Whether previous allopurinol hypersensitivity (allergy) and/or renal impairment is an actual risk factor for the development of serious skin/ hypersensitivity (allergic) reactions related to febuxostat is to be determined yet. In fact these patients are the first candidates to be treated with febuxostat because of the previous allopurinol intolerance and/or the dose limitations of allopurinol in renally impaired patients which could not achieve an optimal control of serum uric acid levels. Based on this, it can be hypothesized that a relatively large percentage of patients with allopurinol hypersensitivity and/or renal impairment will be exposed to febuxostat.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 and corresponding PL section SmPC Section 4.8 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Important identified risk: Severe damage of skeletal muscle (Rhabdomyolysis)	
Evidence for linking the risk to the medicine	Events of severe damage of skeletal Muscle (rhabdomyolysis) did not occur in clinical trials, but, although in some cases collected in the post-marketing experience the role of co-suspect/concomitant drugs was likely, in other cases the relationship with febuxostat was possible. This prompted the insertion of this term in Section 4.8 of the SmPC and, given the severity of this risk, this safety issue has been considered as an important identified risk.
Risk factors and risk groups	Beyond the male gender, lifestyle habits, the use of the above mentioned drugs (e.g., statins and colchicine), other risk factors include renal impairment (which is also a complication of rhabdomyolysis). Renal impairment was a pre-existing condition in several cases collected in post-marketing experience.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Important identified risk: Concomitant co-treatment with certain immunosuppressants called azathioprine or mercaptopurine (Drug-drug interaction with azathioprine or mercaptopurine)	
Evidence for linking the risk to the medicine	Based on the mechanism of action of xanthine oxidase inhibition, co-administration of febuxostat with azathioprine or mercaptopurine was not recommended. Although the potential for inadvertent co-administration is very small because these drugs are used in different populations, the potential consequences, including neutropenia, could be severe or life threatening. Following a preclinical study and an analysis to predict the dose reduction of azathioprine/mercaptopurine to be used when co-administered with febuxostat in humans, a study to assess the pharmacokinetic profile of 6-mercaptopurine following coadministration of two doses febuxostat and azathioprine in healthy subjects has been completed.
Risk factors and risk groups	The populations at risk for this interaction is that which benefit from azathioprine treatment; these populations include patients with Inflammatory Bowel Diseases (Crohn's disease and ulcerative cholitis), with lupus erythematosus, and transplanted patients.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 and corresponding PL section SmPC Section 4.5 and corresponding PL section SmPC Section 5.3 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Important identified risk: Cardiovascular events	
Evidence for linking the risk to the medicine	Multiple CV co-morbidities are present in gout patients, therefore a background of CV events is expected in patients treated with febuxostat, rendering difficult the detection of eventual specific CV issue related to the treatment. Furthermore, in pre-registration studies the number of adjudicated cardiovascular (APTC) events was greater in patients treated with febuxostat than in patients treated with allopurinol. Because of this, two clinical trials (CARES - TMX-67_301 in US and FAST in EU) have been implemented to investigate this issue specifically, although the number of cardiovascular (APTC) events under febuxostat was not statistically significantly greater than in patients treated with allopurinol. In contrast to the previous CARES study (TMX-67_301), from FAST study there was no signal of increased all-cause or CV mortality with febuxostat. Furthermore, there were no unexpected safety signals of concern and the superior uric acid lowering effect of febuxostat was evident. Notably, no increased risk of adverse CV events was found neither in the overall safety population nor in the subgroup of patients with prior myocardial infarction (MI), stroke or acute coronary syndrome (ACS) (33.4%) who were very similar to the patients included in the CARES study.
Risk factors and risk groups	In clinical studies, no specific cardiovascular risk factors were identified as being associated with febuxostat treatment. In these studies, patients' heart failure and ischemic heart diseases were found to be at higher risk to develop cardiovascular (APTC) events. In the post-registrational TMX-67_301 study (CARES), patients with gout and a history of major cardiovascular (CV) disease, a significantly higher risk for all-cause mortality and for CV-related death was observed in patients treated with febuxostat compared with patients treated with allopurinol. In the post-registrational FAST study, patients with clinically diagnosed symptomatic hyperuricaemia who were 60 years of age or older, with at least one additional cardiovascular (CV) risk factor, and who were currently prescribed allopurinol for chronic hyperuricaemia in conditions where urate deposition had already occurred were studied. Even if the FAST study showed no difference in CV and all-cause mortality rate with febuxostat compared to allopurinol, taking into consideration the results of CARES study, the MAH considers that caution should be exercised in patients with pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke or unstable angina) when administering febuxostat.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 and corresponding PL section SmPC Section 4.8 and corresponding PL section SmPC Section 5.1 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Important potential risk: Hepatic events	
Evidence for linking the risk to the medicine	Hepatic events, namely an increase in liver function tests, were among the more common events and ADRs collected in the clinical program on febuxostat. The association between gout and hepatic events may be due to factors such as obesity, alcohol consumption and metabolic disorder (the metabolic syndrome) which are linked to hepatic disease and are also common in the gout population (Luk et al 2005, Brunt et al 2004). Accordingly, the prevalence of chronic hepatitis was approximately 5-20% among patients with gout (Keenan eet al 2011). However other more specific mechanisms for this association is likely to exist as hyperuricemia has been found to be associated with increased risk for development of hepatic damage (nonalcoholic fatty liver disease), NAFLD, independently from the presence of other risk diseases such as obesity or diabetes (Lee et al 2010, Kim et al 2004). The prevalence of NAFLD was also found to be higher among patients with gout (23.1%) in comparison with patients without gout (10.9%) (Kuo et al 2010).
Risk factors and risk	No particular risk factor favouring the development of hepatic events was identified in

