swissmedic

Date: 31 January 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Ryeqo

International non-proprietary name: relugolix, estradiol as estradiol hemihydrate, norethisterone acetate

Pharmaceutical form: film coated tablets

Dosage strength(s): 40 mg / 1 mg / 0.5 mg

Route(s) of administration: oral

Marketing authorisation holder: Gedeon Richter (Schweiz) AG

Marketing authorisation no.: 68495

Decision and decision date: approved on 2 February 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BMD	Bone mineral density
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DXA	Dual x-ray absorptiometry
E2	Estradiol
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
FSH	Follicle stimulating hormone
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP	Good Laboratory Practice
GnRH	Gonadotropin-releasing hormone
Hb	Haemoglobin
HMB	Heavy menstrual bleeding
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LH	Luteinising hormone
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
MBL	Menstrual blood loss
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NETA	Norethisterone acetate
NO(A)EL	No observed (adverse) effect level
NSAID	Non-steroidal anti-inflammatory drug
PASS	Post-authorisation safety study
PBAC	Pictorial blood assessment chart
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
P-gp	P-gycoprotein
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PPI	Proton-pump inhibitor

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PSP	Pediatric study plan (US FDA)
QD	Quantum dots
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
VMS	Vasomotor symptoms

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for relugolix in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Treatment of moderate to severe symptoms associated with uterine fibroids in adult women of reproductive age.

2.2.2 Approved indication

Treatment of fibroid-associated hypermenorrhoea in adult women before the onset of menopause.

In patients with risk factors for osteoporosis or bone loss, a bone density measurement must be carried out using dual X-ray absorptiometry (DXA) before starting treatment with Ryeqo (see "Warnings and precautions").

2.2.3 Requested dosage

Summary of the requested standard dosage:
One tablet of Ryeqo must be taken once daily, at about the same time with or without food. For oral use.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	3 August 2021
Formal control completed	5 August 2021
List of Questions (LoQ)	8 November 2021
Response to LoQ	3 February 2022
Preliminary decision	28 April 2022
Response to preliminary decision	26 June 2022
Labelling corrections	17 August 2022
Response to labelling corrections	14 September 2022
2nd Labelling corrections	14 November 2022
Response to 2nd labelling corrections	6 December 2022
Final decision	2 February 2023
Decision	approval

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3 Medical context

Uterine fibroids, or myomas, are benign, hormone-sensitive, soft tissue tumours of the uterus. In premenopausal women, they represent the most common type of tumour of the reproductive system. Their growth is promoted particularly by oestrogens. But since progesterone is also involved in the pathogenesis of fibroids, the frequently practiced symptomatic treatment with progestogens can also be interpreted as “adding fuel to the fire”.

The prevalence of fibroids is high, with a cumulative rate of up to 70% by the age 50. During the fertile phase of life, the incidence increases with age. Risk factors are black race, nulliparity, positive family history, obesity and hypertension. While their size can increase during pregnancy, fibroids usually regress spontaneously after menopause.

Most fibroids are asymptomatic, and only around a quarter of affected women develop symptoms that require treatment. The most common symptom of fibroids (and also the one that affects patients most severely) is heavy menstrual bleeding (HMB), with an increase in both intensity and duration of menstrual bleeding. HMB can lead to iron deficiency anaemia (and fatigue) and also to absences from work. According to the literature, HMB is the symptom that most commonly leads to a poorer quality of life in women with fibroids. Moreover, fibroid-induced HMB is one of the main reasons for performing a hysterectomy. The second most common symptom is pain, mostly associated with HMB. This pain starts earlier in the cycle and often persists for longer than in "normal" dysmenorrhoea.

Other symptoms can occur as a consequence of pressure on adjacent organs, particularly a feeling of pressure in the (lower) abdomen, increased frequency of urination, low back pain, dyspareunia, constipation and dyschezia. Fibroids can also adversely affect fertility and lead to pregnancy complications.

The current gold standard in the diagnosis of fibroids is transvaginal ultrasound, in which the fibroid size (in cm^3) on the one hand, and the overall size of the uterus on the other, are determined, the latter being stated in comparison to the size of the uterus in a particular week of pregnancy.

Surgical treatment, with its associated risks, used to represent the standard treatment for uterine fibroids. The most common procedure was hysterectomy; conversely, fibroids constitute one of the most common reasons for a hysterectomy. The alternative option is a (minimally-invasive) fibroid enucleation, particularly if the patient still wishes to get pregnant. But since recurrences are not uncommon after this procedure, further measures may be needed at a later date. A further therapeutic alternative is uterine artery embolisation. In cases where HMB is the predominant symptom, endometrial ablation can also be considered.

In recent years, gynaecological endocrinologists are increasingly advocating medical treatment for fibroid-associated symptoms, not least because of the not inconsiderable morbidity and mortality associated with a hysterectomy or fibroid enucleation. However, the drug-based therapeutic options to date have been limited, of restricted efficacy and/or their long-term use is limited by safety concerns. First-line medical treatment usually consists of the off-label use of progestogens or hormonal contraceptives. Non-hormonal alternatives are tranexamic acid, danazol (no longer authorised in Switzerland since 2013), NSAIDs or aromatase inhibitors. However, efficacy of these drugs has never been confirmed in adequate clinical studies.

The most effective treatment for fibroid-associated HMB are GnRH analogues which, at the same time, also reduce fibroid size. All GnRH analogues must be injected subcutaneously (or intramuscularly), and depot preparations administered at three-monthly intervals are available. In other countries, they are widely authorised for this indication. In Switzerland, however, only goserelin (Zoladex®) is authorised for the treatment of fibroids, and only "for preoperative pretreatment of anaemic patients with uterine fibroids, in conjunction with iron therapy".

GnRH analogues act by suppressing oestrogen to castration levels. They primarily reduce the heavy bleeding caused by fibroids and thereby – together with iron therapy – also have a positive effect on anaemia. They also reduce the volume of the fibroids as well as the total uterine volume; it is unknown, however, if the reduction of volume is of any clinical significance. However, the use of GnRH analogues is limited by their safety profile, i.e. particularly the induction of menopause symptoms (particularly vasomotor symptoms, VMS), but also depressive episodes. The most serious risk, however, is a reduction in bone mineral density (BMD), which limits their duration of use to 3-6

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months in all non-malignant indications. In order to extend this treatment period, they are sometimes used together with a so-called “add-back therapy”, i.e. the concurrent administration of an oestrogen-progestogen combination or tibolone.

A further drawback of GnRH analogues is the occurrence of a flare effect at the start of treatment, caused by an initial rise in the secretion of FSH and LH, i.e. the intensity of bleeding can even increase temporarily. Consequently, although GnRH analogues have proved to be effective in the treatment of fibroids, their use in everyday clinical practice is limited.

Not least because of the limited treatment period, the main aim of such treatment was to control symptoms until a corresponding surgical procedure and e.g. reduce the surgical risk by normalising the haemoglobin level. A further objective was to reduce fibroid volume beforehand and possibly enable a less invasive surgical procedure.

Moreover, from 2013-2021 the progesterone receptor modulator ulipristal acetate was authorised for symptomatic treatment of fibroids. Although this drug proved to be very effective in the treatment of fibroid-associated HMB, it had to be withdrawn from the market following isolated cases of severe liver damage.

An alternative option is now available in the form of the new, oral, non-peptide GnRH antagonists, which can also be used as long-term therapy. These active substances are combined with an add-back therapy consisting of 1 mg estradiol (E2) and 0.5 mg norethisterone acetate (NETA) in order to achieve oestrogen levels (ideally between 20 and 60 pg/ml) ensuring adequate efficacy while at the same time mitigating the adverse effects, particularly BMD loss and VMS.

Ryeqo contains the oral GnRH antagonist relugolix in a fixed combination with the aforementioned add-back therapy with E2 and NETA. Thanks to the relatively long half-life of relugolix, the preparation only needs to be taken once daily.

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4 Quality aspects

4.1 Drug substance

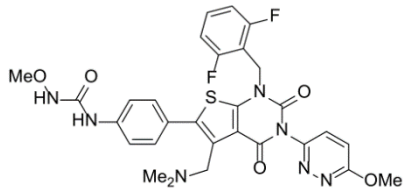
Drug Substance Relugolix
INN: Relugolix

Chemical name: N-(4-{1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-6-yl}phenyl)-N'-methoxyurea

Molecular formula: C29H27F2N7O5S

Molecular mass: 623.63 g/mol

Molecular structure:



Physico-chemical properties:

The active substance is a white to off-white to slightly yellow solid; the solubility of relugolix decreases with an increase of pH and it is considered a BCS (Biopharmaceutical Classification System) Class IV compound.

Synthesis:

The drug substance is manufactured by a multiple step chemical synthesis with final isolation by crystallisation. It is manufactured as the thermodynamically most stable form under the conditions of manufacture and storage.

Specification:

The drug substance specification includes tests for appearance, identification, particle size, assay, impurities, residue on ignition, residual solvents and water content.

Stability:

Appropriate stability data have been presented and justify the established re-test period.

4.2 Drug product

Description and composition:

Ryeqo is presented as a fixed-dose combination product in the form of immediate-release film-coated tablets. Each tablet contains 40 mg relugolix, 1 mg estradiol and 0.5 mg norethisterone acetate. Relugolix/estradiol/ norethisterone acetate (40/1/0.5 mg) is a light yellow to yellow, round film-coated tablet.

Pharmaceutical development:

The composition of the drug product is adequately described, qualitatively and quantitatively. Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including establishment of the Quality Target Product Profile (QTPP), the Critical Quality Attributes (CQA) and the Critical Process Parameters (CPP).

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Manufacture:

The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included. Adequate validation data pertaining to the commercial manufacturing process are available.

Specification:

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance, identification, assay, related substances, dissolution, content uniformity, water content, microbial examination, residual solvents, NDMA (N-nitrosodimethylamine) content. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.

Container Closure System:

The drug product is packaged in high-density polyethylene (HDPE) bottles with desiccant and closed with an induction-sealed child-resistant cap.

Stability:

Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. The data show good stability of the finished product and allow for a distinct assignment of the shelf life.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substances and drug product has been demonstrated.

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5 Nonclinical aspects

Regarding the marketing authorisation application of Ryeqo (relugolix, estradiol and norethisterone acetate), the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the EMA assessment report (Procedure No. EMEA/H/C/005267/0000, dated 20 May 2021) provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Ryeqo in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised and all nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals and in the RMP.

There is no safety concern regarding impurities and excipients.

Based on the preliminary ERAs for the active substances, a risk for the environment cannot be excluded. Several studies are planned or ongoing, and the respective reports and the final ERAs will be submitted as a post-authorisation measure.

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6 Clinical and clinical pharmacology aspects

6.1 Clinical pharmacology

ADME

Absorption and Biopharmaceutical Development

In the pivotal Phase 3 studies, a single-agent relugolix tablet formulation was administered in combination with commercially available combination products containing 1 mg E2 and 0.5 mg NETA. The commercial formulation is a fixed-dose combination (FDC) tablet containing 40 mg relugolix, 1 mg E2 and 0.5 mg NETA.

The commercial FDC formulation and the relugolix tablet formulation plus Activella® (1 mg E2 plus 0.5 mg NETA), as administered in the Phase 3 studies, were bioequivalent after fasted administration.

The absolute bioavailability of relugolix was 11.6%.

The solubility of relugolix increases with decreasing pH. Therefore, a food effect was observed as expected. The relugolix exposures were generally lower after fed administration. After administration of the commercial formulation with a high-fat high-calorie meal, relugolix Cmax and AUC were reduced by 55% and 38%, respectively. A similar effect is expected for the co-administration of relugolix and PPIs.

Dose Proportionality

There was a slightly more than dose proportional increase of relugolix exposures after administration of single doses in the range of 1 mg to 360 mg and after administration of multiple QD doses in the range of 10 mg to 180 mg. The relugolix half-life was independent of the administered dose, indicating that the more than dose proportional increase of relugolix exposures was due to absorption processes, most likely saturation of P-gp.

Pharmacokinetics after multiple Dosing

There was an about 2-fold accumulation after QD dosing. The linearity index was between 1.3 and 1.6, indicating some time dependency of relugolix PK, most likely also due to P-gp saturation. The accumulation was similar over the investigated multiple dose range of 10 mg to 180 mg.

Relugolix reached its steady state after 12 to 13 days of QD dosing.

Distribution

The *in vitro* relugolix plasma protein binding was about 70% and independent of the relugolix concentration (0.05 – 5 µg/mL). Relugolix had no effect on the plasma protein binding of warfarin, ibuprofen, digoxin or propranolol *in vitro*. Because of the relatively low relugolix plasma protein binding, no measurements in subjects with impaired hepatic or renal function were done.

The *ex vivo* whole blood to plasma ratio of total radioactivity was 0.78. The relugolix apparent volume of distribution was 18,878.7 L.

