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 (E2), and norethisterone acetate (NETA) 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 12 months

II.B Summary of important risks

Important potential risk: Loss of bone mineral density	
Evidence for linking the risk to the medicine	**Clinical**: bone mineral density (BMD) 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	MVT-601-035

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. 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. 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. **Clinical**: no pregnancies were reported in the relugolix treatment groups in studies MVT-601-3001, MVT-601-3002 or MVT-601-3003. Pregnancy was reported in one placebo-treated patient in each of studies MVT-601-3001 and MVT-601-3002. 29

	pregnancies, were reported in the relugolix clinical development programme.
Risk factors and risk groups	None
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

Important potential risk: Long term use beyond 12 months	
Risk minimisation measures	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None
Additional pharmacovigilance activities	MVT-601-035

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

Study name	**Purpose of the study**
MVT-601-035	**Primary efficacy objective**: to evaluate the long-term effect of relugolix with E2/NETA once daily, compared with placebo on menstrual blood loss at Week 76 (24 weeks after randomisation). **Secondary efficacy objectives**: To evaluate the long-term effect of relugolix with E2/NETA once daily, compared with placebo on menstrual blood loss at 52-weeks after randomisation. To evaluate the effect of retreatment with relugolix with E2/NETA on menstrual blood loss in patients whose menstrual blood volume returned to ≥ 80 mL during the 52-week randomised period.

	To evaluate the long-term effect of relugolix with E2/NETA at 52 weeks after randomisation on the following: ▪ Achievement of amenorrhea ▪ Resumption of menses ▪ Resumption of heavy menstrual bleeding ▪ Haemoglobin ▪ Health-related quality of life as measured by the Short Form (36) ▪ Patient Global Assessment for function and symptoms ▪ Work and productivity impact as measured by the Work Productivity Activity Impairment-Uterine Fibroids ▪ Disease-specific quality of life as measured by the Uterine Fibroid Symptom and Health-Related Quality of Life. **Pharmacodynamic objectives**: to characterise the pharmacodynamic effect of withdrawal from relugolix with E2/NETA. **Safety objectives: t**o evaluate the safety and tolerability of relugolix with E2/NETA once daily for up to an additional 52 weeks, in patients who previously completed (responders and partial responders) the open label extension study. ▪ Adverse events ▪ Changes in BMD