groups	clinical trials. In the post-marketing experience, beyond the very common co-morbidities which are associated with gout (e.g., hypertension, chronic kidney disease and diabetes), there were more specific co-morbidities that are linked to hepatic events such as chronic alcohol consumption and liver insufficiency. However, as the percentage of patients exposed to febuxostat with chronic alcohol consumption and liver insufficiency is unknown, it is doubtful if these conditions actually represent risk factors for the development of hepatic events. A study (Perez-Ruiz et al., 2013) has determined that treatment of patients with high basal level of liver enzymes (79 patients) with febuxostat for 12 months did not worsen these levels rather there was an improvement of laboratory parameters (gamma-glutamyl transferase) after 3 and 6 months of treatment.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 and corresponding PL section SmPC Section 4.4 and corresponding PL section SmPC Section 4.8 and corresponding PL section SmPC Section 5.1 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Important potential risk: Renal events	
Evidence for linking the risk to the medicine	Renal diseases are one of the most important co-morbidity of gout (actually gout itself is a renal disease since in about 90% of cases, it consists in a deficiency in the renal excretion of uric acid), but also one of the target organs where signs of serious skin/hypersensitivity adverse reactions to febuxostat and a possible risk factor for the development of these reactions. Impairment of renal function is both a major risk factor for developing gout and a common co-morbidity in patients with the condition (Perez-Ruiz et al 1999, Luk et al 2005). Indeed, hyperuricemia is caused by underexcretion of urate in approximately 90% of cases (Luk et al 2005, Choi et al 2005). Accordingly, the age standardized prevalence of gout in the 2009-2010 cycle of the US national health and Nutrition Examination Surveys was 2.9% in patients with normal GFR and 24% in patients with GFR<60 mL/min/1.73m2 (Krishnan 2012). Published studies of patients with gout/hyperuricemia have reported some degree of renal impairment in approximately 33% of patients (Akkasilpa et al 2004) , although renal failure is less common (1-17%) (Mikuls et al 2005, Koh etal 1998). Approximately 1% of subjects with gout have a history of nephrolithiasis ((Mikuls et al 2005), although kidney stones will form in 10-40% of gout patients (Richette et al 2010). Patients with gout have also a higher risk to develop end stage renal disease than non-gout patients (incidence rates: 1.73 vs. 0.41 per 1000 patient-years, respectively) (Yu et al 2012).
Risk factors and risk groups	Although gout has traditionally been considered to represent a significant risk for renal disease (Nickeleit et al, 1997; Talbott et al, 1960), such complications are usually attributable to alternative factors such as age, hypertension, vascular disease, and pre-existing renal conditions (Nickeleit et al, 1997; Berger et al, 1975; Yu et al, 1982). However, uric acid and hyperuricaemia have also been linked to progression of renal disease (Kang et al, 2002; Kang et al, 2005), and chronic use of NSAIDs may cause or worsen renal impairment (Henry et al, 1997). As compared with gout patients without chronic kidney disease, gout patients with chronic kidney disease are more likely to be older, women, had a greater number of co-morbidities, and more likely treated with allopurinol (Fuldeore et al., 2011). Common co-morbidities of patients developing renal events in post-marketing experience included arterial hypertension, chronic kidney disease (CKD) not otherwise specified, diabetes mellitus, ischemic heart disease, cardiac failure. As these are the usual co-morbidities found in the gout population, these co-morbidities cannot be considered specific risk factors for the development of renal events.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 and corresponding PL section