Metabolism - In vitro Data

Relugolix was mainly metabolised by CYP3A4 (formation of metabolite A, O-desmethyl relugolix), followed by CYP2C8 (formation of metabolite B, OH- relugolix) and CYP2C19.

Quantitatively, 45% of the relugolix metabolism was mediated by CYP3A4, CYP2C8, CYP2C19 and by other CYPs or pathways not evaluated. Metabolite C was formed by gut microbiota by N-demethoxylation.

Metabolism & Elimination - Clinical Data

After administration of a ^{14}C-labelled oral dose, unchanged relugolix accounted for 41.5% to 68.2% of the total radioactivity in plasma. Metabolites A and B together accounted for 2.2% to 3.8%, and metabolite C accounted for 0.8% to 4.5% of the total radioactivity in plasma. About 30% to 40% of the total radioactivity in plasma was not identified. Cmax, AUC168 and AUCinf of the total radioactivity in plasma were 1.26-, 2.75- and 4.63-fold higher compared to unchanged relugolix. The pharmacological activity of the metabolites A, B and C has not been determined *in vitro*. However,

considering their low contribution to the total radioactivity in plasma, their impact on the overall activity of relugolix appears negligible.

The terminal half-life of relugolix was about 60 h. However, considering the observed degree of accumulation after QD dosing, the pharmacokinetically relevant half-life is about 30 h. After administration of a ^{14}C-labelled oral dose, the half-life of the total radioactivity in plasma was 226.2 h due to the presence of radioactivity unaccounted for.

The excretion of unchanged relugolix in urine was < 4% of the administered dose after both single and multiple dosing.

After administration of a ^{14}C-labelled oral dose, 4.4% and 82.7% of the administered radioactivity were excreted in urine and faeces, respectively. Similar to plasma, a large proportion of the radioactivity excreted in urine (47.4%) and faeces (44.0%) was not identified. Relugolix was the main compound excreted in urine, accounting for 52.6% of the excreted radioactivity (2.2% of the administered dose). In faeces, metabolite C was the main compound excreted (50.6% of the radioactivity, 40.6% of the dose), followed by relugolix (5.1% of the radioactivity, 4.2% of the dose).

Special Populations

The impact of mild or moderate hepatic impairment on the relugolix exposures was small. In subjects with mild hepatic impairment, the relugolix AUC0-∞ and Cmax were decreased by 31% and 24%, respectively, compared with healthy controls. In subjects with moderate hepatic impairment, the relugolix AUC0-∞ was decreased by 5% whereas the Cmax was increased by 17% compared with healthy controls. The relugolix half-life was also similar between subjects with mild or moderate hepatic impairment and subjects with normal hepatic function. There was no statistically significant correlation between hepatic function parameters and relugolix exposures. No dose adjustments are required in patients with mild or moderate hepatic impairment.

Relugolix Cmax and AUCinf were 1.47-fold and 1.45-fold higher in subjects with moderate renal impairment compared to healthy controls, respectively. Relugolix Cmax and AUCinf were 1.10-fold and 1.49-fold higher in subjects with severe renal impairment compared to healthy controls, respectively. Renal function had no effect on relugolix half-life. There was no statistically significant correlation between renal function and relugolix exposures. No dose adjustments are required in patients with renal impairment of any degree.

The possible impact of body weight, age, race and (mild) renal impairment on relugolix PK was investigated in a pop PK analysis including one Phase 1 study, two Phase 2 studies and two pivotal Phase 3 studies. The selection of the studies to be included in the pop PK analysis was based on similar conditions of relugolix administration with regard to food, i.e. fasted administration.

The dataset included 952 female patients aged between 19 and 53 years. The overall weight range was 37.7 – 144.4 kg. About half of the patients (48.9%) were of Asian origin and most of them received 40 mg relugolix QD.

The final pop PK model was a two-compartment model with lag time, first order absorption and first order elimination. Dose as a covariate of the bioavailability accounted for the more than dose proportional increase in relugolix exposures. Of the covariates investigated, the final model included Asian origin as a covariate of the bioavailability, as well as Caucasian origin and body weight as covariates of CL/F.

The dataset included 103 (15.8%) patients with mild renal impairment and one patient with moderate renal impairment. Renal function did not reach statistical significance in the covariate analysis. In agreement with the results of the dedicated renal impairment studies, a graphical comparison of the individual post-hoc estimates of relugolix CL/F showed similar data for subjects with normal renal function and mild renal impairment.

Regarding the impact of each covariate separately, dose as a covariate of the bioavailability had the largest effect on relugolix AUCss or Ctrough,ss. The effects of ethnic origin and body weight on relugolix AUCss and Ctrough,ss were ≤ ± 20.2% and ≤± 33.9%, respectively.

Relugolix Ctrough,ss, which was used as an exposure measure in the ER analyses, was 33.9% higher in Black patients, 11.8% lower in Asian patients, 21% lower in a patient with a body weight of 107 kg and 14.5% higher in a patient with a body weight of 45.8 kg compared to the reference. The final model described the data reasonably well.

No dose adjustments are required for the covariates investigated.

Interactions

EFFECT OF OTHER DRUGS ON RELUGOLIX

In vitro Data

As mentioned above, relugolix was mainly metabolised by CYP3A4 and, to a lesser extent, by CYP2C8. Relugolix was a substrate for P-gp, but not for OATP1B1, OATP1B3 or BCRP.

Clinical Data

Perpetrator	**GMR (90% CI)**
Erythromycin (P-gp inhibitor, moderate CYP3A4 inhibitor)	REL Cmax: 617.95 (475.14, 803.69) REL AUCinf: 624.66 (531.04, 734.79)
Fluconazole (moderate CYP3A4 inhibitor, does not inhibit P-gp)	REL Cmax: 143.95 (113.01, 183.35) REL AUCinf: 118.85 (106.18, 133.03)
Atorvastatin (used as weak CYP3A4 inhibitor)	REL Cmax: 77.81 (51.34, 117.93) REL AUCinf: 94.76 (76.57, 117.27)
Voriconazole (strong CYP3A4 inhibitor, does not inhibit P-gp)	40 mg REL REL Cmax: 120.74 (91.93, 158.57) REL AUCinf: 151.15 (124.58, 183.39)
Voriconazole (strong CYP3A4 inhibitor, does not inhibit P-gp)	120 mg REL REL Cmax: 81.85 (42.61, 157.24) REL AUCinf: 111.81, (68.06, 183.71)
Rifampicin (strong CYP3A4 and P-gp inducer)	REL Cmax: 77.2 (55.98, 106.46) REL AUCinf: 45.4 (33.45, 61.59)
E2/NETA	Week 3 REL Cmax: 100 (71, 140) REL AUC0-24: 102 (78, 133) Week 6: REL Cmax: 107 (76, 151) REL AUC0-24: 110 (84, 1.44)

None of the perpetrators listed above had a major impact on the relugolix half-life, indicating that they primarily interfered with the absorption of relugolix, mainly with its transport by P-gp.

EFFECT OF RELUGOLIX ON OTHER DRUGS

In vitro Data

Signals for a potential *in vivo* interaction at therapeutic relugolix exposures were observed for the induction of CYP2B6 and 3A4 and the inhibition of intestinal CYP3A4. An induction or inhibition of CYP1A2, as well as the inhibition of CYP2B6, 2C8, 2C9, 2C19 or 2D6 at therapeutic relugolix exposures appeared unlikely based on the static DDI risk assessment.

With regard to transporters, the inhibition of intestinal BCRP could not be excluded at therapeutic relugolix exposures. The inhibition of P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K or BSEP at therapeutic relugolix exposures appeared unlikely based on the static DDI risk assessment.

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Clinical Data

Victim	GMR (90% CI)
E2/NET	Unconjugated E2 Cmax: 95.01 (86.19, 104.72) AUCinf: 81.48 (73.00, 90.95)
	Total E1 Cmax: 94.42 (84.60, 105.38) AUCinf: 87.49 (83.54, 91.63)
	Unconjugated E1 Cmax: 95.14 (90.69, 99.80) AUCinf: 92.10 (86.01, 98.62)
	Estrone Sulfate Cmax: 82.92 (76.51, 89.86) AUCinf: 84.36 (80.10, 88.84)
	NET Cmax: 112.31(101.78, 123.92) AUCinf: 102.60 (97.57, 107.89)
Midazolam (CYP3A4 substrate)	Midazolam + 40 mg REL Cmax: 74.32 (60.62, 91.12) AUCinf: 82.34 (69.88, 97.02)
	1-OH Midazolam + 40 mg REL Cmax: 83.79 (67.10, 104.64) AUCinf: 84.27 (73.92,.96.07)
	Midazolam + 120 mg REL Cmax: 85.76 (72.09, 102.04) AUCinf: 77.96 (71.25, 85.30)
	1-OH Midazolam + 120 mg REL Cmax: 90.16 (70.34, 115.57) AUCinf: 72.77 (55.60, 95.23)
Rosuvastatin (BCRP and OATP substrate)	Rosuvastatin + 40 mg REL Cmax: 76.53 (65.24, 89.77) AUCinf: 87.21 (74.23, 102.47)
	Rosuvastatin + 120 mg REL Cmax: 66.45 (58.45,.75.54) AUCinf: 72.94 (62.76, 84.)77
Cocktail study with 20 mg REL QD	
Caffeine (CYP1A2 substrate)	Cmax: 91.5 (86.7, 96.5) AUCinf: 96.5 (89.1, 104.6)
1,7-paraxanthine	Cmax: 96.9 (92.7, 101.3) AUCinf: 99.4 (93.6, 105.6)
Dextromethorphan (CYP2D6 substrate)	Cmax: 80.8 (69.4, 94.1) AUCinf: 80.8 (66.5, 98.2)
Dextrorphan	Cmax: 107.8 (100.8, 115.3) AUCinf: 108.7 (104.1, 113.5)
Midazolam (CYP3A4 substrate)	Cmax: 106.5 (91.2, 124.4) AUCinf: 110.8 (99.6, 123.2)
1-OH-Midazolam	Cmax: 96.4 (80.6, 115.4) AUCinf: 96.1 (86.9, 106.2)
Tolbutamide (CYP2C9 substrate)	Cmax: 101.8 (97.9, 105.8) AUCinf: 98.9 (93.3, 104.9)
4-hydroxytolbutamide	Cmax: 101.3 (95.0, 108.0)

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	AUCinf: 98.0 (94.5, 101.5)
Carboxytolbutamide	Cmax: 99.3 (94.0, 105.0) AUCinf: 97.5 (94.9, 100.2)

The interaction potential of relugolix as a perpetrator appeared to be low. The *in vitro* signals of CYP3A4 inhibition and induction translated into a mild induction *in vivo*.

The inhibition of intestinal BCRP expected from the *in vitro* data was not confirmed *in vivo*: the rosuvastatin exposures were slightly reduced in the presence of relugolix, supporting the hypothesis of relugolix as a mild inducer.

Pharmacodynamics

Mechanism of Action and primary Pharmacology

Relugolix is an oral, non-peptide GnRH antagonist that competitively binds to the GnRH receptor on gonadotropic neurons, thereby preventing activation of the receptor by endogenous GnRH. This, in turn, reduces the release of FSH and LH from the anterior lobe of the pituitary, leading to lower peripheral FSH and LH levels and the inhibition of follicular growth and maturation. This decreased follicular maturation reduces the production and secretion of oestrogens. At the same time, the physiological preovulatory LH surge is suppressed with a consequent suppression of ovulation. This in turn means that a corpus luteum is not formed. In physiological cycles, the corpus luteum is responsible for the production and secretion of progesterone into the systemic circulation. As a result, this process causes both oestrogen and progesterone levels to be reduced via the blockade of GnRH receptors, leading to reduced proliferative effects on the fibroids.

Secondary Pharmacology (Safety)

After single dose administration of 60 mg or 360 mg, relugolix had no effect on QTcF or heart rate. There was no relationship between relugolix plasma concentrations and QTcF. Assay sensitivity was demonstrated, as moxiflocaxin showed the expected effect.

The relugolix Cmax achieved after the single 360 mg dose was 13.8-fold higher than Cmax,ss after 40 mg QD. As no major relugolix metabolites were detected, the administration of single doses in the tQT study was acceptable in principle. The only uncertainty was the relatively high amount of unidentified radioactivity in plasma, i.e. other unaccounted metabolites might be present and could accumulate if repeated relugolix doses were given

Relationship between Plasma Concentration and Effect

EFFICACY

Because of the different endpoints, the Phase 2 and Phase 3 data were analysed separately.

Phase 2 Data

The efficacy endpoint in the Phase 2 study TAK-385-CCT-001 was the pictorial blood assessment chart (PBAC) percent change from baseline at weeks 6 to 12.

