Swiss Risk Management Plan Summary

Adenuric® (Febuxostat)

Document Version 1.0 (23.01.2023)
Based on EU RMP version 10.0 (signed on 01.12.2021)

Marketing authorization holder: A. Menarini GmbH, Switzerland
Adenuric® film-coated tablets

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Adenuric is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Adenuric in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. A. Menarini GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Adenuric.

SUMMARY OF RISK MANAGEMENT PLAN FOR ADENURIC (FEBUXOSTAT)

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).

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

List of important risks and missing information	
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 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 (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 febuxostat. 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 6^{th} 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.