	SmPC Section 4.8 and corresponding PL section SmPC Section 5.2 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Important potential risk: Neuropsychiatric events	
Evidence for linking the risk to the medicine	Isolated cases occurred during clinical development. In general, neurological disorders are not commonly associated with gout. Hyperuricemia has been associated with an increased risk to develop dementia (Ruggiero et al. 2009). Indeed, a decreased cognitive function in hyperuricemia has been attributed with the occurrence of cerebral ischemia (Vannorsdall et al., 2008). Cognitive impairment and behavioral disturbances are also characteristic of genetic defect (Lesch-Nyhan syndrome) that is associated to hyperuricemia. Another important aspect to consider is the lifestyle of gout patients where the excessive alcohol consumption can precipitate psychiatric disturbances.
Risk factors and risk groups	No specific risk groups or risk factors for neurological events were identified. Patients consuming an excessive quantity of alcohol may be at higher risk to develop psychiatric events. Co-morbidities of patients developing neuropsychiatric events in post-marketing experience include: arterial hypertension, renal insufficiency, diabetes, hypercholesterolemia or hyperlipidemia or other cardiac conditions (including atrial fibrillation). As these are the usual co-morbidities found in the gout population, these co-morbidities cannot be considered specific risk factors for the development of neuropsychiatric events.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Important potential risk: Haematological / Bleeding events	
Evidence for linking the risk to the medicine	Some reports have been collect in clinical development experience Hematological and hemostasis disturbances have not traditionally linked to gout or hyperuricemia, although renal impairment, which is a significant co-morbidity of the gout population, may predispose to these conditions. Anemia has been identified as co-morbidity associated to about 2% of gout population (Primatesta et al., 2011). More importantly, beyond being a side effect of anti-gout treatments such as allopurinol and colchicine, hematological/bleeding ADRs are common of anticoagulant treatment taken by a significant proportion of gout patient which are at risk of thrombotic events, such as, acetylsalicylic acid, clopidogrel or warfarin.
Risk factors and risk groups	The most common co-morbidities of patients having experienced hematological/bleeding events in post-marketing experience with febuxostat are the following: arterial hypertension, renal insufficiency, other cardiac conditions (including atrial fibrillation), diabetes, malignancies or hyperplasias, ischemic heart disease, hypercholesterolemia or hyperlipidemia, cardiac failure, allopurinol allergy, overweight. Beyond the well-known gout co-morbidities, there were groups of patients such as those with malignancies or hyperplasias and allopurinol intolerance that appears susceptible to develop hematological/bleeding events under febuxostat therapy. Actually a quite large percentage of patients with history of malignancies or hyperplasias were concomitantly treated with colchicine or warfarin or fluindione, so it cannot be excluded that these drugs could be the cause of hematological/bleeding events.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 and corresponding PL section

	Additional risk minimisation measures: No risk minimisation measures

Important potential risk: Thyroid events	
Evidence for linking the risk to the medicine	Some thyroid damages have been observed in preclinical studies in rats exposed to toxic doses (very high) of febustoat. Isolated cases of laboratory changes (TSH increase) have been collected in clinical development. Significantly increased ($p < 0.05$) prevalence rates of hypothyroidism have been reported in patients with gout, with rates of 25% to 40% reported in women and 12% to 15% reported in men (Erickson et al., 1994). In patients with hypothyroidism, a significantly increased prevalence of hyperuricemia and gout has been reported compared to prevalence rates reported in the general population. While no significantly increased prevalence of gout was observed in hyperthyroid patients, a significantly increased prevalence of hyperuricemia was reported (Giordano et al., 2001).
Risk factors and risk groups	Thyroid effects could be linked to the dose of febuxostat but a mechanism by which febuxostat could cause thyroid effects has not been identified. In a study involving 68 normothyroid patients (Perez-Ruiz et al, 2012), TSH levels were measured before and 6 months after febuxostat treatment. Baseline TSH and dose of febuxostat at the 6th month were independently associated with TSH levels at the 6th month. A significant prevalence of reduced thyroid function (hypothyroidism) has been reported in patients with gout, with rates of 25-40% reported in women and 12-15% reported in men (Erickson et al, 1994).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 and corresponding PL section SmPC Section 4.8 and corresponding PL section SmPC Section 5.1 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Important potential risk: Off label use in paediatric patients (TLS specific)	
Evidence for linking the risk to the medicine	No studies have been performed in the past on the effect of febuxostat in children (one is now ongoing). In addition no formulation of febuxostat suitable for young patients is available.
Risk factors and risk groups	Children affected by malignancies at risk of TLS developing are at risk to be exposed to this off label use.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.1 and corresponding PL section SmPC Section 4.2 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Missing information -No experience in: Children and adolescents	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Missing information -No experience in: Subjects in whom the rate of serum urate formation is greatly increased (e.g. Lesch-Nyhan syndrome)	
Risk minimisation measures	Routine risk minimisation measures:

	SmPC Section 4.4 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Missing information -No experience in: Organ transplantation	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Missing information -No experience in: Severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 and corresponding PL section SmPC Section 5.2 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Missing information -No experience in: Pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Missing information -No experience in: Off label use in patients with solid tumors (TLS specific)	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: No risk minimisation measures

Missing information -No experience in: Interaction with standard therapy of haematological malignancies (TLS specific)	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Missing information - Limited experience in: Severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 and corresponding PL section SmPC Section 5.2 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

Missing information - Limited experience in: Moderate hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 and corresponding PL section SmPC Section 5.2 and corresponding PL section Additional risk minimisation measures: No risk minimisation measures

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Adenuric.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Adenuric.

PART VII: ANNEXES

Annex 4 - Specific adverse drug reaction follow-up forms

TABLE OF CONTENTS

Annex 4A: Adverse event follow-up form for serious skin / hypersensitivity reactions

FOLLOW UP TO CUTANEOUS ADVERSE REACTION TO FEBUXOSTAT

1.Case ID n⁰ | **2.Country** | **3.Date received** _ _/__/_ _ _ _

4. Reported diagnosis*

5.Hospitalization:
- Hospital name:.....
- Duration:.....
- Discharge diagnosis:.....
- Dermatologist referral ☐Yes ☐No
If yes specify diagnosis.....
- Discharge summary attached ☐Yes ☐No

6.Reporter
- Name
- Address
- Tel
- Specialty

7.Patient
- Initials: ..... •Gender:.....
- Weight:..... •Height: .....
- Date of birth:.....
- Ethnicity:.....

I. History of previous allopurinol use

☐Yes ☐No ☐Unk. *If yes please continue:*

1. **Did the patient develop severe cutaneous reaction or serious hypersensitivity ADRs to allopurinol?** ☐Yes ☐No ☐Unk *If yes please continue:*
2. **Before the ADR, allopurinol dose.....and duration .....**
3. **Hospitalization** ☐Yes ☐No ☐ Unk *If yes please specify:*

a. Duration....., b. Dicharge diagnosis....., c. Outcome.....,
d. Discharge summary attached ☐Yes ☐No

3. **Skin biopsy** ☐Yes ☐No ☐UnK
4. **Skin detachment** ☐Yes ☐No ☐UnK If yes please specify %BSA§ _ _ _
5. **Facial edema** ☐Yes ☐No ☐UnK
6. **Mucosal involvment** ☐Yes ☐No ☐UnK
7. **Fever** ☐Yes ☐No ☐UnK
8. **Eosinophilia** (>450 cell/mcl) ☐Yes ☐No ☐Unk
9. **HHV test** ☐Yes ☐No☐UnK If yes please specify.....
10. **Systemic involvement** ☐Yes ☐No ☐UnK If yes please specify.....
11. **Hystory renal disease/impairment before and during allopurinol**

☐Yes ☐No ☐Unk If yes please specify degree or CrCl (mL/min).....
.....
12. **Genomic characterisation for HLA-B*5801** ☐Yes ☐No ☐Unk
13. **Hospitalization** ☐Yes ☐No ☐Unk
14. **Outcome**.....

II. Any other previous hypersensitivity hystory

☐Yes ☐No ☐UnK *If yes please specify:*

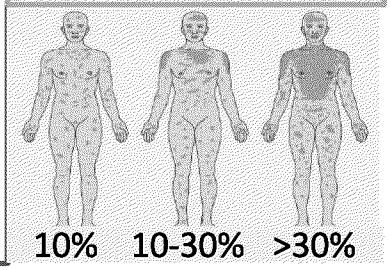
1. **Cause**.....

If pharmacological treatment , please specify:

a. Dose.....
b. Duration.....

2. **Hospitalization** ☐Yes ☐No ☐Unk
3. **Action taken**.....
4. **Outcome**.....