The dataset included 212 patients, evenly randomised to placebo or relugolix 10 mg, 20 mg and 40 mg monotherapy. The observed data indicated that 40 mg relugolix alone after fasted administration was at the plateau of the exposure response (ER) relationship.

An Emax model with Hill coefficient described the relationship between PBAC and relugolix Ctrough,ss reasonably well.

The model was used to predict the effect of reduced relugolix Ctrough,ss levels on efficacy, with the intention to evaluate the impact of fed administration, as relugolix was administered fasted only in the Phase 2 (and 3) studies. The model predicted a PBAC change from baseline of -67% for a 50% reduction of relugolix Ctrough,ss compared to a PBAC change from baseline of -90% for relugolix Ctrough,ss after fasted administration of 40 mg QD.

The relationship between relugolix Ctrough,ss and E2 serum concentrations was also well described by an Emax model with Hill coefficient. A 50% reduction in relugolix Ctrough,ss resulted in 2.25-fold higher E2 levels.

Phase 3 Data

The efficacy endpoint in the Phase 3 studies was the primary response, defined as menstrual blood loss (MBL) <80 mL and at least 50% reduction from baseline during the evaluation period, the 35 days prior to last dose.

The dataset included 476 patients. A descriptive analysis of the data indicated that the responder rate was higher after relugolix compared to placebo, but there was no pronounced exposure response.

The relationship between the endpoint and relugolix Ctrough,ss was reasonably well described by an Emax logistic regression model. As for the Phase 2 data, the impact of reduced relugolix concentrations on efficacy was evaluated. A 50% reduction of Ctrough,ss was associated with a responder rate of 73% compared to 79% at the relugolix Ctrough,ss after 40 mg QD after fasted administration.

Covariates planned to be investigated as additional predictors of the effect were age, race, baseline MBL and the average E2 serum concentration at weeks 8-12. A graphical analysis of the data showed slightly higher response rates in older women, women with lower baseline MBL and women with lower E2 levels. Body weight had no impact on the response rate. In the formal covariate analysis, only race and the average E2 serum concentration at weeks 8-12 had a statistically significant effect on the response rate. The estimated MBL responder rate was slightly lower in non-White patients compared to White patients. It appeared to be higher in patients with lower average E2 concentrations during Week 8 to Week 12.

SAFETY

Exposure-response analyses for safety endpoints were not provided.

6.2 Dose finding and dose recommendation

In Phase I studies (see above), a dose of 40 mg relugolix produced near maximum suppression of ovarian activity and a corresponding subsequent reduction in the ovarian production of E2 and progesterone. Moreover, an initial Phase II study with relugolix monotherapy compared doses of 10, 20 and 40 mg with placebo. This study showed dose-dependent efficacy on HMB, but also a dose-dependent reduction of BMD. Since the two lower doses failed to achieve an adequate reduction of bleeding, the 40 mg dose was selected for further development, and this was the only dose investigated in Phase III.

In order to minimise the risks, particularly of BMD loss, this dose was combined with E2 at the standard dose of 1 mg normally used in menopausal hormone replacement therapy (HRT). Since this kind of administration of exogenous oestrogen is associated, in turn, with a risk for endometrial hyperplasia, the progestin NETA was added, likewise at the dose usually authorised for HRT preparations, for which adequate protection of the endometrium has been shown.

6.3 Efficacy

To confirm the efficacy of the combination, two pivotal studies, each lasting 24 weeks, were submitted (LIBERTY 1 and 2). The title of these studies was as follows: "Efficacy & Safety Study of Relugolix in Women With Heavy Menstrual Bleeding Associated With Uterine Fibroids". Studies with relugolix monotherapy from the early development in Japan are also available.

Both studies had a comparable design, enabling pooling of data. They were followed by a joint open-label 28-week extension study in which all patients were treated with Ryeqo. This in turn was followed by a further 52-week withdrawal study. Consequently, for those patients who were randomly assigned to continued active treatment, and depending on the treatment group in the pivotal studies, data are available for a treatment period of 80-104 weeks with Ryeqo. This study had not yet been completed when the application was first submitted; its final study report was submitted together with the

answers to the List of Questions. Both pivotal studies were conducted predominantly in the USA. Centres in Europa, South America and South Africa were also involved, but European centres only accounted for 16% of the study population, whereas around three quarters of the patients were recruited in the USA.

Study medication was always taken in the morning in the fasted state, at least one hour before breakfast.

Patients had to use non-hormonal methods of contraception, and a monthly pregnancy test was carried out.

When assessing the data, it should be noted that, as a result of the effect of relugolix on the bleeding pattern, unblinding presumably occurred in some cases. Thus, bleeding was strongly suppressed in the active treatment groups, and amenorrhoea occurred in a relevant proportion of patients. By contrast, the normal cyclical bleeding pattern was maintained in the placebo group.

Both of the pivotal studies were 1:1:1 randomised, double-blind, placebo-controlled studies in which two active arms were compared with placebo: In one group, the proposed combination was administered from the start, i.e. at the end of the double-blind studies, these patients had been exposed for 24 weeks. In the other group, patients received relugolix monotherapy for the first 12 weeks, and only after this were they switched to the combination ("delayed" group). This group was designed to show, on the one hand, that efficacy of relugolix is not adversely affected to any relevant extent by its combination with the add-back treatment. The other aim with this group was to show that oestrogen deficiency symptoms, i.e. particularly BMD loss (but also VMS), can be effectively attenuated by addition of the add-back therapy. In the absence of an authorised comparator, an active control arm was not included.

Premenopausal patients aged from 18-50 years with documented regular cycles during the three months before the start of treatment (i.e. during the screening phase) and menstrual periods not exceeding 14 days were enrolled in the pivotal studies. HMB must have been confirmed during the screening phase. This was defined as a menstrual blood loss (MBL) of ≥160 ml in a single cycle or of ≥80 ml per cycle in two consecutive cycles. The presence of fibroids as a likely cause of the HMB had to be confirmed by centrally analysed transvaginal ultrasound scans.

The menstrual blood loss in both pivotal studies, and also during the open-label extension and withdrawal studies, was always determined by the alkaline haematin method, the most objective, but also the most elaborate method for measuring MBL. This method can be considered as validated. A blood loss of ≥80 ml is defined as heavy menstrual bleeding. For this purpose, the subjects were given hygiene products (sanitary towels and tampons), which had to be collected and returned. The blood contained in these products was then determined by the specified method.

All patients with contraindications for oestrogen therapy were excluded. Other relevant exclusion criteria were any sonographic abnormalities, apart from the fibroids, that could be contributing to any HMB (e.g. cervical polyps), as well as fast-growing fibroids (according to a subjective assessment by the investigator). Patients must also not have undergone any surgical procedure for the fibroids within the 6 months preceding the study inclusion. Further exclusion criteria were a GFR <60 ml/min/m^2, untreated thyroid function disorders and major depression not stably controlled.

Additional exclusion criteria were specified due to the risk of BMD loss. These included:

- a baseline Z-score <-2 for the lumbar spine, hip or femoral neck.
- hypocalcaemia or hypophosphataemia.
- any disorders constituting a risk factors for the bone (including a history of such disorders). In addition to pre-existing osteoporosis and other metabolic bone diseases, these include e.g. hyperparathyroidism, hyperthyroidism or anorexia nervosa.
- any previous pharmacological treatment of osteoporosis (e.g. bisphosphonates), with the exception of vitamin D therapy.
- anticipated need for systemic steroid treatment during the study, with an oral prednisolone-equivalent dose of more than 5 mg every other day.

In addition, patients with a Z-score <-2 or a BMD loss from baseline of ≥7% at the end of the preceding study were not eligible for inclusion in the open-label extension or withdrawal study.

Use of analgesics (preferably ibuprofen) was permitted if required. However, the permitted pain treatment (in the sense of rescue therapy) was not sufficiently standardised.

The primary endpoint, both in the pivotal studies and during the open-label extension phase, was the proportion of patients who experienced a blood loss of <80 ml and a reduction in MBL from baseline of ≥50% during the last 35 days of the treatment phase (i.e. during the last cycle on treatment) (termed the response rate). Since this therefore required HMB to fall below the stated limit (and not just a clinically relevant reduction compared to baseline), this definition of a response can be considered as relatively strict. The corresponding requirement in the withdrawal study was only the maintenance of a blood loss of <80 ml during the study (i.e. disregarding the baseline value on admission to the pivotal study).

The pivotal study also defined seven "key secondary endpoints with alpha-protection", which also had to be subjected to confirmatory testing. In order to adjust for multiple testing, for the first four of these endpoints, a hierarchical approach was employed. By contrast, the final three endpoints were adjusted using the Hochberg step-up procedure. These main secondary endpoints were (in the stated order): Proportion of patients presenting with amenorrhoea over the last 35 days of treatment; percentage change from baseline in MBL volume; changes in Bleeding and Pelvic Discomfort (BPD) scores of the UFS-Qol (a sub-scale developed specifically for these studies); proportion of patients with a baseline Hb <10.5 g/dl who achieved an increase of ≥2 g/dl by week 24; proportion of patients with a maximum baseline pain score ≥4 ("pain evaluable population") on a numerical rating scale (NRS) from 0-10, whose score had dropped to ≤1 during the last 35 days of the treatment phase; percentage change from baseline in uterine fibroid volume and uterine volume. Numerous other secondary endpoints were defined (e.g. time to the achievement of responder status), but these were not subjected to confirmatory testing.

Bleeding and pain were documented in an electronic patient diary.

In the withdrawal study, three key secondary endpoints were defined and tested hierarchically.

The comparison between the combination and placebo in the pivotal studies was subjected to confirmatory testing. Descriptive analysis was performed for the comparison between the delayed group and placebo, as well as the comparison of both active treatment groups. The primary analysis in these studies was performed for the so-called mITT population, which was defined as all randomised patients who had received at least one dose of the study medication.

A total of n=388 patients were randomised in the LIBERTY 1 study, compared to n=382 patients in the LIBERTY 2 study. The difference between the number of screened (2279 and 2899, respectively) and the number of randomised patients was substantial, since a relevant percentage of the women (>80% in each case) did not satisfy the inclusion criteria. This suggests that the blood loss is often overestimated subjectively.

On the other hand, the drop-out rate during the studies themselves, at around 20%, was relatively low (particularly for a predominantly American population). In study 3001, AEs were the reason for study discontinuation in 7.7% of cases, compared to 6.0% of cases in study 3002. In both studies, this reason for discontinuation was much more common in the delayed group than in the other two groups (13.6% and 11.8%, respectively) and was not more common for Ryeqo than for placebo.

A good 60% of the patients in both studies joined the open-label extension phase, whereas the withdrawal study contained just under 30% of the original study population.

Demographic and baseline characteristics only showed small differences between treatment groups. One striking finding (but comparable across all groups) was a high average BMI (31-32 kg/m^2), which is probably attributable to the dominance of American patients. Overall, a good 10% of the patients had a BMI ≥40 kg/m^2. Likewise as a result of the location of the study centres, almost half of the enrolled patients were black. In both studies, the proportion of white patients receiving the combination was slightly higher than in the other two treatment groups.

The average baseline MBL volume in both studies was just under 230 ml, and the percentage of patients with an MBL ≥ 225 ml was around 35%. The average Hb at baseline was approx. 11.2 g/dl; around 30% of the patients had a baseline Hb <10.5 g/dl.

The average uterine fibroid volume at baseline was 76-79 cm^3, and the average uterine volume was approx. 400 cm^3.

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Approx. 70% of the patients showed – in addition to HMB – a maximum NRS score ≥4 at baseline. However, since only around three quarters of the patients satisfied the corresponding compliance criterion for recording pain in the electronic diary, ultimately only about half of the overall population were included in the "pain evaluable population".

The average baseline BMD in the lumbar spine was approx. 1.2 g/cm^2, compared to a good 1.0 g/cm^2 in the hip. Slightly less than 25% of the patients received vitamin D supplementation during the studies.

Overall, the study population was sufficiently representative of a population of patients with symptomatic fibroids. The only pertubing aspect is the considerable dominance of American patients, since it means that, at least for the subjective endpoints, the transferability of the findings to a Swiss population appears questionable.

In both pivotal studies, for the primary endpoint, numerically distinct and statistically significant superiority was shown for the combination versus placebo. Response rates for the active treatment were 73.4% and 71.2%, respectively, but only 18.9% and 14.7%, respectively for placebo. Various sensitivity analyses showed consistent results for these figures.

The onset of effect was rapid, since a statistically significant difference for the MBL volume between the active substance and placebo was already apparent during the first on-treatment cycle. This was followed by just a small further reduction, with a plateau being reached from around week 16.

