SUMMARY OF THE RISK MANAGEMENT PLAN

FOR

ZURAMPIC® (LESINURAD)

200 mg film coated tablets

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Summary of the risk management plan (RMP) for Zurampic (lesinurad)

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 minimize them.

The RMP summary for Zurampic 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“ approved and published in Switzerland, eg by mentioning risks occurring in populations or indications not included in the Swiss authorisation. Please note that the reference document which is valid and relevant for the effective and safe use of Zurampic in Switzerland is the „Arzneimittelinformation“ (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Grünenthal Pharma AG is fully responsible for the accuracy and correctness of the content of the here published summary RMP for Zurampic.

Overview of disease epidemiology

Zurampic is a medicine used in adults with gout to reduce high levels of uric acid in the blood. Gout results from a build-up of uric acid crystals in and around the joints, especially in the toes, which causes pain and swelling. Lowering the level of uric acid in the blood can prevent the formation of uric acid crystals and reduce uric acid deposits..

The prevalence of gout is increasing and it is now the most common type of inflammatory arthritis. Gout is estimated to occur in 1% to 2% of the adult population; about 9 million people in Europe suffer from attacks of gout. It is 3 to 4 times more common in men than in women and, in general, increases with age.

Summary of Treatment Benefits

Zurampic contains the active ingredient lesinurad which acts in the kidney to help to remove uric acid from the body. Zurampic is used in combination with other gout medicines called ‘xanthine oxidase inhibitors’ such as allopurinol or febuxostat. It is used when a xanthine oxidase inhibitor on its own does not satisfactorily control the uric acid level in the blood.

Zurampic was studied in two main studies involving over 1,200 adults with gout who were previously treated with allopurinol. Their blood level of uric acid was not sufficiently controlled with allopurinol alone and was above 60 mg/litre at the start of the study. These studies compared the effect of adding Zurampic or placebo (a dummy treatment) to patients’ allopurinol treatment. The main measure of

effectiveness was the number of patients whose blood level of uric acid dropped below 60 mg/litre after 6 months of treatment. Adding Zurampic 200 mg once daily was effective in 55% (222 of 405) patients. This compared with 26% (104 of 407) in patients who added placebo.

A third main study involved 324 adults who had at least one measurable tophus (large deposit of uric acid in or around a joint or under the skin) and with high blood levels of uric acid (over 80 mg/litre without gout medicines or above 60 mg/litre despite treatment with allopurinol or febuxostat). Patients were first treated with febuxostat alone for three weeks and then with febuxostat plus either Zurampic or placebo. The main measure of effectiveness was the number of patients whose blood level of uric acid dropped below 50 mg/litre after 6 months of treatment. Overall, Zurampic 200 mg once daily was effective in 57% (60 of 106) patients. This compared with 47% (51 of 109) patients given placebo. Looking just at patients whose blood uric acid level did not fall sufficiently on treatment with febuxostat alone, the level dropped to less than 50 mg/litre in 44% (26 of 59) patients taking Zurampic compared to 24% (12 of 51) patients taking placebo.

Unknowns Relating to Treatment Benefits

In studies with Zurampic given in combination with allopurinol or febuxostat, most patients were Caucasian men aged between 18 and 65 years. Although the studies included fewer non-Caucasians, women, patients aged over 65 years and patients with moderate reduction of renal function (creatinine clearance of 30–45 mL/minute), there is no evidence that Zurampic would not work as well in these individuals.

Summary of Safety Concerns

Important identified risks

Risk	What is known	Preventability
Reduced kidney function (renal impairment)	In studies, more patients taking Zurampic – either alone or with allopurinol or febuxostat – suffered kidney-related side effects compared with those taking placebo (a dummy treatment), allopurinol or febuxostat alone. Kidney-related side effects occurred in about 6% of the patients taking Zurampic 200 mg and about 12% of those taking Zurampic 400 mg	Zurampic must always be taken together with a xanthine oxidase inhibitor. The recommended dose is 200 mg once a day in the morning. Kidney problems are more likely if the patient takes Zurampic on its own. The patient should drink plenty of water during the day; two litres a day is a good amount.