§ % Body surface area (BSA)



III. Hystory of the current ADR to febuxostat

1. **Hystory of renal disease/impairment before taking febuxostat** ☐Yes ☐No ☐Unk If yes please specify degree of renal impairment/CrCl(ml/min).....
2. **Onset reaction date** _ _/_ _/_ _ _ _
3. **Initial symptoms**

- Malaise ☐Yes ☐No ☐Unk
- Fever ☐Yes ☐No ☐Unk
- Conjunctivitis ☐Yes ☐No ☐Unk
- Cutaneous reactions ☐Yes ☐No ☐Unk
- Lymphoadenopathy ☐Yes ☐No ☐Unk

If yes please specify onset date and duration .....

4. **Skin eruption presentation**

Erythema	☐Yes ☐No ☐Unk	.....
Rash	☐Yes ☐No ☐Unk	.....
Pruritic macules with blisters	☐Yes ☐No ☐Unk	.....
Extensive, non follicular postules	☐Yes ☐No ☐Unk	If yes please specify.....
Hemorrhagic blisters	☐Yes ☐No ☐Unk	.....
Urticaria	☐Yes ☐No ☐Unk	.....
Erosions	☐Yes ☐No ☐Unk	.....
Nikolsky's sign	☐Yes ☐No ☐Unk	.....
Sheet-like detachment	☐Yes ☐No ☐Unk	If yes please specify %BSA§ _ _ _

* See main diagnostic criteria in the appendix page 4

5. Lesions distributions

- Localized ☐
- Widespread ☐

If widespread please specify:

a. Pattern distribution (i.e. simmetrical, upper part of the body, entire body, etc.).....

b. % Body surface area ☐ BSA<10% ☐ BSA 10-30% ☐ BSA>30%

- Oral mucosal involvement ☐Yes ☐No ☐Unk
- Genital mucosal involvement ☐Yes ☐No ☐Unk
- Other mucosal involvement ☐Yes ☐No ☐Unk If yes please specify.....

6. Associated signs

- Fever ☐Yes ☐No ☐Unk
- Malaise ☐Yes ☐No ☐Unk
- Pruritus ☐Yes ☐No ☐Unk
- Skin pain, burning ☐Yes ☐No ☐Unk
- Impaired alimentation ☐Yes ☐No ☐Unk
- Conjunctivitis ☐Yes ☐No ☐Unk
- Photophobia ☐Yes ☐No ☐Unk
- Visual loss ☐Yes ☐No ☐Unk
- Painful micturia ☐Yes ☐No ☐Unk
- Facial edema ☐Yes ☐No ☐Unk
- Periorbital edema ☐Yes ☐No ☐Unk
- Peripheral edema ☐Yes ☐No ☐Unk
- Neurological symptoms ☐Yes ☐No ☐Unk
- Arthralgia/myalgia ☐Yes ☐No ☐Unk
- Lymphoadenopathy ☐Yes ☐No ☐Unk
- Diarrhea ☐Yes ☐No ☐Unk
- Respiratory distress ☐Yes ☐No ☐Unk
- Tachycardia ☐Yes ☐No ☐Unk
- Superinfection ☐Yes ☐No ☐Unk
- Hypotension ☐Yes ☐No ☐Unk

IV. Suspect drug febuxostat

1. **Indication**.....
2. **Daily dose**.....
3. **Therapy dates**.....
4. **Action taken**
   - ✓Withdrawn ☐
   - ✓Dose reduced ☐
   - ✓Dose not changed ☐
   - ✓Unknown ☐
5. **Dechallenge outcome**
   - ✓Improvement ☐
   - ✓Not change ☐
   - ✓Worsening ☐
6. **Reappeared on rechallenge** ☐Yes ☐No ☐Unk
7. **Death**
   - ✓If yes please specify cause.....
   - .....
   - ✓Autopsy report available ☐Yes ☐No ☐Unk
   - ✓Related to the ADR ☐Yes ☐No ☐Unk

7. Internal organ involvement at the time the ADR was detected (if baseline values are available, please report them between brackets)

- **Liver**
  - ✓ Jaundice ☐Yes ☐No ☐Unk

  results (normal range)
  - ✓ ALT.....
  - ✓ AST.....
  - ✓ Alkaline phosphatase.....
  - ✓ Bilirubin total.....
  - ✓ Bilirubin direct.....
  - ✓ Albumin.....
- **Pancreas**
  - ✓Amylase.....
  - ✓Lipase.....