The findings for the key secondary endpoints were also consistent with those for the primary endpoint. With the exception of fibroid volume, a statistically significant superiority for the combination versus placebo was demonstrated for all these endpoints. Thus, in parallel with the intensity of bleeding, the pain score (in the "pain evaluable population") also declined markedly during the first 8 weeks and subsequently reached a plateau, which was maintained up to week 24. The predefined endpoint, i.e. a reduction in the score from ≥4 to <1 point, was achieved with both active treatments in a good 40% of the patients, compared to just 10% of patients receiving placebo ($p<0.0001$), and this was not accompanied by any increase in the use of analgesics. However, the effect of fibroid-associated pain was investigated only in patients also experiencing HMB, and pain in patients with uterine fibroids can be assumed to be directly associated with hypermenorrhoea. On the other hand, a study with pain as primary endpoint, including also patients without HMB, is not available for the combination.

By contrast, the effect on fibroid volume was small and not clinically relevant. Thus, the volume decreased by just 12% and 17%, respectively, in the active treatment arms of both pivotal studies.

The efficacy findings in the delayed group were essentially comparable with those in the combination group, with response rates of 79.5% and 73.2%, respectively. However, amenorrhoea in this group (i.e. during the initial monotherapy) was achieved sooner than when the combination was administered from the outset (4.4 vs. 5.3 weeks).

Pharmacodynamic findings for the combination group showed a smaller reduction in the E2 concentration than in the delayed group.

Overall, efficacy of the preparation for treatment of fibroid-associated HMB could be shown in both pivotal studies. The studies also revealed a positive impact on other symptoms (particularly menstruation-related pain) and in the health questionnaires used. However, given the inclusion criteria of the pivotal studies, it cannot conclusively be determined whether these improvements should be viewed as a self-contained finding or only as a consequence of the reduction in HMB.

N=477 patients were enrolled in the open-label extension study, at the end of which the response rate was 81%.

N=229 patients were subsequently also enrolled in the withdrawal study. The number of patients participating in this study was lower than had been presumed when the development programme was planned. Of the 229 patients, 37% had already received the combination therapy from the start of the pivotal study. The symptoms at the time of admission to this study were mild, and the quality of life was only slightly impaired, since only responders from the preceding study were enrolled in the withdrawal study.

Since this study had a treatment period of 52 weeks, an overall exposure period of up to 104 weeks was possible. The main aim of the study was to establish whether the efficacy on menstrual blood

loss can be maintained with continued treatment. Patients were randomised 1:1 to active treatment or placebo. As soon as an MBL of 80 ml was exceeded once, patients were switched to an open-label retreatment with Ryeqo. As a result of this procedure, only few data are available for placebo, since most of these patients quickly suffered a relapse and were switched to the open-label active treatment from as early as week 4 up to week 24. In the active treatment group in turn, the strict criterion implied that a high proportion of patients were switched to open-label treatment. Since MBL is subject to considerable intra-individual variability, a slight exceeding of the value of 80 ml was often just an isolated case, whereas the blood loss in the following cycle fell back below this limit. It would have been better here to switch to an open-label treatment only if the limit was exceeded in two consecutive cycles.

The primary endpoint of the withdrawal study was the sustained responder rate, defined as the proportion of patients whose MBL remained less than 80 ml up to week 76. Here, there was a clear and statistically highly significant advantage for the active treatment, and the relapses in those taking placebo generally occurred very quickly (i.e. already within the first two cycles after discontinuing Ryeqo). The response rate in week 76 was 78.4% for the active treatment, compared to just 15.1% with placebo ($p<0.0001$). In week 104 the response rate in the active treatment group was still almost 70%. For placebo, median time to relapse (MBL >80 ml) was just 5.9 weeks, whereas in the active treatment group, the median was not reached by the end of the study.

Of the n=89 patients in the placebo group who received retreatment, 98% again achieved a response.

Overall, the results of this study suggest the maintenance of efficacy by the combination in most cases during long-term treatment. After discontinuation, on the other hand, a relapse rapidly occurs, and when the treatment is reintroduced, an efficacy comparable with that during the initial administration can be expected.

6.4 Safety

A total of n=888 patients were exposed to Ryeqo during the studies. The investigation of safety focused on the pooled data from the two pivotal studies. The database can be considered as adequate for assessing short-term safety.

In addition to the safety data from the studies with Ryeqo, the applicant also referred to further external data for the E2/NETA component by way of comparison. Moreover, the course of BMD during Ryeqo use was compared with that of an untreated control group of premenopausal women with uterine fibroids.

The question of possible dose-dependence of the adverse effects can be assessed only on the basis of early studies with relugolix monotherapy, since 40 mg was the only dose investigated in the Phase II studies with the combination. The findings of these studies indicate dose-dependence for the overall incidence of AEs. With the dosage of 40 mg, the overall incidence was comparable with that observed for the active comparator leuprorelin. Dose-dependence was only observed for oestrogen deficiency symptoms.

In the data pool of the two pivotal studies, the safety profile corresponded with what would be expected of a hormone therapy with the three components contained in Ryeqo, i.e. most of the AEs could be attributed to the pharmacological effects of relugolix or the add-back therapy. Oestrogen deficiency symptoms, particularly VMS, were paramount. On the other hand, no unexpected safety signals were registered. The incidences were largely comparable overall between Ryeqo (61%) and placebo (63%), but the incidence was slightly higher (72%) in the delayed group, particularly because of a higher incidence during the monotherapy phase. During administration of the combination, on the other hand, the incidence of oestrogen deficiency symptoms was only marginally higher than during placebo administration.

The most common AEs with Ryeqo were headache (9.8%), hot flushes (8.3%), hypertension (4.7%) and alopecia (3.5%). The only AE that was observed with an incidence >5% (and that was more common with Ryeqo than with placebo) was hot flushes. Other AEs that occurred more frequently with Ryeqo were hypertension, alopecia, menorrhagia, libido decreased and irritability (i.e. AEs that are also known for HRT).

SAEs were rare overall, with incidences of 3.1% for Ryeqo and 2.3% for placebo. With the exception of two cases of cholecystitis (a known risk of HRT), all SAEs were isolated cases.

Study discontinuations due to AEs occurred mainly in the delayed group (11.6%), particularly during the monotherapy phase (and due to oestrogen deficiency symptoms, particularly hot flushes). With the combination, they were rarer (3.9%) and, in particular, did not occur more frequently than with placebo (4.3%).

The safety findings during both the open-label extension and the withdrawal study were comparable with those for the two pivotal studies. No new, unexpected safety signals were observed. Nor have the (limited) postmarketing data available to date indicated any additional safety concerns.

In addition to the studies investigating the indication of "uterine fibroids", data are also available from studies focusing on the indication of "endometriosis". An especially noteworthy finding of these studies was the occurrence of several psychiatric SAEs (including suicidal ideation and suicide attempt), although depressive disorders are known to be co-morbid with endometriosis. However, no such cases were observed in the pivotal studies in patients with fibroid-associated HMB receiving the combination. In the early monotherapy studies, on the other hand, such AEs were observed in approx. 2% of the patients, and this incidence was comparable with the one observed for the active comparator leuprorelin. From the withdrawal study, as well, there was a total of five reports of such AEs. But overall, the incidences were no higher than the incidence expected in the general population in women in this age group. However, a risk of depressive disorders similar to that for CHC does appear plausible.

No fatalities were observed in the gynaecological studies at any stage of development.

Overall, the safety profile for Ryeqo was largely comparable with that for placebo, but differed from that for relugolix monotherapy. Whereas typical symptoms of oestrogen deficiency were observed with a relevant frequency during the latter, such symptoms were rare with the combination and observed with a similar frequency as with placebo. This supports the assumption that the oestrogen deficiency caused by the GnRH antagonist can be effectively attenuated by the add-back therapy.

Endometrial safety of the preparation was confirmed by endometrial biopsies.

Special safety aspects

The risk of BMD loss, as would be expected during monotherapy with a GnRH antagonist, must be deemed particularly relevant during this type of treatment. Therefore, the effect of the combination on the long-term course of bone density was comprehensively investigated during the development programme.

Early studies with relugolix monotherapy showed a dose-dependent BMD loss that, at a dose of 40mg, was comparable with that for the active comparator leuprorelin.

In the Phase III studies, regular DXA scans were performed to assess bone density, focusing on the lumbar spine and hip. In order to enable a comparison with an untreated population, an observational study whose participants were matched to those in the pivotal studies was also carried out. In this study, the patients were observed for a total of 52 weeks, and a DXA scan was performed in all cases after 24 and 52 weeks.

The analyses of the BMD findings are very comprehensive overall and cannot be reproduced in detail here. Overall, it can be stated that the applicant has investigated the effects on BMD very carefully and in detail (and using various analytical methods, including changes in absolute values, percentage changes, categorical analyses to identify outliers, etc., as well as the analysis of those AEs that may indicate BMD loss, such as "osteoporosis" or fractures). Not least, these extensive investigations aimed at identifying differences between monotherapy with relugolix (which is associated with a considerable risk of BMD loss) and the combination, i.e. to confirm the benefit of the add-back therapy.

In both pivotal studies, BMD showed a statistically significant reduction from baseline during the first 12 weeks in both active groups, but this was significantly more pronounced in the delayed group than in the combination group. At the end of the study, after 24 weeks, the absolute values for BMD no longer differed between the combination and placebo to any relevant extent. In the delayed group,

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although the BMD did not decrease any further after week 12 (i.e. after the addition of the add-back therapy), the initial loss was maintained until the end of the study. In most cases however – including in the delayed group – the BMD loss was less than 2% of the baseline value.

In the comparison with the observational study, no relevant differences were observed between patients treated with Ryeqo and untreated controls, which can be viewed as an indication that the effect of relugolix on bone is mitigated by the add-back therapy.

During the open-label extension study, the profile of the BMD in the former placebo group corresponded to that observed for the combination group during the double-blind studies. In those patients who had been treated with the combination right from the outset, the BMD showed a further slight decrease during the extension period. In the delayed group, no further decrease in BMD occurred during the extension phase, although it consistently remained at a lower level than in the group that had received the add-back therapy from the start.

With the withdrawal study data are now available for a duration of exposure of up to 24 months – albeit for a limited number of patients. Although the data for the second year of treatment are extremely limited, the findings indicate that the average BMD does not decline any further after the first year of treatment. However, the data submitted hitherto are not sufficient to rule out the possibility of a further relevant BMD loss occurring in individual patients after this time. Specific predisposing risk factors for such BMD loss are unknown.

For those patients who showed a BMD loss of over 2% from baseline at the end of the respective study, the follow-up period was extended, i.e. a further DXA scan was performed 6 months after the end of treatment. If a loss of >2% was still present at this time, DXA scan was repeated after a further 6 months. If the BMD had still not returned to normal by then, the patient was to be referred to a bone specialist. Data for these follow-up investigations are still limited, particularly since drop-out rates were very high. They do not show any critical findings, and a persisting BMD reduction was attributed in most cases to other factors (e.g. longstanding pre-existing vitamin D deficiency, substantial weight reduction).Overall, the data indicate that the BMD recovers, at least partially, after treatment is discontinued. However, the corresponding data are limited, and it cannot be conclusively answered whether the baseline values will be completely achieved again in the majority of patients. In particular, on the basis of the data available so far, it cannot be established, whether the observed slight decrease in BMD (which in most cases would probably occur in the period shortly before menopause) might increase the risk of postmenopausal osteoporosis (and thus of fractures) in these patients. In any case, regular monitoring is needed so that patients with "above-average" or progressive BMD loss can be identified at an early stage and their treatment discontinued where it seems appropriate.

It should also be noted that, apart from existing osteoporosis or other types of metabolic bone disease, all risk factors for BMD loss constituted an exclusion criterion in the clinical trials, and co-medication associated with a corresponding risk (such as high-dose glucocorticoids or certain antiepileptic agents) was not permitted during the studies. Consequently, it is not possible to assess a possible bone risk for such at-risk patients.

The incidences of AEs possibly connected with BMD loss were comparable for Ryeqo and placebo in both pivotal studies. There was no evidence of an increased fracture risk. On this point, the findings for the open-label extension study were consistent, nor were any fractures observed during the withdrawal study.

As a further specific safety aspect, the return of menstruation after discontinuation of the preparation was investigated. A return of menstruation was documented for over 90% of the patients, although the time to the first menstruation in the pivotal studies was slightly longer with Ryeqo, at 31-36 days, than with placebo, at just 24 days. Basically, however, these findings do not give any cause for concern.

6.5 Final clinical and clinical pharmacology benefit risk assessment

Fibroids are benign, hormone-sensitive, soft tissue tumours of the uterus, whose growth is stimulated particularly by oestrogens. They have a high prevalence which increases during the course of the fertile phase of life, reaching a cumulative rate of up to 70% by the age 50.

Most fibroids are asymptomatic, and only around a quarter of affected women develop symptoms that require treatment. The primary problem is heavy menstrual bleeding (HMB), which can lead to iron deficiency and anaemia.