Risk	What is known	Preventability
	compared with around 5% of patients taking placebo. The most frequent of these side effects was raised blood creatinine, a measure of how well the kidneys work (about 4% with Zurampic 200 mg and 8% with Zurampic 400 mg compared with about 2% with placebo). Most patients recovered, many while continuing to take Zurampic.	Kidney function should be measured before starting Zurampic and during treatment.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Major disorders of the heart and circulation (mainly in patients who have had such disorders)—such as heart attack, stroke, heart failure	In studies with Zurampic, serious events such as heart attacks, strokes,and sudden death occurred in a few patients. The effects were slightly more frequent in patients taking Zurampic 200 mg and 400 mg compared with those taking placebo. All the patients who had these effects and were receiving Zurampic 200 mg already had disorders such as heart failure, stroke, or heart attack that were in stable condition for at least 12 months. It has not been determined whether Zurampic caused these events. Zurampic is not recommended in patients with unstable angina, heart failure, uncontrolled high blood pressure or who had a heart attack, stroke or deep vein thrombosis in the last 12 months.

Missing information

Risk	What is known
Use in children	Because gout does not usually occur in children there is no experience with Zurampic in children. Not studies in children are planned.
Use in pregnant or breastfeeding women	The use of Zurampic in pregnant or breastfeeding women has not been studied. Animal studies found that the active ingredient lesinurad appeared in milk.

Risk	What is known
Patients who have liver disease	Patients with liver disease were not allowed to take part in the clinical studies with Zurampic. There is no experience with Zurampic in such patients.
Use in patients aged 75 years or more	There is limited experience with Zurampic in patients aged 75 years or more. No change in dose is needed based on age; however, elderly patients are more likely to have poorer kidney function. Thus, Zurampic should be used with caution in such cases.
Use in patients with moderately reduced kidney function with creatinine clearance 30–45 mL/minute	There is limited experience in patients with moderately reduced kidney function with creatinine clearance 30-45 mL/minute.
Interference with the transfer of bile salts into bile fluid (bile salt export pump inhibition) and use in patients with variant forms of an enzyme that converts Zurampic to its breakdown product M4 (epoxide hydrolase polymorphism)	No information is available on Zurampic's inhibition of bile salt export pump or on epoxide hydrolase polymorphism.

Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The Summary of Product Characteristics and the Package leaflet are part of the medicine's product information. The product information for Zurampic can be found on www.swissmedicinfo.ch.

This medicine has no additional risk minimisation measures.

Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Prospective postmarketing observational cohort study, lesinurad observational post-authorization safety study	A well-defined large observational database study to detect and evaluate the risk of heart and circulation effects with Zurampic, with focus on major effects on the heart (major adverse cardiac events).	Major disorders of the heart and circulation (mainly in patients with a history of cardiovascular events)	Proposed	Final report planned 2nd quarter 2019.
A, randomized, double-blind, multicenter, placebo-controlled study to evaluate the efficacy and safety of lesinurad 200 mg in combination with a xanthine oxidase inhibitor (XOI), compared with an XOI alone, in subjects with gout and creatinine clearance 30 to 45 mL/min who have not achieved target serum uric acid levels on an XOI alone	Study in gout patients to assess Zurampic's effectiveness in patients with creatinine clearance 30–45 mL/minute. This study will also provide additional safety data in these patients.	Patients with creatinine clearance of 30-45 mL/min	Proposed	Date to be provided with final protocol 2nd quarter 2016.

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Laboratory (in vitro) study	To assess the ability of Zurampic and related molecules to inhibit bile salt export pump.	Bile salt export pump inhibition with potential for adverse effects on the liver	Proposed	2nd quarter 2016.
Retrospective analysis of clinical samples, study title not available	A study on Zurampic's breakdown products, including metabolite M4, formed by epoxide hydrolase, over 24 hours.	Potential accumulation of metabolites over 24 hours	Ongoing	1st quarter 2016.

Studies which are a condition of the marketing authorization

Performing the large observational database safety study on Zurampic's effects on heart and circulation is a condition of the marketing authorisation.

Summary of changes to the Risk Management Plan over time

Not applicable.