- **Kidney**
  - ✓Biopsy ☐Yes ☐No ☐Unk

  results (normal range)
  - ✓BUN.....
  - ✓Serum creatinine.....
  - ✓CrCl (mL/min).....
  - ✓Albuminuria.....
  - ✓Eosinophiluria.....
- **Other**

8. Blood tests

results count (normal range)

- RBC total .....
- Reticulocytes .....
- WBC total .....
- Neutro .....
- Eos .....
- Linfocytes .....
- Circulating abnormal cells

If yes please specify.....

9. Skin biopsy ☐Yes ☐No ☐Unk

If yes please provide a copy of the pathology report

10. Autoantibodies ☐Yes ☐No ☐Unk

If yes please specify.....

11. Genotyping for HLA-B*5801 ☐Yes ☐No ☐Unk

12. Viral detection

- **Serology**
  - ✓ IgM anti HAV ☐Yes ☐No ☐Unk
  - ✓ IgM anti HBs ☐Yes ☐No ☐Unk
  - ✓ IgM anti HBc ☐Yes ☐No ☐Unk
  - ✓ IgG and IgM antiHHV-6 ☐Yes ☐No ☐Unk
  - ✓ IgG and IgM antiHHV-7 ☐Yes ☐No ☐Unk
  - ✓ IgG and IgM antiHHV-8 ☐Yes ☐No ☐Unk
  - ✓ HBsAg and HBeAg ☐Yes ☐No ☐Unk
- **PCR**
  - ✓ CMV from plasma ☐Yes ☐No ☐Unk
- **Reverse transcriptase-PCR**
  - ✓ HCV from plasma ☐Yes ☐No ☐Unk
  - ✓ HHV-6 from PBMC ☐Yes ☐No ☐Unk
  - ✓ HHV-7 from PBMC ☐Yes ☐No ☐Unk
  - ✓ HHV-8 from PBMC ☐Yes ☐No ☐Unk

V. Comorbidities

- ➢ Decreased renal function ☐Yes ☐No ☐Unk
- ✓ If yes degree renal impairment/CrCl (ml/min)
  ……
- ➢ Hepatic impairment ☐Yes ☐No ☐Unk
  - ✓Degee hepatic impairment……
  - ……
- ➢ Diabetes ☐Yes ☐No ☐Unk
- ➢ HIV infection ☐Yes ☐No ☐Unk
- ➢ Cancer ☐Yes ☐No ☐Unk
- ➢ Radiotherapy ☐Yes ☐No ☐Unk
- ➢ Autoimmune disorders ☐Yes ☐No ☐Unk

If yes please clarify in the narrative

VI. Relevant comedications

		dose	start date dd/mm/YYYY	end date dd/mm/YYYY
✓	ACE-inhibitor ☐Yes ☐No ☐Unk ……			
✓	Sulphonamides ☐Yes ☐No ☐Unk ……			
✓	Anticonvulsants ☐Yes ☐No ☐Unk……			
✓	Nevirapine ☐Yes ☐No ☐Unk ……			
✓	Other (Specify)……			

VII. Case narrative (including investigations and consulting during hospitalization; if available please provide copy of the: hospital admission signed form and discharge signed form, biopsy report, autopsy report, other key elements requested in this form, etc)

VIII. Are there photographic records of the cutaneous lesions?

☐Yes ☐No

If there are, please attach a copy

Appendix: diagnostic criteria clarifications

Drug eruption with eosinophilia and systemic symptoms (DRESS) syndrome, formerly termed drug hypersensitivity syndrome, is a rather distinct severe potentially fatal ADR which is now considered as paralleling the reactivation of human herpes virus 6 (HHV6) (Markel A. 2005). It is characterized by skin eruption with facial and acral oedema, fever, lymphnode enlargement, and single or multiple organ involvement, characteristically occurring in a delayed fashion 3 to 8 weeks after starting treatment with the responsible drug (first exposure) (Wolf R. et al. 2005). Three or more of the above are required as in Kardaun S.H. et al., British Journal of Dermatology 2007

Skin Eruption	Exanthematous (mostly) plus oedema
Onset of symptoms	1-8 weeks
Fever	Present
Internal organ involvement	Present (at least one)
Arthralgia	Absent
Lymphadenopathy	Present (at least two sites)
Eosinophilia	Present ≥700µl
Atypical circulating lymphocytes	Present

Stevens-Johnson syndrome (SJS) is an immune-related reaction complex that typically involves the skin and the mucous membranes. While minor presentations may occur, significant involvement of oral, nasal, eye, vaginal, urethral, gastrointestinal, and lower respiratory tract mucous membranes may develop in the course of the illness. GI and respiratory involvement may progress to necrosis. Stevens-Johnson syndrome is a serious systemic disorder with the potential for severe morbidity and even death.
Toxic epidermal necrolysis (TEN) represent the same disease with a higher level of severity and larger skin detachment.
Please refer to: Clinical features that distinguish SJS, TEN and SJS-TEN OVERLAP (Harr T. et French L.E. 2010)