Surgical treatment, particularly in the form of a hysterectomy, used to represent the standard treatment for uterine fibroids, but the surgical procedures are associated with non-negligible risks. In recent years, however – not least because of the development of new, effective drugs – there has been an increasing trend towards a primarily pharmacological treatment of fibroid-associated symptoms. It should be emphasised, however, that this constitutes symptomatic treatment.

In the past, GnRH analogues (which have to be injected subcutaneously) represented the only available effective medical treatment. They act by suppressing oestrogen to castration levels which, in turn, is associated with corresponding adverse effects. In particular, due to the risk of BMD loss, the duration of treatment his restricted (usually to a maximum of 6 months). In addition to reducing HMB, GnRH analogues also reduce fibroid volume.

By contrast, the aim of the new, oral, non-peptide GnRH antagonists and their combination with add-back therapy consisting of E2 and NETA is to achieve an E2 level in a range that, on the one hand, offers good effectiveness and, on the other, mitigates the adverse effects. Ryeqo contains the GnRH antagonist relugolix in a fixed combination with the add-back therapy.

Beneficial effects and respective uncertainties

From a pharmacokinetic point of view, no dose adjustments are required for patients with mild or moderate hepatic impairment or renal impairment of any degree. No data are available for subjects with severe hepatic impairment.

Apart from the co-administration with P-gp inhibitors and CYP/P-gp inducers, the interaction potential of relugolix as a victim appeared to be low. The interaction potential of relugolix as a perpetrator was also low, but its mild inducing effect resulted in slightly reduced E2 exposures.

Relugolix had no impact on heart rate and did not cause QTcF prolongations at therapeutic and supratherapeutic exposures. Considering the known relugolix metabolites, the administration of a single relugolix dose in the tQT study is acceptable. However, a high percentage of radioactivity in plasma was not identified.

The efficacy of the triple combination in treating heavy menstrual bleeding associated with fibroids was demonstrated in two pivotal studies with an identical design. Treatment with Ryeqo reduced MBL by 84% compared with placebo. In previously anaemic patients, the treatment also produced a rise in Hb.

In an open-label extension study and a subsequent withdrawal study (with a treatment period of up to 24 months in total), it was also shown that the efficacy of the combination was maintained during long-term treatment. On the other hand, discontinuation of the preparation was quickly followed (i.e. in most cases already within two cycles) by a recurrence of the HMB, which then responded, in turn, to the resumption of treatment with Ryeqo in most cases.

By contrast, since fibroid-associated pain was not investigated as a separate symptom, but only in those patients who also suffered from HMB, it must be assumed that the pain was caused by the hypermenorrhoea in a large proportion of cases. In the pivotal studies, however, the effect on pain was investigated as a key secondary endpoint with confirmatory testing, and here, too, Ryeqo performed significantly better than placebo.

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Uncertainties regarding benefit

In all studies with Ryeqo, only HMB was investigated as primary endpoint. Although other potentially fibroid-associated symptoms were likewise positively influenced by the treatment, the extent to which these symptoms occurred independently of bleeding, and whether adequate efficacy would also be expected in patients without HMB, cannot be evaluated.

Whereas no relevant food effect was found for the add-back therapy (as expected), relugolix reduced Cmax by 55% and AUC by 38% after a high-fat, high-calorie meal. Although a slight reduction in efficacy is expected only from estradiol concentrations higher than 60 pg/ml, the possibility of reduced efficacy in individual cases with (regular) postprandial administration or with concurrent administration of acid-reducing drugs cannot be ruled out (see Information for Healthcare Professionals). In the Phase III studies, the study medication was always administered in the fasted state.

Both, efficacy and safety data are qualified to a certain extent by the fact that blinding was likely not maintained during the studies, as the patients receiving placebo continued to experience cyclical bleeding, whereas the bleeding pattern was significantly altered in those receiving active treatment. Although this is hardly relevant for the – objective – primary endpoint of the studies, it probably is relevant for the findings for the key secondary endpoints such as pain and health questionnaires.

Unfavourable effects and respective uncertainties

The absolute bioavailability of relugolix is low, increasing the risk of interactions with P-gp inhibitors. Their co-administration is not recommended.

The solubility of relugolix is pH-dependent, resulting in a substantial food effect with reduced exposures. The clinical efficacy data were obtained exclusively after fasted administration of relugolix. The expected reduction of efficacy after fed administration is entirely based on simulations. There are no data available regarding the impact of PPIs and other drugs increasing gastric pH on relugolix absorption. As for food, reduced relugolix exposures and efficacy are expected for the co-administration of PPIs.

Only three relugolix metabolites were identified. There was a substantial percentage of unidentified radioactivity in plasma, urine and faeces after administration of a ^{14}C labelled dose.

The safety profile observed for the combination largely corresponded with what would be expected of this kind of hormonal therapy. No new, unexpected safety signals were observed. The main risk of treatment with a GnRH antagonist is BMD loss. In this connection, the submitted data showed that this BMD loss (as well as other oestrogen deficiency symptoms, particularly hot flushes) can be mitigated by the administered add-back therapy; however, see also "Uncertainties regarding risks".

The data also showed that adequate protection of the endometrium is achieved by the addition of NETA to the combination of relugolix and E2.

The data can be considered as sufficient for assessing short-term safety. There were no prohibitive concerns.

Uncertainties regarding risks

Uncertainties exist particularly regarding long-term safety, since the data that are now available up to a maximum treatment period of 104 weeks reveal limitations that complicate assessment. The available BMD data, in particular, indicate that, after an initial slight reduction in BMD during Ryeqo administration, no relevant further reduction in BMD occurs in most cases, but rather that (at the latest during the course of the second year of treatment) a plateau is reached. But the data still cannot be considered as sufficient to rule out, with adequate certainty, a relevant BMD loss also during treatment given for an unlimited period. In particular, it should be assumed that, although the average values for BMD do not give cause for concern, individual outliers may be affected by much greater BMD loss. Risk factors that might be used to identify such patients beforehand (so that they might either not be treated or subjected to close BMD monitoring) are not known.

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Interpretation of the BMD profile is complicated by the fact that a proportion of the patients presumably reached menopause during the studies. Not only does this affect the assessment of bleeding endpoints, but any influence on BMD would also be difficult to differentiate from physiological postmenopausal reduction. In this connection, the question arises as to how the onset of menopause can be identified in patients on Ryeqo – i.e. the point at which treatment can, or should, be discontinued.

In particular, the risk of a (further) BMD loss in patients who already have risk factors for osteoporosis cannot be assessed, since such patients were excluded from the studies.

A PASS study is already being planned to investigate the long-term effect of the preparation on bone density under real life conditions. This will cover a treatment period of 4 years and a subsequent treatment-free follow-up over 24 months.

Benefit-risk balance

From a clinical pharmacology point of view, the administration of relugolix independently of food and the implicitly allowed co-administration of drugs increasing gastric pH are the main critical points.

Overall, the benefit-risk balance for the preparation can be assessed as positive. However, this assessment applies only to the specific symptom investigated as primary endpoint in the pivotal studies, i.e. HMB. By contrast, separate proof of efficacy for the other possible symptoms of uterine fibroids cannot be considered as having been provided, since these were investigated only in patients with concurrent HMB.

Furthermore, the available data on bone safety do not permit treatment for an unlimited period without regular monitoring of BMD. Therefore, until further notice (i.e. at least until the findings of the PASS study are available), DXA scans every two years should be recommended. In addition, in premenopausal women the drug should be withdrawn at least transiently every two years in order to determine whether menopause has occurred and the drug can be discontinued. This allows for patients not to be exposed to unnecessary risks of BMD loss if the drug is no longer needed.

In younger patients, fibroid size should also be monitored, likewise at two-yearly intervals, so that any fibroid growth resulting from the add-back therapy can be identified in time.

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7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Ryeqo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are encouraged to report any suspected new or serious side effects. See the section on “Adverse effects” for how to report side effects.

Ryeqo 40 mg/1 mg/0.5 mg film-coated tablets

Composition

Active ingredients

Relugolix, estradiol (as estradiol hemihydrate) and norethisterone acetate (NETA).

Excipients

Tablet core: Lactose monohydrate, mannitol (E 421), sodium starch glycolate (type A), hydroxypropyl cellulose (E 463), magnesium stearate (E 572).

Tablet coating: Hypromellose (E 464), titanium dioxide (E 171), lactose monohydrate, triacetin (E 1518), yellow iron oxide (E 172).

Lactose monohydrate: approx. 80 mg per film-coated tablet.
Sodium: approx. 0.58 mg per film-coated tablet.

Pharmaceutical form and quantity of active ingredient per unit

Each film-coated tablet contains 40 mg relugolix, 1 mg estradiol (as estradiol hemihydrate) and 0.5 mg norethisterone acetate.

Light yellow to yellow, round film-coated tablet of 8 mm diameter, with “415” inscribed on one side and plain faced on the other side.

Indications/Applications

Treatment of fibroid associated hypermenorrhea in adult women before the onset of menopause.

In patients with risk factors for osteoporosis or bone loss, a bone density measurement must be carried out using dual X-ray absorptiometry (DXA) before starting treatment with Ryeqo (see “Warnings and precautions”).

Dosage/Administration

Pregnancy must be ruled out prior to initiating treatment with Ryeqo.

Usual dosage

One dose of 1 tablet once a day at about the same time of the day (see also “Method of administration" below).

Starting Treatment

The first tablet should be taken within 5 days of the onset of menstrual bleeding. If treatment is initiated on another day of the menstrual cycle, irregular and/or heavy bleeding may initially occur.

Duration of therapy

Ryeqo can be taken without interruption. Conducting a DXA scan is recommended after the first year of treatment (see “Warnings and precautions”). Afterwards, it is recommended to monitor the progression of bone density (using a DXA scan) at two-year intervals. The fibroid(s) size should be monitored according to standard clinical practice, but at least every two years as well. In premenopausal patients, a withdrawal attempt should be made every two years. Treatment should be discontinued after the onset of the menopause.

Forgotten intake

If a dose is missed out, it should be taken as soon as possible. On the next day, it should continue to be taken at the usual time.

Method of administration

Tablets should be taken with some liquid. When taken after a high-fat meal, relugolix exposure was reduced by around half (see “Pharmacokinetics”), which could be associated with reduced efficacy. Concomitant use of acid-reducing drugs (i.e. H2 blockers or proton pump inhibitors) similar changes in the pharmacokinetics of relugolix can be expected.

Special dosage instructions

Children and young people

Ryeqo is not indicated in children or adolescents and paediatric data is not available for this product.

Older patients

Ryeqo has only been studied in premenopausal patients. There is generally no indication in postmenopausal women, as myomas normally regress spontaneously after menopause.

Patients with liver dysfunction

No dose adjustment is required for Ryeqo in patients with mild or moderate hepatic impairment (see “Pharmacokinetics”). Ryeqo is contraindicated in patients with severe hepatic disease (see “Contraindications”).

Patients with kidney dysfunction

No dose adjustment is required in patients with renal impairment (see “Pharmacokinetics”, section “Kinetics of special patient groups”).

Contraindications

- known osteoporosis
- known or suspected sex hormone-dependent malignancies (e.g. of the breast or genital organs)
- genital bleeding of unknown cause
- existing or previous venous thromboembolic disorders (e.g. deep vein thrombosis, pulmonary embolism)
- existing or previous arterial thromboembolic disorders (e.g. ischemic heart disease, myocardial infarction, cerebrovascular accident)
- known thrombophilic disorders (e.g. protein C, protein S or antithrombin deficiency or activated protein C (APC)-resistance, including Factor V Leiden) (see “Warnings and precautions”).
- headaches with focal neurological symptoms or migraine headaches with aura (see “Warnings and precautions”).
- presence or history of liver tumours (benign or malignant) (see “Warnings and precautions").
- acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- pregnancy or suspected pregnancy and breastfeeding (see “Pregnancy, lactation”).
- concomitant use of hormonal contraceptives
- hypersensitivity to the active substances or to any of the excipients.

Warnings and precautions

Ryeqo must only be prescribed after careful diagnosis. Pregnancy must be excluded before starting or restarting treatment with Ryeqo. Before starting treatment, all hormonal contraceptives must be discontinued (see “Contraindications”). During therapy and for at least 1 month after discontinuing Ryeqo, non-hormonal contraception methods should be used (see “Pregnancy / Lactation”). The patient should be consulted with regard to all suitable contraception methods.

Medical examination/consultation

A full medical history (including family history) must be obtained before initiating or resuming treatment with Ryeqo. Blood pressure must be measured and a physical examination performed based on the contraindications (see “Contraindications”) and warnings (see “Warnings and precautions”). Regular check-ups must be carried out during treatment in accordance with standard clinical practice.

Influence on bone mineral density (BMD)

A monotherapy with the GnRH antagonist relugolix leads to a reduction in bone mineral density as a result of estrogen suppression. The estradiol also contained in Ryeqo reduces the risk of BMD loss. In the Ryeqo clinical trials, the decrease in BMD from the baseline was no more than 2% in most cases. However, a BMD loss of >3–8% has been observed in some patients.

