swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

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:	extension of therapeutic indication approved on 30.04.2025

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.

Table of contents

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
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
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
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
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)

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Ryeqo is indicated in adult women before the onset of menopause for:

- Treatment of hypermenorrhoea associated with uterine fibroids
- Symptomatic treatment of endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis (see "Pharmacodynamics").

In patients with risk factors for osteoporosis or bone density loss, bone density should be measured using dual X-ray absorptiometry (DXA) before starting treatment with Ryeqo (see "Warnings and precautions"). A DXA scan is recommended after one year of treatment.

2.2.2 Approved indication

Ryeqo is indicated in adult women before the onset of menopause for:

- Treatment of fibroid associated hypermenorrhea
- Treatment of moderate to severe endometriosis-associated pain in women which have had an inadequate response to progestogen therapy or if progestogen therapy is not possible

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

Treatment with Ryeqo must be initiated and supervised by a doctor experienced in the diagnosis and treatment of uterine fibroids and/or endometriosis.

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	15 December 2023
Formal objection	29 December 2023
Response to formal objection	8 January 2024
Formal control completed	10 January 2024
List of Questions (LoQ)	8 April 2024
Response to LoQ	4 July 2024
Preliminary decision	9 September 2024
Response to preliminary decision	28 November 2024
Labelling corrections and/or other aspects	28 January 2025
Response to labelling corrections and/or other aspects	26 February 2025
Final decision	30 April 2025
Decision	approval

3 Medical context

After uterine fibroids, endometriosis is the most common benign gynaecological disorder in women of childbearing age. A complex oestrogen-dependent disease whose exact cause and pathophysiology are still unknown, endometriosis is a chronic condition that, despite severe symptoms, is often only diagnosed after a long delay (7-10 years) and requires decades of treatment. In most cases, the symptoms disappear after menopause.

The disease is defined by the occurrence of endometrium outside the uterine cavity. While it usually affects the peritoneum in the lesser pelvis or the ovaries, ectopic endometrial lesions can also occur elsewhere in the abdominal cavity and, in rare cases, at other sites such as the navel or even pleura or brain. If endometriotic foci are found not just superficially on the organs of the lesser pelvis, but also, for example, in the intestine or bladder, this form of the disease is defined as deep infiltrating endometriosis.

Although endometriosis is a benign condition, it does possess certain features of malignant diseases, particularly its invasive growth.

The prevalence of endometriosis in the total population of women during their fertile phase of life is usually stated as approx. 10%. A much higher figure of 20-50% is quoted for women with fertility problems.

Common symptoms are chronic pelvic pain, primarily in the form of dysmenorrhoea but also pain that is unrelated to menstruation (known as non-menstrual pelvic pain, NMPP), and dyspareunia. According to a publication by the American Society for Reproductive Medicine, endometriosis is identified as the cause in 70-90% of women affected by regular episodes of pelvic pain. Both visceral and somatic pain can be experienced in endometriosis. While severity of the symptoms is highly variable, asymptomatic cases are rare. Not infrequently, the pain can be severe enough to significantly disrupt the patients' daily activities and impair their quality of life. In addition, non-specific symptoms such as headache, back pain and nausea are frequently reported, particularly in cases where the endometriosis has been present for a long time. In up to 50% of cases, endometriosis is associated with reduced fertility.

The exact pathogenesis of endometriosis remains unclear; it is probably a multifactorial condition. Although retrograde menstruation has long been assumed to be the cause, it is now increasingly being questioned whether this actually constitutes the (only) significant pathogenetic factor, not least because endometriotic lesions outside the peritoneal cavity cannot be explained by retrograde menstruation.

Since ectopic endometrium is identical to intrauterine endometrium and expresses both oestrogen and progesterone receptors, it is subject to the same hormonal influences as intrauterine endometrium and is similarly sensitive to the influence of exogenous steroid hormones. This means that the growth of endometriotic lesions is stimulated by oestrogens. An overproduction of both oestrogens (with concurrently reduced inactivation) and prostaglandins and cytokines is found in the lesions themselves.

The hormonal sensitivity of the ectopic endometrium represents the approach for hormonal treatments aiming at the suppression of systemic or local oestrogens and/or inhibition of tissue proliferation and inflammation.