Clinical entity	SJS	SJS-TEN overlap	TEN
Primary lesions	Dusky red lesions Flat atypical targets	Dusky red lesions Flat atypical targets	Poorly delineated erythematous plaques Epidermal detachment Dusky red lesions Flat atypical targets
Distribution	Isolated lesions Confluence (+) on face and trunk	Isolated lesions Confluence (++) on face and trunk	Isolated lesions (rare) Confluence (+++) on face , trunk and elsewhere
Mucosal involvement	Yes	Yes	Yes
Systemic symptoms	Usually	Always	Always
Detachment (% body surface area)	<10	10-30	>30

Drug exanthema is an immune-related reaction characterized by widespread erithematous macules and/or papules, sometimes confluent, associated with itching that may be severe. The reaction appears after 7-8 days on first exposure to a drug and after 1-2 days after subsequent exposure. It may progress to exfoliative dermatitis (i.e. generalized erythema and skin failure). Drug-related exanthema should be distinguished from infection-related exanthema based on concomitant symptoms like fever and the progression of the skin lesions (Lee HY et al 2010).

Drug-related vasculitis usually involves small vessels and it is characterized on the skin by palpable purpuric lesions sometimes associated with frankly necrotic lesions. More frequently the lesions involve lower limbs. Urticaria-like lesions maybe present as well. Histological documentation is important. It is characterized by a leucocytoclastic pattern (i.e. fragmentation of neutrophils). Arthralgia and abdominal pain may associate, and internal organ involvement is possible (Radic M et al 2012).

Annex 4B: Adverse event follow-up form for serious hepatic reactions

HEPATIC AE FORM

ADVERSE EVENT REPORT
(PLEASE TYPE OR PRINT CLEARLY)

PATIENT INFORMATION

Patient Name/Initials _____ ☐ **Male** ☐ **Female – Pregnant?**

DOB ___/___/___ **Age** _____ **Weight** _____ **Height** _____ **Ethnicity** _____
DD MMM YYYY

FEBUXOSTAT THERAPY INFORMATION
(Please complete with dates/times the product was stopped and restarted if applicable.)

FEBUXOSTAT Indication _____

Start Date _____ Stop Date _____
Dosage _____

Route _____ Frequency _____ Duration of Therapy _____

If dosage changed please provide details:
_____
_____

CONCOMITANT & OTHER SUSPECT MEDICATIONS

#	Drug/Product Name	Indication	Dosage, Route & Frequency	Start Date	Stop Date	Duration
1						
2						
3						
4						

Did any of the above concomitant medications contribute to the adverse event?
☐ Yes, Drug # _____ contributed to Adverse Event # (listed on next page) _____
☐ No

ADVERSE EVENT(S) (AE) INFORMATION:

ADVERSE EVENT		Please describe the event using one of the options below *Please provide autopsy report for fatal events	Event Outcome	Provide your assessment of causality between the event and Febuxostat
	Event onset: ____ End Date ____	☐ fatal* ☐ hospitalization ☐permanent disability ☐ congenital anomaly ☐ None of the above	☐ resolved ☐resolving ☐ recovered w/ sequelae ☐not recovered ☐unknown	☐possible ☐not related ☐unknown
	Event onset: ____ End Date ____	☐ fatal* ☐ hospitalization ☐permanent disability ☐ congenital anomaly ☐ None of the above	☐ resolved ☐resolving ☐ recovered w/ sequelae ☐not recovered ☐unknown	☐possible ☐not related ☐unknown
	Event onset: ____ End Date ____	☐ fatal* ☐ hospitalization ☐permanent disability ☐ congenital anomaly ☐ None of the above	☐ resolved ☐resolving ☐ recovered w/ sequelae ☐not recovered ☐unknown	☐possible ☐not related ☐unknown
	Event onset: ____ End Date ____	☐ fatal* ☐ hospitalization ☐permanent disability ☐ congenital anomaly ☐ None of the above	☐ resolved ☐resolving ☐ recovered w/ sequelae ☐not recovered ☐unknown	☐possible ☐not related ☐unknown

If the Febuxostat was discontinued, specify which event(s) listed above resolved
____

If the Febuxostat was restarted, specify which event(s) listed above re-occurred?
____

Relevant medical history/conditions

☐ Viral hepatitis ☐ Autoimmune disease ☐ Alcohol consumption ☐ Biliary tract disorders ☐ Cardiac disorders right heart failure or hypotension ☐ Recent viral illness ☐ Recent travel	☐ Blood transfusion ☐ Allergies ☐ Recent anaesthetic / surgery ☐ Drug abuse ☐ Toxic exposure ☐ Recent tattoos ☐ Family history of liver disease

2. Further details of the AE:

Include information related to signs, symptoms, treatment and outcome of AE, as appropriate. If no treatment has been given, please specify.