Therefore, a DXA scan is recommended after the first 52 weeks of treatment to rule out the presence of an increased BMD loss, which outweighs the benefits of treatment. In case of longer-term administration of Ryeqo this examination should be repeated at two-year intervals.

Patients with risk factors for osteoporosis or other metabolic bone diseases were excluded from the clinical studies, and co-medications that could affect BMD were not allowed during the studies. A particularly careful risk-benefit assessment should therefore be conducted in patients with such risk factors. A DXA scan must be conducted in such cases prior to initiating treatment with Ryeqo. Treatment with Ryeqo should not be initiated if the risk associated with BMD loss exceeds the potential benefits of the treatment.
A potential impact of vitamin D on the progression of BMD was not examined. Nevertheless, ensuring sufficient calcium and vitamin D intake is recommended during treatment with Ryeqo.
In the case of co-medication with inducers of the CYP enzymes, it should be noted that the effectiveness of estradiol may be reduced, which may impair the protection against clinically relevant BMD loss.

Depressive Disorders and suicidality

Depression and depressive moods are known to be possible adverse reactions when using sex hormones. Cases of mood swings and depressive disorders have also been observed with the use of Ryeqo. Such disorders can occur shortly after starting treatment. Depression can be severe and is a risk factor for suicide or suicidal behaviour. The patient must therefore be informed about possible symptoms of depressive disorders. Patients should be strongly advised to contact a doctor immediately if they experience mood swings or other symptoms of depression while using Ryeqo.
Patients with a history of depression must be carefully monitored. If severe depression recurs, Ryeqo should be discontinued.

Prolapse or expulsion of myomas
In the case of submucosal myomas, these can prolapse through the cervix or be expelled, which can temporarily cause increased uterine bleeding. Such cases have also been reported with the use of Ryeqo. Patients who are known or suspected of having a submucosal myoma should be made aware of these possible complications and asked to contact their doctor if excessive bleeding occurs again after an initial reduction in bleeding with Ryeqo.

Changes in bleeding pattern
Patients must be informed that treatment with Ryeqo usually leads to a reduction in menstrual blood loss or even amenorrhea. In the clinical studies with Ryeqo, the amenorrhea rate was around 50% after 24 weeks of treatment and around 70% after 12 months of therapy. Irregular bleeding was observed, especially at the start of treatment. In particular, irregular or heavy bleeding is possible if therapy is started later than the first 7 days of the menstrual cycle.

The patient should be asked to consult a doctor in the event of persistent excessive bleeding.

Reduced ability to detect a pregnancy

During treatment with Ryeqo, menstrual bleeding is usually reduced in intensity and/or duration, and amenorrhea is present in a high proportion of patients. This can make it difficult to detect pregnancy early. If a pregnancy is suspected, a pregnancy test should be carried out. In the case of a confirmed pregnancy, the treatment should be discontinued.

Venous and arterial thromboembolic events

Ryeqo is contraindicated in patients who are experiencing, or have in the past experienced, venous or arterial thromboembolic events or who are at increased risk for such events (particularly if they have thrombophilia).

The use of medicinal products containing an estrogen and a progestin increases the risk of venous and arterial thromboembolism (such as deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction) as compared to women who do not use such medicinal products. This applies in particular to patients with the simultaneous presence of other risk factors for such diseases. Smokers >35 years of age, as well as persons suffering from obesity, lipid metabolism disorders, uncontrolled arterial hypertension or pre-existing vascular diseases are at increased risk.
The specific risk for Ryeqo in this context is not known.
The risk of venous thromboembolism may be temporarily increased in the event of prolonged immobilisation, major surgical interventions or after severe trauma. In such cases, it is advisable to stop administering Ryeqo (in the case of a scheduled operation, at least four weeks in advance) and to resume only two weeks after regaining full mobility.
If symptoms that indicate a thromboembolic event occur (such as unilateral swelling / pain in one leg, sudden shortness of breath, sudden numbness or weakness in the face or in an extremity, chest pain, etc.), Ryeqo must be discontinued immediately and appropriate diagnostics initiated. The patient must be informed about the possible signs of thromboembolic events and asked to consult a doctor immediately if such symptoms occur.

Hypertension

Ryeqo should not be used in patients with uncontrolled hypertension.
Slight increases in blood pressure have been reported with both combined hormonal contraceptives and hormone replacement therapy; however, clinically relevant elevated values are rare. Similar findings were also observed with Ryeqo. If persistent clinically relevant hypertension occurs during treatment with Ryeqo, this should be treated and the benefit-risk ratio for continuing therapy should be assessed. If Ryeqo is discontinued, treatment may be resumed if normotensive levels can be achieved with antihypertensive therapy.

Liver tumours

The use of Ryeqo is contraindicated in patients with benign or malignant liver tumours.

Other liver diseases / influence of Ryeqo on liver function
The use of Ryeqo is contraindicated in the presence of liver disease for as long as the liver function tests have not returned to normal. Treatment must be discontinued if jaundice develops.

Occasional, asymptomatic, transient increases in serum transaminase (especially ALT) to at least 3 times the upper limit of normal were observed with Ryeqo. If changes in liver function tests occur during treatment with Ryeqo, treatment should be interrupted until the liver values have normalised again.

Gallbladder disorders

Estrogens can increase the lithogenecity of bile. In epidemiology studies, an increased risk of gallbladder disease (e.g. cholelithiasis, cholecystitis) has been reported with the use of both combined hormonal contraceptives and with hormone replacement therapy (HRT). Such events have also been observed within the Ryeqo clinical trials. This should be taken into account in particular in patients who have additional risk factors for cholelithiasis (such as obesity or hyperlipidemia).

Further precautions

Relugolix exposure is increased in patients with moderately or severely impaired renal function (see “Pharmacokinetics”). However, no dose adjustment is necessary (see “Dosage/Administration”). The extent to which relugolix is eliminated with hemodialysis is not known.

Hair loss and alopecia were reported more often in the placebo-controlled Phase III Studies using Ryeqo than under placebo. This did not constitute a specific pattern of alopecia, and the majority of patients continued to participate in the studies despite this adverse effect. Whether hair loss is reversible after discontinuing Ryeqo is not known. Nevertheless, giving consideration to a discontinuation of the medical product is recommended if it results in clinically relevant hair loss.

Reduced glucose tolerance has been reported with estrogen-progestogen combinations. An adjustment of the antidiabetic therapy, however, is generally not required. Nonetheless, blood sugar level of patients with diabetes should be carefully monitored during therapy with Ryeqo, especially during the first few months of treatment.

In patients with pre-existing (especially familial) hypertriglyceridemia, a sharp increase in plasma triglycerides has been reported in rare cases with the use of estrogen-progestogen combinations, which is associated with an increased risk of pancreatitis.

Excipients of particular interest

Ryeqo film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This product contains less than 1 mmol sodium (23 mg) per film-coated tablet, i.e. it is essentially “sodium-free”.

Interactions

Information on interactions with Ryeqo is based on evaluations of interactions of the individual components.

Influence of other drugs on the pharmacokinetics of relugolix

Oral P-glycoprotein (P-gp) inhibitors:
Concomitant use of Ryeqo with oral P-gp inhibitors is not recommended. Relugolix is a substrate of P-gp (see “Pharmacokinetics”). In an interaction study with erythromycin, a P-gp and moderate cytochrome P450 (CYP)3A4 inhibitor, the area under the curve (AUC) and maximum concentration (C_{max}) of relugolix were found to be 6.2-fold elevated. Concomitant use of P-gp inhibitors may increase the exposure to relugolix. These include certain anti-infectives (e.g. erythromycin, clarithromycin, gentamicin, tetracycline), antimycotics (e.g. itraconazole), antihypertensives (e.g. carvedilol, verapamil), antiarrhythmics (e.g. amiodarone, dronedarone, propafenone, quinidine), antianginal products (e.g. ranolazine), cyclosporine, HIV or HCV protease inhibitors (e.g. ritonavir, telaprevir). If concomitant use with once or twice daily oral P-gp inhibitors (e.g. azithromycin) is unavoidable, Ryeqo should be taken first, and the oral P-gp inhibitor should be taken at least 6 hours later. In addition, patients should be monitored closely for adverse reactions.

Strong cytochrome P450 3A4 (CYP3A4) and/or P-gp inducers:

Concomitant use of Ryeqo with strong CYP3A4 and/or P-gp inducers is not recommended. In a clinical interaction study with rifampicin, a strong CYP3A4 and P-gp inducer, the C_{max} and AUC of relugolix were reduced by 23% and 55%, respectively. Medicines that cause a strong CYP3A4 and/or P-gp induction, such as anticonvulsants (e.g. carbamazepine, topiramate, phenytoin, phenobarbital, primidone, oxcarbazepine, felbamate), anti-infectives (e.g. rifampicin, rifabutin, griseofulvin); St. John’s wort (Hypericum perforatum); bosentan and HIV or HCV protease inhibitors (e.g. ritonavir, boceprevir, telaprevir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz) may reduce the plasma concentrations of relugolix and lead to a decrease in the therapeutic effect.

CYP3A4 inhibitors:

Concomitant use of relugolix with strong CYP3A4 inhibitors devoid of P-gp inhibition (voriconazole) did not increase the exposure to relugolix in a clinically meaningful manner. Furthermore, in a clinical

interaction study, concomitant administration with atorvastatin, a weak CYP3A4 enzyme inhibitor, did not change the exposure to relugolix in a clinically meaningful manner.

Influence of other drugs on the pharmacokinetics of estradiol (E2) and norethistherone acetate (NETA)

CYP3A4 inhibitors:

Medicinal products that inhibit the activity of hepatic drug-metabolising enzymes may increase circulating concentrations of the estrogen and norethisterone components in Ryeqo.

CYP enzyme inducers:

The metabolism of estrogens and progestogens can be accelerated by the simultaneous use of inducers of drug-metabolising enzymes, in particular of cytochrome P450 enzymes. This applies, for example, to barbiturates, bosentan, carbamazepine, efavirenz, felbamate, modafinil, nevirapine, oxcarbazepine, phenytoin, primidone, rifabutin, rifampicin and topiramate, as well as to medicinal products containing St. John's Wort (Hypericum perforatum). Protease inhibitors such as ritonavir, nelfinavir or telaprevir are known to be powerful inhibitors, but are also inducers and can also reduce exposure to estrogens and progestogens.
In clinical terms, an acceleration in estrogen metabolism can lead to a reduction in protection against loss of BMD. Long-term co-medication with liver enzyme inducers with Ryeqo is therefore not recommended.

Interference with enterohepatic circulation of estradiol and NETA

A reduction in systemic concentrations of E2 or NETA as a result of an interference with the enterohepatic circulation (e.g. due to penicillins or tetracyclines) cannot be ruled out. There is insufficient data in particular of the possible interactions in respect of long-term co-medication with antibiotics (e.g. borreliosis or osteomyelitis). In the event of lower systemic E2 concentrations, protection against BMD loss may be reduced.

Influence of relugolix on the pharmacokinetics of other substances

CYP3A4-Substrate: Relugolix is a weak inducer of CYP3A4. After co-administration with daily 40-mg doses of relugolix, the AUC and C_{max} of midazolam, a sensitive CYP3A4 substrate, were reduced by 18% and 26% respectively. However, based on the clinical study with midazolam, clinically meaningful effects of relugolix on other CYP3A4 substrates are not expected.

BCRP-Substrate: Relugolix is an inhibitor of breast cancer resistant protein (BCRP) *in vitro*, and therefore an interaction study was conducted with rosuvastatin, a BCRP and organic anion transporting polypeptide 1B1 (OATP1B1) substrate. After co-administration with daily 40-mg doses of relugolix, the AUC and C_{max} of rosuvastatin were reduced by 13% and 23% respectively. The effects are not considered to be clinically meaningful, and therefore no dose adjustment of rosuvastatin is recommended in the case of concomitant use. Clinical effects of Ryeqo on other BCRP substrates have not been evaluated and the relevance for other BCRP substrates is unknown.

P-gp-Substrate: Relugolix may cause saturation of intestinal P-gp at the 40 mg dose, which could result an increase in absorption and exposure to co-administered medicines that are sensitive substrates of P-gp. No clinical interaction studies have been conducted with P-gp substrates such as dabigatran etexilate or fexofenadine. Therefore, co-administration with sensitive P-gp substrates is not recommended.

Influence of estradiol and norethisterone acetate on the pharmacokinetics of other substances

Estrogens and progestogens can affect the metabolism of certain other active substances. Accordingly, their plasma concentrations can either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine) when Ryeqo is used. Adjustment of the dose of these drugs may be necessary. Any dosage recommendations shall be considered in the relevant Information for healthcare professionals.

