4.2 Part VI.2 Elements for a Public Summary

4.2.1 Part VI.2.1 Overview of disease epidemiology

All forms of hyperuricemia not controllable by diet, including secondary hyperuricemia of differing origin and in clinical complications of hyperuricemic states, particularly manifest gout, urate nephropathy and for the dissolution and prevention of uric acid stones (Increased levels of uric acid in blood not controllable by diet, and in conditions particularly swelling of joints due to high uric acid and uric acid stones related kidney disease and dissolution and prevention of uric acid stones)

Increased level of uric acid is the main cause of gout, an urate caused kidney disease and uric acid stones. In Italy the number of people with uric acid levels at the upper limit of normal or higher rose from 8.5% in 2005 to 11.9% in 2009. In the USA increased level of uric acid in blood tests is seen in 21% of the population. The mean uric acid level increased from 3.4 mg/dl in the 1920s to 6.25 mg/dl in the 1970s. Normal values for women are 2.5 to 6.0 mg/dl and 3.5 to 7.0 mg/dl for men. The number of patients with gout in Italy increased from 0.7% in 2005 to 0.9% in 2009, with a relation of numbers in male and female of 4:1 [Desideri G, 2014].

The management of recurrent mixed calcium oxalate stones in concurrent hyperuricemia, when fluid, dietary and similar measures have failed in adults (Treatment of recurring kidney stones consisting of calcium and an oxalic acid compound in adults who have elevated blood uric acid levels, when fluid, dietary and similar measures have failed)

National Health and Nutrition Examination Survey from 2007 to 2010 revealed that 8.8% of American adults do suffer from kidney stones. 10.6% of American male adults were affected and 7.1% among American women. Recurrence is a problem with kidney stones, here is a 50% chance of forming a second stone within 7 years if left untreated [Xu H, 2013].

Secondary hyperuricemia of differing origin in children and adolescents (Increased levels of uric acid in blood as a consequence of another disease or use of certain drugs that increases uric acid levels in children and adolescents)

There are several reasons for elevated levels of uric acid in children, different from causes in adults. Usually metabolic syndrome (collection of symptoms that can lead to heart diseases and increased blood sugar levels), a combination of medical issues which increase the risk of heart disease, stroke (life-threatening medical condition which occurs when blood supply to a part of brain is cut off) and Type 2 diabetes (disease with increased blood sugar levels), does not constitute the main source but other diseases, including malignant disease with a high rate of exchange of specialized cells by not specialized cells, e.g. leukemia (a type of blood cancer) or their treatment leading to massive cell death. Additionally genetic disease like Glycogen (the storage form of glucose in cells) storage diseases do lead to increased uric acid levels in blood with need for therapy. Altogether these diseases are rare.

Uric acid nephropathy during treatment of leukemia in children and adolescents (Uric acid stones related kidney disease during treatment of a type of blood cancer in children and adolescents)

During leukemia massive cell destruction happens first due to the disease of leukemia itself and second during therapy e.g. chemotherapy, thus leading to highly increased levels of uric acid in the blood. Annually, around 3000 children in the United States are diagnosed with Acute Lymphoblastic Leukemia (ALL), a type of leukemia which affects white blood cells producing antibodies and participating in other immune reactions. The annual frequency of new ALL cases within the United States is 3.7-4.9 cases per 100,000 children 0-14 years of age with a similar estimated worldwide frequency, although it has been questioned whether the frequency may be less in low-income countries [Cancer Facts & Figures, 2014].

Hereditary enzyme deficiency disorders, Lesch-Nyhan syndrome (partial or total hypoxanthin-guanin phosphoribosyl transferase deficiency) and adenine phosophoribosyl transferase deficiency in children and adolescents (Genetic enzyme deficiency disorders, Lesch-Nyhan syndrome (a disorder caused by deficiency of an enzyme called hypoxanthin-guanin phosphoribosyl transferase resulting in high uric acid levels in the body) and adenine phosophoribosyl transferase deficiency (APRT), an enzyme deficiency which may lead to kidney stones of adenine and salts in children and adolescents)

The reported worldwide presence of Lesch-Nyhan disease is 1 case per 380,000 population. The disease has been reported in most races, with approximately equal rates for most ethnic groups. Few patients live beyond 40 years.