Signs and any symptoms associated with the event (anorexia, fatigue, nausea, vomiting, pruritus, jaundice, fever, abdominal pain, confusion, tremor, coma, etc.):

_____

Treatment: _____

_____

Outcome: _____ **Other medical conditions of importance before onset of the event:** _____

_____

Prior History / History Preceding the Event

_____

Prior history

Alcohol use ☐ no ☐ yes – Amount & Frequency*: _____

* e.g. mL of type of beverage (spirits, beer or wine etc.) per day, week, or month

Liver disease ☐ no ☐ yes – Details: _____

Viral Hepatitis ☐ no ☐ yes – ☐HAV, ☐HBV, ☐HCV, ☐other: _____

Cholelithiasis ☐ no ☐ yes Details: _____

Drug induced hepatotoxicity/toxic exposure ☐ no ☐ yes Details: _____

Prone to bleeding or bruising ☐ no ☐ yes Details: _____

Cardiac disorders (right heart failure) ☐ no ☐ yes Details: _____

Recent hypotension ☐ no ☐ yes Details: _____

Allergies ☐ no ☐ yes Details: _____

HIV ☐ no ☐ yes Details: _____

Family history of liver disease ☐ no ☐ yes Details: _____

Other relevant history ☐ no ☐ yes Specify: _____

History preceding the event

Travel ☐ no ☐ yes Details: _____

Viral illness ☐ no ☐ yes Details: _____

Blood Transfusion: ☐ no ☐ yes Details: _____

Anaesthetic / surgery ☐ no ☐ yes Details: _____

Drug abuse ☐ no ☐ yes Details: _____

Toxic exposure ☐ no ☐ yes Details: _____

Tattoos ☐ no ☐ yes Details: _____

Use of herbal supplements or teas ☐ no ☐ yes Details: _____

Other relevant history ☐ no ☐ yes Specify: _____

Comments: _____

_____

3. Diagnostic & Laboratory Findings: Please indicate if any additional tests have been ordered*.

Laboratory data	Peak (if applicable)		Nadir (if applicable)		Baseline or historical		Normal Range (Specify units)	Recovery (or current)	
	Value	Date	Value	Date	Value	Date		Value	Date
ALT (GPT)									
AST (GOT)									
ALP									
T-Bil									
D-Bil									
GGT									
LDH									
Other									

Anti-Hepatitis A virus IgM ☐ no ☐ yes – date ( ) Details: _____
Anti-nuclear antibodies (ANA) ☐ no ☐ yes – date ( ) Details: _____
Anti-Hepatitis C antibody ☐ no ☐ yes – date ( ) Details: _____
Anti-smooth muscle antibodies (ASMA) ☐ no ☐ yes – date ( ) Details: _____
Hepatitis B Surface Antigen ☐ no ☐ yes – date ( ) Details: _____
Anti-Hepatitis B core antigen IgM ☐ no ☐ yes – date ( ) Details: _____
Anti-Hepatitis B surface antigen ☐ no ☐ yes – date ( ) Details: _____
Additional viral serologies (CMV, EBV) ☐ no ☐ yes – date ( ) Details: _____
Coagulation parameter ☐ no ☐ yes – date ( ) Details: _____
Eosinophil count ☐ no ☐ yes – date ( ) Details: _____
Abdominal Ultrasound ☐ no ☐ yes – date ( ) Details: _____

Computed Tomography (CT) Scan ☐ no ☐ yes – date ( ) Details: _____

Endoscopic Retrograde Cholangio Pancreatography (ERCP) ☐ no ☐ yes – date ( ) Details: _____
Liver Biopsy ☐ no ☐ yes – date ( ) Details: _____

☐ Other _____

** Please attach or summarize available results.*

Thank you for taking time to provide this information.
Your patient's welfare is important to us.

Signature _____ Date _____

Name _____ Title _____
Please Print

Address _____

Phone _____ Fax _____

Date and Time to call for follow-up _____

Annex 6 – Details of proposed additional risk minimisation activities (if applicable) – *Not Applicable*