Interactions of unknown mechanism

In clinical studies, when combined contraceptives containing ethinylestradiol were administered concomitantly with certain combinations of active ingredients used in the treatment of HCV infections (ombitasvir/paritaprevir/ritonavir with or without dasabuvir; glecaprevir/pibrentasvir; sofosbuvir/velpatasvir/voxilaprevir), this led significantly more frequently to a clinically relevant increase in ALT (including cases of an increase to over five times the upper limit of the normal range) as compared to patients who were treated exclusively with the antiviral active ingredients. When using other estrogens (especially estradiol, in the form in which it is present in Ryeqo), however, the incidence of an increase in transaminases was not higher than in patients without estrogen therapy. Due to the limited number of patients who took such other estrogen-containing medicinal products, caution should be exercised when administering estrogen-containing medicinal products together with one of the above-mentioned combinations of active ingredients.

Pregnancy, lactation

Pregnancy

Ryeqo is contraindicated in pregnancy. Pregnancy must be ruled out before starting treatment. If pregnancy occurs or is suspected treatment must be discontinued.
There is a limited amount of data from the use of relugolix in pregnant women. Animal studies have shown that exposure to relugolix early in pregnancy may increase the risk of early pregnancy loss (see “Preclinical data”). Based on the pharmacological effects of the active ingredient, an adverse effect on pregnancy cannot be ruled out.
Animal studies have also shown that there were indications for potential foetal risks for estrogens and progestogens (see “Preclinical data"). However, most epidemiological studies to date have not shown any clear evidence of teratogenic or embryotoxic effects when estrogens and/or progestogens have been inadvertently used during pregnancy. It should be noted that virilisation of female foetuses has been reported in humans with norethisterone but in doses higher than those occurring in Ryeqo.
If pregnancy occurs during treatment with Ryeqo, the marketing authorisation holder should be informed (see "Marketing authorisation holder" below for address).

Lactation

No data is available on the concentrations of relugolix or its metabolites in human breast milk or on possible effects on the breastfed infant. Relugolix was excreted in milk in animal studies (see “Preclinical data”).
If exogenous estrogens and progestogens are consumed, low concentrations of active substances can be detected in the breast milk, and milk production may be reduced. Effects on breastfed infants cannot be excluded.
While using Ryeqo and for up to 2 weeks after stopping Ryeqo patients must not breast feed (see “Contraindications”). The benefits of breastfeeding for the child should be weighed against the benefits of therapy for the mother before a decision is made on whether to stop breastfeeding or to postpone treatment with Ryeqo.

Fertility

No data is available on the possible effects of Ryeqo on human fertility. Ryeqo inhibits ovulation and often causes amenorrhea. Ovulation and menstrual bleeding return quickly after treatment is discontinued (see “Pharmacodynamics”). Animal studies (see “Preclinical data”) and the mechanism of action of Ryeqo components indicate that fertility can be impaired.

Effect on ability to drive and use machines

Comprehensive studies have not been carried out. However, Ryeqo is believed to have negligible influence on the ability to drive or use machines.

Adverse effects

The following summarises the adverse effects by organ system (MedDRA) and frequency with which they were observed in the clinical studies for Ryeqo. The statements here rely on data for n=254 patients, who were given Ryeqo for the treatment of heavy bleeding due to uterine fibroids in the two pivotal studies.
The most frequent adverse effects were hot flushes (8.3%) and uterine bleeding (4.7%).

The frequencies are defined according to the following convention:
“very common” (≥1/10)
“common” (≥1/100, <1/10),
“uncommon” (≥1/1,000, <1/100)
“rare” (≥1/10,000, <1/1,000)
“very rare” (<1/10,000)

Metabolism and nutritional disorders
Common: increase in weight

Psychiatric disorders
Common: Reduced libido, depression, irritability, anxiety
Uncommon: mood swings

Disease of the nervous system
Common: Headache
Uncommon: Migraine

Vascular disorders
Common: Hot flushes, blood pressure changes

Disorders of the gastrointestinal tract
Common: Stomach pain, dyspepsia

Skin disorders
Common: Alopecia, hyperhidrosis

Reproductive system and breast disorders

Common:	Bleeding disorders (e.g. menorrhagia, metrorrhagia, irregular periods), abdominal pain, breast cysts
Uncommon:	Expulsion of submucosal fibroids, breast tenderness

General illnesses

Common:	Night sweats, peripheral oedema

It is extremely important to report suspected side effects after the drug has been approved. It enables continuous monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are encouraged to report any suspected new or serious side effects through the EIViS (Electronic Vigilance System) online portal. You can find information on this at www.swissmedic.ch.

Overdosage

Overdosage cases have not been reported for relugolix, whereas healthy subjects have been administered single doses of up to 360 mg (i.e. 9-times the recommended clinical dose) of relugolix in studies.
Overdosing on estradiol and NETA can cause nausea and vomiting. Accidental ingestion by girls before menarche may cause vaginal bleeding.

There is no specific antidote for relugolix. In the event of an overdose, supportive treatment is recommended. It is not known if or what extent relugolix, estradiol or norethisterone can be removed by haemodialysis.

Properties/effects

ATC code

H01CC54

Mechanism of action

Relugolix is a non-peptide GnRH receptor antagonist that binds to and inhibits GnRH receptors in the anterior pituitary gland. In humans, inhibition of GnRH receptors results in a dose dependent decrease in the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. The reduction in FSH concentration prevents follicle growth and maturation, which in turn

reduces estrogen secretion. Prevention of an LH surge inhibits ovulation and development of the corpus luteum, which also reduces the production of progesterone.

The estradiol contained in Ryeqo is chemically and biologically identical to the endogenous human estradiol. It relieves symptoms related to estrogen deficiency, such as vasomotor symptoms, and reduces the risk of a decrease in bone mineral density.

Norethisterone acetate is a synthetic progestogen. It inhibits the proliferative effect of estradiol on the endometrium, thereby reducing the risk of endometrial hyperplasia or endometrial cancer.

Pharmacodynamics

After administration of relugolix, there is a rapid, dose-dependent decrease in plasma concentrations of LH, FSH and estradiol, with a dose of 40 mg leading to an almost maximum decrease in estradiol concentrations up to the postmenopausal range. Simultaneous administration of estradiol increases the average estradiol concentrations compared with relugolix monotherapy. Median E2 trough concentrations in the phase 3 studies with Ryeqo were around 33 pg/mL after 24 weeks and thus corresponded to those in the early follicular phase of a physiological menstrual cycle. Progesterone levels were maintained at < 3.0 ng/mL under Ryeqo.
To ensure acceptable bone protection from the combination in case of adequate effectiveness against hypermenorrhoea, the estradiol concentration should be in the range of 20-60pg/ml. At the end of the open extension of the two pivotal studies (i.e. after 52 weeks; see below) the estradiol concentration was in this target range in more than half of patients. Only <10% of the patients had values <20pg/ml.

In addition, the influence of Ryeqo on ovarian activity was investigated in n = 67 healthy premenopausal women over a period of 84 days. The follicle growth was significantly suppressed during the entire 84-day treatment period (mean size of the dominant follicle was approximately 6 mm) and ovulation was suppressed in all 67 subjects as assessed by the Hoogland-Skouby score. After discontinuation of treatment, the mean time to return to ovulation was 23.5 days. 43 days after discontinuation of Ryeqo, ovaluation had returned or menstruation had started in all subjects. Data on the Pearl Index when administering Ryeqo are not yet available.

Safety pharmacodynamics

Influence on bone mineral density (BMD)

The impact of Ryeqo on BMD was examined in the two pivotal studies (see “Clinical efficacy”) and their open extension (every 12 weeks), as well as during a 12-month, randomised, double-blind withdrawal study using DXA. Patients with a Z-score <-2 were excluded from study participation. Data are

available for a therapy duration of up to 24 months, including the two extensions. In the open extension n=477 women, who had completed the 24-week pivotal studies, were treated with Ryeqo. In addition BMD findings are available for n=82 patients from the randomised withdrawal study after a total therapy duration of 24 months.

Patients with pre-existing osteoporosis or other metabolic bone diseases (including a history of such) as well as all patients with risk factors for BMD loss (such as hyperparathyroidism, hyperthyroidism or anorexia nervosa, or with previous fractures without adequate trauma) were excluded from participation in the study. In addition, no co-medications with a potential risk for BMD (such as systemic glucocorticoids or certain anti-epileptic drugs) were allowed to be used during the study. Patients, who had a Z score <-2 on the lumbar spine, hip or femoral neck at the end of a study, or who had a decrease in BMD of ≥7% against the baseline, could not be included in the following study.

Up to week 24, the average decrease in BMD on the lumbar spine against the initial value was 0.23% with the use of Ryeqo, by comparison with an increase of 0.24% under placebo. The decrease in BMD was lower in the patients receiving Ryeqo than in those in the so-called “delayed” group (for the definition of the latter see below under “Clinical efficacy”) and in comparison to studies with relugolix monotherapy.

In addition, BMD measurements were carried out in an observational study on n=262 untreated patients of comparable age with uterine fibroids and were compared with those for patients treated with Ryeqo in the pivotal studies and their extension. Following a treatment period of 52 weeks the percentage reduction in BMD in patients treated with Ryeqo was 0.80%, as against a 0.41% reduction in untreated external controls. A reduction in BMD on the lumbar spine by >3% was found after 12 months using Ryeqo in 23% of patients, by comparison with 17% of untreated fibroid patients.

Effects on endometrium

Endometrial biopsies were carried out on a sub-group of patients after 24 and 52 weeks in the two pivotal studies and their open extension. Data on endometrial biopsies after 52 weeks of treatment with Ryeqo are available for n = 74 patients. No cases of endometrial hyperplasia or endometrial cancer have been observed.

Clinical efficacy

The efficacy and safety of Ryeqo were investigated in two pivotal, multinational, randomised, double-blind, placebo-controlled studies with identical design (LIBERTY 1 and 2) over a duration of 24 weeks each in a total of n = 770 patients aged 18-50 with heavy menstrual bleeding associated with uterine

fibroids. The patients had to have at least one sonographically confirmed myoma and have menstrual blood loss (MBL) of ≥ 80 ml. The blood loss was determined using the alkaline hematin method.

The patients were each randomised 1:1:1 into three treatment arms and were given either relugolix 40 mg + estradiol 1 mg + norethisterone acetate 0.5 mg (E2/NETA) (Ryeqo) or placebo in the mornings, on an empty stomach, one hour before breakfast in each case, for 24 weeks or relugolix 40 mg for 12 weeks, followed by relugolix 40 mg in combination with E2/NETA for a further 12 weeks (the so-called "delayed" group). The average age of the patients included was 42, and the mean body mass index was 31.7 kg/m^2. Approximately 49.4% of the patients were Black, 44.7% White, and 5.9% belonged to another ethnic group.
The primary endpoint of the two studies was the proportion of patients who achieved an MBL <80ml by week 24 with a simultaneous reduction in blood loss compared to the baseline of at least 50% (defined as "responders"). In addition, a total of 7 secondary endpoints were also tested for confirmatory purposes, including parameters related to the bleeding intensity on the one hand, and myoma-associated pain and health questionnaires on the other.

In both studies, there was a statistically significantly higher proportion of responders with Ryeqo than with placebo (73.4% vs. 18.9% and 71.2% vs. 14.7%, each p <0.0001). A reduction in MBL volume was already observed at the end of the first menstrual cycle.

The findings of the most relevant secondary endpoints were consistent with this. Around half of patients developed an amenorrhoea by week 24 in both studies when using Ryeqo, by comparison with 4.3% of patients under placebo (p<0.0001).

Moreover, the total of 121 patients, who have baseline anaemia (Hb ≤10.5g/dl), were significantly more likely to have a relevant increase in haemoglobin with Ryeqo than under placebo (56% versus 12%, p<0.0001).

In those patients who had moderate to severe myoma-associated pain in addition to hypermenorrhoea (during menstruation or independently of menstruation) at the start of the study, a potential influence of the therapy on pain symptoms was also examined (on a numeric rating scale of 0-10). For this, there was also a significant advantage for Ryeqo over placebo (45.2% vs 13.9%, p<0.0001).

The reduction in myoma volume by comparison with the initial finding was low in both studies however (-12% and -17%) and did not differ significantly when using Ryeqo from the progression of myoma size under placebo. In contrast, total uterine volume decreased significantly more with Ryeqo than with placebo (-13.6% vs. 0.2% p<0.0001).

After completion of the studies, patients could be treated further in a 28-week open extension, in which all patients were given Ryeqo. Responders could then participate in a 12-month withdrawal study in which 1:1 randomisation was carried out for Ryeqo versus placebo. The effectiveness of the medical product was maintained in these two studies. A relapse in hypermenorrhoea quickly arose on the other hand (usually within the first 1-2 cycles) in patients who were randomised in the withdrawal study under placebo.