The cause of endometriosis-related pain can likewise only be explained by hypotheses. Growth factors and cytokines are thought to play a role, as are direct and indirect effects of menstruation-like bleeding from the lesions. Irritation of nerves in the pelvic floor (or even direct invasion by the endometriotic lesions) is also discussed.

No known causal treatment for endometriosis currently exists. Until a few years ago, surgical (usually laparoscopic) treatment with, if possible, complete removal of all lesions was considered to be the gold standard. However, there has been a paradigm shift in recent years, not least thanks to the availability of new drugs, and long-term drug treatment is increasingly viewed as a viable alternative,

particularly since surgical treatment on its own rarely solves the problem and recurrences are common. The general recommendation nowadays is to tailor the treatment to the individual patient's needs and life situation (severity of symptoms, wish to have children, etc.) (see e.g. the ESHRE Guideline published in 2022: https://www.eshre.eu/guideline/endometriosis).The drug treatment of endometriosis is based on hormone suppression and aims to induce amenorrhoea and avoid ovulatory cycles, and thereby inhibit the inflammatory process and halt the progression of the disease. The treatment focuses mainly on oestrogen inhibition, in order to achieve atrophy of the lesions, which usually leads to a reduction in pain. Combined oral contraceptives (COC; off label, usually in long cycles), progestogens or GnRH agonists are used for this purpose: in addition, selective progesterone receptor modulators (mifepristone, ulipristal acetate) are also being used experimentally. In Switzerland, the progestogen dienogest (Visanne®) is explicitly authorised for this indication.

All drug treatments employed to date have significant drawbacks. Although GnRH analogues have proved to be the most effective treatment so far, they lead to a pronounced hypoestrogenic state associated with a reduction in bone mineral density (BMD) and other relevant side effects. Moreover, following discontinuation of the treatment (which, due to its associated risks, is limited to a period of 3-6 months), the pain symptoms return in up to 50% of patients.

Non-steroidal anti-inflammatory drugs are also frequently used to manage pain (although their efficacy in this indication has only been poorly investigated in studies). In severe cases, opiates are also used.

In contrast to surgery, the medical alternatives represent a form of symptomatic treatment and have not hitherto shown any reduction in lesions. Nor is there any reliable evidence to indicate that medical treatment might have a positive effect on fertility. Furthermore, the efficacy on pain symptoms usually only lasts for the duration of treatment.

Overall, existing drug treatments must be viewed as limited, and there is a medical need for further treatment options.

4 Nonclinical aspects

The nonclinical documentation submitted with the initial marketing authorisation application supports the approval for the addition of the new indication “endometriosis-associated pain” for Ryeqo, film-coated tablets.

Based on the preliminary environmental risk assessments (ERAs) for the active substances, a risk to the aquatic compartment was identified based on the use of Ryeqo as indicated in the Information for Healthcare Professionals. The MAH has committed to conducting additional studies, with the respective reports and final ERAs to be submitted as a post-authorisation measure.

From a nonclinical perspective, there are no objections to the approval of the proposed extension of indication.

5 Clinical aspects

5.1 Clinical pharmacology

Special populations

The pharmacokinetics of relugolix in patients with endometriosis was investigated in a pop PK analysis including the data from several clinical studies, including the pivotal Phase 3 study in endometriosis patients, MVT-601-3101. This was the only addition to the existing relugolix pop PK dataset for myoma patients. No PK data were collected in the second Phase 3 study in endometriosis, MVT-601-3102.

The dataset included 1328 patients, of whom 376 were included in study MVT-601-3101. The mean body weight of the subjects was 68.9 kg (range 37.7 – 153 kg). The overall mean age of the subjects was 38.1 years (range 18.0 - 53.0 years). The subjects with endometriosis were slightly younger than the remaining subject (mean age 34.2 years versus 39.6 years), but the distribution of the remaining continuous covariates was comparable between both groups.

