Summary of the Swiss Risk Management Plan (RMP) for

Ryeqo, film-coated tablets

RMP version number: 1.1

Data Lock Point for RMP: 01 December 2021

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Name of the Marketing Authorization Holder: Gedeon Richter (Schweiz) AG

Disclaimer

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 of Ryeqo 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 Ryeqo in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Gedeon Richter (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ryeqo

Part VI: Summary of the risk management plan

Summary of the risk management plan for Ryeqo (relugolix 40 mg with estradiol 1 mg and norethisterone acetate 0.5 mg)

This is a summary of the risk management plan (RMP) for Ryeqo. The RMP details important risks of Ryeqo, how these risks can be minimised, and how more information will be obtained about Ryeqo's risks and uncertainties (missing information).

Ryeqo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ryeqo should be used.

This summary of the RMP for Ryeqo 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 Ryeqo RMP.

I. The medicine and what it is used for

Ryeqo is authorised for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. It contains relugolix, estradiol, and norethisterone acetate as the active substances and it is given by oral route.

Further information about the evaluation of Ryeqo's benefits can be found in Ryeqo EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/ryeqo

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Ryeqo, together with measures to minimise such risks and the proposed studies for learning more about the risks associated with Ryeqo, 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 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 Ryeqo is not yet available, it is listed under missing information below.

II.A List of important risks and missing information

Important risks of Ryeqo 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 Ryeqo. 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 (e.g. on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	None
Important potential risks	Loss of bone mineral density Embryo-foetal toxicity
Missing information	Long-term use beyond 24 months

II.B Summary of important risks

Important potential risk: Loss of bone mineral density	
Evidence for linking the risk to the medicine	**Clinical**: BMD LS mean percent change was comparable between relugolix+E2/NETA and placebo, with no clinically meaningful difference observed. **Class effect**: ***elagolix,*** there was a duration-dependent decrease in BMD in elagolix+E2/NETA-treated subjects compared to an increase in placebo-treated subjects.
Risk factors and risk groups	Common risk factors for loss of bone mineral density include gender (more common in females), age, body size (smaller women are at a higher risk), ethnicity (risk is higher in Caucasian and Asian women), family history, hormonal changes (including low levels of estrogen), medication use (e.g. glucocorticoids and certain anticonvulsants, and medications affecting hypothalamic-pituitary gonadal axis) and lifestyle (including inactivity, smoking and alcohol use).
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section: 4.2, 4.3, 4.4, 4.5, 5.1 PL section: 2 Recommendation for dual-energy X-ray absorptiometry (DXA,

	measuring bone mineral density using spectral imaging) prior to starting treatment in patients with risk factors for osteoporosis or bone loss and recommendation for DXA after 1 year of treatment are provided in SmPC section 4.2 and 4.4. Contraindication in known osteoporosis is provided in SmPC section 4.3. Warning and precaution regarding interval clinical assessment of benefit: risk in women with a history of low trauma fracture or risk factors for osteoporosis is provided in SmPC section 4.4. Prescription only medicine. **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	None

Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	**Non-clinical**: in pregnant rats and rabbits orally dosed with relugolix during the period of organogenesis, spontaneous abortion and total litter loss were observed in rabbits at exposures 0.25 times the recommended human dose of 40 mg/day based on AUC. No effects on embryo-foetal development were observed in rats. In both rats and rabbits, there were no foetal malformations present at any dose level of relugolix tested in either species, which were associated with relugolix exposures approximately 733- and 1.0-fold higher, respectively, than exposures in women at the recommended human dose of 40 mg/day. **Literature**: clinically, data on a limited number of exposed pregnancies indicate AEs of NETA on the foetus. At doses higher than those now normally used in oral contraceptives and HRT-formulations, masculinisation of female foetuses was observed (Voorhess 1967). The results of most epidemiological studies to date, relevant to inadvertent foetal exposure to combinations of estrogens and progestins, indicate no teratogenic or fetotoxic effect (Raman-Wilms 1995). In rabbits, leuprolide acetate for depot suspension produced a dose-related increase in major foetal abnormalities. Similar studies in rats failed to demonstrate an increase in foetal malformations. There was increased foetal mortality and decreased foetal weights with the two higher doses of leuprolide acetate for depot suspension in rabbits and with the highest dose (0.024 mg/kg) in rats (Lupaneta Pack USPI). **Clinical**: as of 10 September 2021, no pregnant subject was exposed to combination therapy in the uterine fibroid clinical programme. Eleven pregnant subjects were exposed to combination therapy in the endometriosis clinical programme.

	Three pregnant subjects were exposed to relugolix monotherapy in the entire clinical development. Of the 14 pregnancies in subjects who became pregnant during treatment with relugolix (monotherapy or combination therapy), 8 resulted in live birth (7 full term, 1 premature), 1 resulted in spontaneous abortion, 1 resulted in a missed abortion, 1 resulted in elective abortion and 3 were of unknown status/lost to follow-up.
Risk factors and risk groups	Women of childbearing potential
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section: 4.2, 4.3, 4.4, 4.6, 5.3 PL section: 2, 4 Contraindication in pregnancy is provided in SmPC section 4.3 and advice regarding the need to discontinue treatment if pregnancy occurs is provided in SmPC section 4.6. Prescription only medicine **Additional risk minimisation measures**: None

Missing information: Long term use beyond 24 months	
Risk minimisation measures	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	None

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 obligations of relugolix combination therapy.

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

Not applicable