Lesch-Nyhan disease is a genetic disorder usually affecting males only. Only rarely has the disease been reported in females [Torres RJ, 2007].

Adenine phosophoribosyl transferase (APRT) deficiency is estimated to affect 1 in 27,000 people in Japan. The condition is rarer in Europe, where it is thought to affect 1 in 50,000 to 100,000 people. The presence of APRT deficiency outside these populations is unknown [Harambat J, 2012].

4.2.2 Part VI.2.2 Summary of treatment benefits

Allopurinol proved its ability to improve the glomerular filtration rate, a parameter to measure flow of urine through filtration in the kidneys, in several trials. Additionally, levels of certain blood parameters were also improved, e.g. creatinine levels and uric acid levels were lowered. Systolic and diastolic blood pressure (first and last value of the blood pressure) and the amount of protein that is increased in severe kidney damage in the urine was reduced with the administration of allopurinol [Kanji T, 2015].

Allopurinol decreases the formation of new uric acid and reduces the incidence of blockage of urine flow in patients with cancer at risk for tumor lysis syndrome (a group of abnormalities that can occur during the treatment of cancer) [Larson RA, 2016].

4.2.3 Part VI.2.3 Unknowns relating to treatment benefits

There is insufficient proof of safety of allopurinol in human pregnancy. Animal studies have shown reproductive toxicity.

Allopurinol is excreted in human breast milk. However, there are no data concerning the effects of allopurinol or its degradation products on the breast-fed baby.

4.2.4 Part VI.2.4 Summary of safety concerns

Table 4-5 Important identified risks

Risk	What is known	Preventability
Serious hypersensitivity (allergic) reactions and increased risk for certain serious skin reactions in people of Han Chinese or Thai origin	Serious skin rashes (Hypersensitivity syndrome [severe, unexpected allergic reaction to a medicine], Stevens-Johnson syndrome and toxic epidermal necrolysis [life-threatening skin conditions that are usually caused by a reaction to drugs]) have been reported with the use of allopurinol. Skin rash is a common side effect of allopurinol Uncommon signs of allergic reaction include : • flaking skin, boils or sore lips and mouth • very rarely signs may include sudden wheeziness, fluttering or tightness in the chest and collapse. Rare side effects of allopurinol involving more serious hypersensitivity (allergic) reactions are fever, skin rash, joint pain, and abnormalities in blood, bleeding in the lips, eyes, mouth, nose or genitals, ulcers of the mouth, throat, nose, genitals, conjunctivitis (red and swollen eyes), widespread blisters or peeling These serious skin rashes can be more common in patients with chronic renal impairment and in people of Han Chinese or Thai Origin.	If patients develop a rash or any of the mentioned skin symptoms, they should stop taking allopurinol and contact their doctor immediately.

Table 4-6 Important potential risks

Risk	What is known
Use of ampicillin/amoxicillin i.e. medicine used to treat bacterial infections along with allopurinol (Concomitant administration of ampicillin/amoxicillin)	Allergic reactions are more likely to occur among patients receiving ampicillin or amoxicillin concurrently with allopurinol. Patients should inform their doctor before they start to take allopurinol if they are taking ampicillin or amoxicillin.

	Patients should be given antibiotics other than ampicillin/amoxicillin wherever possible while they are being treated with allopurinol.

Table 4-7 Missing information

Risk	What is known
Use during pregnancy and breast feeding (Administration during pregnancy and lactation)	There is insufficient proof of safety of allopurinol in human pregnancy. Animal studies have shown a hazard associated with allopurinol to result in abnormal development of unborn child when used during pregnancy but with conflicting results. Use of allopurinol during pregnancy should only be considered when there is no safer alternative and when the disease itself carries risks for the mother or unborn child. In case of unintentional exposure during the first three months in pregnancy scanning is recommended to confirm normal development of unborn child. Reports indicate that allopurinol and oxipurinol (product that remains after the drug is broken down) are excreted in human breast milk. However, there are no data concerning the effects of allopurinol or its degradation products on the breast-fed baby. If patients are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, they should ask their doctor or pharmacist for advice before taking this medicine.

4.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

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

This medicine has no additional risk minimization measures.

4.2.6 Part VI.2.6 Planned post authorization development plan

None

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

N/A (first submission)