Pharmacokinetics

The pharmacokinetic parameters of relugolix, estradiol (E2), total estrone (E1) and norethisterone (NET) following oral administration of a single Ryeqo tablet to healthy postmenopausal women on an empty stomach are summarised in Table 1.

Table 1. Pharmacokinetic parameters of Relugolix, estradiol, total estrone and norethisterone following a single dose in postmenopausal women

	Relugolix	**Estradiol (E2)**	**Unconjugated Estrone (E1)**	**Norethisterone (NET)**
$AUC_{0-\infty}$ (ng*hr/mL or pg*hr/mL)	198.1 (111.6)	818.7 (334.4)	4‘126 (1‘650)	17.5 (8.46)
C_{max} (ng/mL or pg/mL)	25.99 (18.21)	27.95 (19.15)	188.4 (59.09)	3.57 (1.43)
T_{max} (hr)	2.00 (0.25, 5.00)	7.00 (0.25, 24.00)	6.00 (2.00, 12.00)	1.01 (0.50, 4.00)
Terminal $t_{1/2}$ (hr)	61.5 (13.2)	16.6 (7.67)	15.9 (6.52)	10.9 (3.05)

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity; C_{max} = maximum observed concentration; E1 = estrone; E2 =estradiol; NET = norethisterone; T_{max} = time to the maximum observed concentration; $t_{1/2}$ = half-life
*Note: Baseline-adjusted pharmacokinetic parameters for estradiol and unconjugated E1 are presented in this table. Arithmetic means and standard deviations are shown except for t_{max}, where the median and the range (minimum, maximum) are shown. $AUC_{0-\infty}$ is presented in ng*hr/mL for relugolix and NET and in pg*hr/mL for unconjugated E2 and unconjugated E1. C_{max} is presented in ng/mL for relugolix and NET and in pg/mL for unconjugated E2 and unconjugated E1.*

The pharmacokinetic parameters of relugolix, estradiol (E2), total estrone (E1) and norethisterone (NET) at steady state after once daily administration of Ryeqo for 6 weeks to healthy premenopausal women are summarised in Table 2.

Table 2. Pharmacokinetic parameters of Relugolix, estradiol, total estrone and norethisterone after multiple dose administration in premenopausal women

	Relugolix	Estradiol (E2)	Unconjugated Estrone (E1)	Norethisterone (NET)
AUC_{0-24} (ng*hr/mL or pg*hr/mL)	157 (94.7)	784 (262)	4‘450 (1‘980)	25.5 (11.4)
C_{max} (ng/mL or pg/mL)	26 (21.4)	46.8 (17.3)	303 (137)	5.21 (1.53)
T_{max} (hr)	3 (0.5, 6)	3 (0.50, 12.00)	4 (1, 8.08)	1 (1, 2)
Effective $t_{1/2}$ (hr)	~25	17.1 (4.03)	13.9 (4.14)	8.28 (1.87)

Abbreviations: AUC_{0-24} = area under the concentration-time curve during a dosing interval (24); C_{max} = maximum observed concentration; E1 = estrone; E2 =estradiol; NET = norethisterone; t_{max} = time to the maximum observed concentration.
*Note: Arithmetic means and standard deviations are shown except for t_{max}, where the median and the range (minimum, maximum) are shown. AUC_{0-24} is presented in ng*hr/mL for relugolix and NET and in pg*hr/mL for unconjugated E2 and unconjugated E1. C_{max} is presented in ng/mL for relugolix and NET and in pg/mL for unconjugated E2 and unconjugated E1. Effective half-life for relugolix is estimated from accumulation ratios based on AUC values after multiple-dose administration of relugolix at 40 mg.*

Absorption

Relugolix: The absorption of relugolix after oral administration is primarily mediated by the P-gp efflux transporter. After oral administration, relugolix is rapidly absorbed, reaching an initial peak by 0.25 hours post-dose followed by one or more subsequent absorption peaks through up to 12 hours post-dose. The absolute bioavailability of relugolix is 11.6%.

Estradiol: After oral administration of a single dose of Ryeqo in the fasted state, unconjugated estradiol concentrations increased slowly, with mean concentrations reaching peak concentrations at 8 hours post-dose.

Norethisterone acetate: After oral administration, NETA undergoes rapid biotransformation in the intestine and liver to norethisterone (NET). After oral administration of a single dose of Ryeqo in the fasted state, NET concentrations were initially quantifiable at 0.5 hours post-dose, increasing rapidly thereafter with mean concentrations reaching peak concentrations within 1 hour.

Influence of meals:

Administration with food reduced AUC and C_{max} of relugolix by 38% and 55%, respectively, compared with the fasted state. No clinically meaningful effects of concomitant food intake on the exposure to estradiol, estrogen metabolites or norethisterone were observed.

Distribution

Relugolix: Relugolix is 68% to 71% bound to human plasma proteins with a mean whole blood-to-plasma ratio of 0.78. Estradiol and norethisterone circulating in the blood bind to a similar extent to

sex hormone-binding globulin (SHBG; 36% to 37%) and to albumin (61%), while only approximately 1-2% are unbound. The value for apparent volume of distribution (Vz) of 19 x 10^3 L derived from the absolute bioavailability study after intravenous administration indicates that relugolix distributes widely into tissues.

Estradiol: The distribution of exogenous and endogenous estradiol is similar. Estrogens are widely distributed in the body and are generally present in higher concentrations in the sex hormone-specific target organs.

Metabolism

Relugolix: In vitro studies indicate that the primary CYP enzymes contributing to the overall hepatic oxidative metabolism of relugolix were CYP3A4/5 (45%) > CYP2C8 (37%) > CYP2C19 (< 1%) with the oxidative metabolites, metabolite-A and metabolite-B, formed by CYP3A4/5 and CYP2C8 respectively.

Estradiol: The metabolism of exogenous and endogenous estradiol is similar. Metabolism of estradiol occurs mainly in the liver and the gut but also in target organs and involves the formation of less active or inactive metabolites, including estrone, catecholestrogens and several estrogen sulphates and glucuronides. Estrogens are subject to an enterohepatic cycle and are mainly excreted in the urine in a biologically inactive form. Oxidation of estrone and estradiol involves cytochrome P450 enzymes, mainly CYP1A2, CYP1A2 (extra hepatic), CYP3A4, CYP3A5, as well as CYP1B1 and CYP2C9.

Norethisterone acetate: The most important metabolites of norethisterone are isomers of 5alpha-dihydro-norethisterone and tetrahydro-norethisterone, which are excreted mainly in the urine as sulphate or glucuronide conjugates.

Elimination

Relugolix:

After oral administration of a single dose of radiolabelled 80 mg/4.7 MBq [127 µCi] relugolix, 80.6% of the radioactive dose was retrieved in the faeces (4.2% as unaltered relugolix) and 4.1% in the urine (2.2% as unaltered relugolix).

Metabolite C, which is formed from intestinal microflora and reflects the non-resorbed active substance, is the primary metabolite excreted in the faeces (40.6% of the radioactive dose). No primary excreted metabolite was detected in the urine.

The mean terminal phase elimination half-life ($t_{1/2}$) of relugolix, estradiol and norethisterone following single-dose administration of the Ryeqo tablet are 61.5 hours, 16.6 hours and 10.9 hours respectively. Steady state of relugolix is reached after 12 to 13 days of once daily administration. The degree of accumulation of relugolix upon once daily administration is approximately 2-fold, reflecting an effective half-life of approximately 25 hours and supporting once daily administration of relugolix.

Estradiol/norethisterone acetate: The accumulation for E2 and NET upon once daily administration is reported to be 33-47%, although when co-administered with relugolix, a weak inducer of intestinal (pre-systemic) CYP3A-mediated metabolism, the accumulation for E2 is expected to be similar or slightly lower.

Linearity/Non-linearity

Relugolix is associated with greater-than-proportional increases in exposure with respect to dose, within the dose range of 1 to 80 mg, which is most pronounced at doses greater than 20 mg. This is thought to be related to the saturation of intestinal P-gp, resulting in an increase in oral bioavailability. The pharmacokinetics of relugolix upon once daily administration of 40 mg relugolix is time independent.

Kinetics of special patient groups

The pharmacokinetic parameters did not differ between Japanese and Caucasian healthy subjects after administering a single dose of relugolix, indicating that ethnicity has no impact on the pharmacokinetics of relugolix. Population PK analysis suggests that there are no clinically meaningful differences in exposure of relugolix based on age, race or ethnicity, weight, or BMI. As both estradiol and NETA are well-known components of hormonal combination products, no studies in special populations were conducted.

Liver dysfunction

After administration of a single 40-mg dose of relugolix to patients with mild hepatic impairment, the $AUC_{0-\infty}$ and C_{max} of relugolix were reduced by 31% and 24%, respectively, compared with healthy control subjects with normal hepatic function. After administration of a single 40-mg dose of relugolix to patients with moderate hepatic impairment, the $AUC_{0-\infty}$ and C_{max} of relugolix were decreased by 5% and increased by 1.2-fold, respectively, compared with healthy control subjects with normal hepatic function. No data are available in patients with severe liver dysfunction (see “Dosage/Administration” and “Contraindications”).

Kidney dysfunction

After administration of a single 40-mg dose of relugolix to patients with severe renal impairment, the $AUC_{0-\infty}$ and C_{max} of relugolix were increased by 1.5- and 1.1-fold, respectively, compared with healthy controls with normal renal function. After administration of a single 40-mg dose of relugolix to patients with moderate renal impairment, the exposure of $AUC_{0-\infty}$ and C_{max} were increased 1.5-fold compared with healthy controls with normal renal function (see “Dosage/Administration”). Mild renal impairment was not a relevant covariate for any of the pharmacokinetic parameters of relugolix in a population pharmacokinetic model.
The effect of terminal renal insufficiency on the pharmacokinetics of estradiol, norethisterone and relugolix has not been examined. The amount of relugolix, estradiol or norethisterone removed by haemodialysis is unknown.

Preclinical safety data

No preclinical studies have been performed with relugolix in combination with estradiol and NETA. However, studies with the individual active ingredients are available. Preclinical data based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential reveal no special hazard for humans. However, it should be noted that sex steroid hormones can promote the growth of certain hormone-dependent tissues and tumours.

Relugolix

Reproductive and developmental toxicity

Pregnant rabbits given oral relugolix during the organogenesis phase at an exposure level (AUC) comparable to that achieved in humans at the recommended dose of 40 mg/day experienced spontaneous abortion and loss of the entire litter. No effects on embryo-foetal development were observed in rats; however, relugolix interacts only weakly with the GnRH receptors in this species.
In male mice with human GnRH receptor knock-in, oral administration of relugolix reduced the weight of the prostate and seminal vesicles in doses of ≥ 3 mg/kg twice daily for 28 days, meaning that an effect on male fertility cannot be excluded.

Lactation

In lactating rats administered a single oral dose of 30 mg/kg radiolabelled relugolix on post-partum day 14, relugolix and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose decreasing to low levels by 48 hours post-dose. The majority of relugolix-derived radioactivity in milk consisted of unchanged relugolix.

Estradiol

Reproductive and developmental toxicity

In animal studies, estradiol or estradiol valerate showed an embryo-lethal effect even in relatively low doses and a dose-dependent reduction in fertility in rats. There were malformations of the genitourinary tract and a feminisation of male foetuses was observed.

Norethisterone acetate

Reproductive and developmental toxicity

Norethisterone, like other progestogens, caused virilisation of female foetuses in rats and monkeys. After high doses of norethisterone, embryo-lethal effects were observed.

Additional information

Effect of diagnostic methods

Sex hormones can influence the results of certain laboratory tests, such as the biochemical parameters of liver, thyroid, adrenal and kidney function, the plasma level of binding proteins (e.g. corticosteroid-binding globulin), the lipid/lipoprotein fractions, the parameters of the carbohydrate metabolism, as well as the coagulation and fibrinolysis parameters.

Shelf life

The medicine may only be used up to the date indicated after “EXP” on the package.

Special precautions for storage

Not to be stored above 30° C.
To be kept out of reach of children.

Instructions for use

Ryeqo tablets that are no longer required must not be disposed of in wastewater or household waste. The hormonally active ingredients in the tablet can have harmful effects if released into the aquatic environment. The tablets must be returned to the pharmacy or otherwise safely disposed of in accordance with local requirements. These measures will help protect the environment.

Marketing authorisation number

68495 (Swissmedic)

Packaging

Ryeqo tablets are packaged in high-density polyethylene (HDPE) bottles with desiccant and closed with an induction-sealed child-resistant polypropylene cap.
Box with 28 film-coated tablets (1 bottle of 28 film-coated tablets). [B]
Box with 84 film-coated tablets (3 bottles of 28 film-coated tablets). [B]

Marketing authorisation holder

Gedeon Richter Schweiz AG, 1027 Geneva

Information valid at

January 2023