The majority of the subjects were White (43.2%) or Asian (35.2%) and had normal renal function (88.0%). The dataset included 157 (11.8%) of subjects with mild renal impairment, 2 (0.2%) subjects with moderate renal impairment and no subjects with severe renal impairment or ESRD. Most subjects (75.6%) in the overall dataset and all subjects from study MVT-601-3101 received 40 mg relugolix.

The observed relugolix plasma concentrations indicated no major pharmacokinetic differences between the newly added subjects with endometriosis and the previous population.

The existing relugolix pop PK model was a 2-compartment model with first-order absorption and elimination. It included the following covariate-relationships:

- Dose and Asian origin as covariates of F1
- Weight and Caucasian origin as covariates of CL/F

This model was applied to the updated dataset without any changes and with fixed parameters. It described the data of study MVT-601-3101 reasonably well. As control, the parameters were re-estimated for the updated dataset. The results were very similar to the previous analysis.

In summary, there were no relevant pharmacokinetic differences between subjects with endometriosis and the previous population, including healthy subject and subjects with myoma.

Interactions

The application included several references to several interaction studies. The results of the studies are summarised below.

Perpetrator	GMR (90% CI)
Erythromycin (P-gp inhibitor, moderate CYP3A4 inhibitor) (REL: 40 mg SD)	REL Cmax: 382.09 (293.71, 497.06) REL AUCinf: 406.31 (324.47, 508.79)
Erythromycin (P-gp inhibitor, moderate CYP3A4 inhibitor) (REL: 120 mg SD)	REL Cmax: 288.58 (197.92, 420.78) REL AUCinf: 352.98 (257.67, 483.54)

Azithromycin (weak P-gp Inhibitor, does not inhibit CYPs) (REL: 120 mg SD simultaneously)	REL Cmax: 162.16 (94.87, 277.18) REL AUCinf: 147.05 (103.65, 208.63)
Azithromycin (weak P-gp Inhibitor, does not inhibit CYPs) (REL: 120 mg SD 6 h prior to azithromycin)	REL Cmax: 131.05 (71.68, 239.59) REL AUCinf: 143.14 (97.00, 211.23)
Victim	**GMR (90% CI)**
Dabigatran (P-gp substrate) (REL: 120 mg SD)	DABI Cmax: 118.52 (89.98, 156.11) DABI AUCinf: 117.27 (91.49, 150.32)

Pharmacodynamics

MECHANISM OF ACTION AND PRIMARY PHARMACOLOGY

Relugolix produces a rapid and reversible, dose-dependent suppression of FSH and LH levels. The lower FSH concentrations suppress follicular growth, which in turn reduces oestrogen production by the follicles. Monotherapy with 40 mg Relugolix has been shown to lead to a near maximum inhibition of ovarian activity.

In the fixed combination contained in Ryeqo, the addition of estradiol as "add-back therapy" is designed to ensure that oestrogen levels are sufficient to minimise the risk of bone density loss and reduce oestrogen deficiency symptoms (particularly hot flushes).

As exogenous oestrogen intake is, in turn, associated with the risk of endometrial hyperplasia and endometrial cancer, the fixed combination also contains norethisterone acetate, which produces a downregulation of the oestrogen receptors in the uterus, thereby inhibiting the proliferative effect of the oestrogens.

The aim of the combination with add-back therapy is to enable it to be administered for a longer period thus offer an alternative to surgical treatments.

EXPOSURE EFFICACY/SAFETY RELATIONSHIP

EFFICACY

The relationship between relugolix exposures and efficacy was investigated for studies TAK-385/CCT-101 (phase 2) and MVT-601-3101. As different endpoints were used in the phase 2 and 3 studies, the data were analysed separately.

Phase 2

Study TAK-385/CCT-101 included a total of 487 patients. Of these, 99 received placebo, 82 leuprorelin and the remaining 306 patients received relugolix. The mean age in the three relugolix treatment groups (see below) was approximately 35 years (range 20 to 50 years). The mean body weight was approximately 55 kg (range 37.7 to 88.9 kg).

In study TAK-385/CCT-101, relugolix doses of 10 mg, 20 mg or 40 mg were administered. In this study, dysmenorrhoea and non-menstrual pelvic pain (NMPP) were assessed by a visual analogue scale (VAS).

The relationship between relugolix Ctrough,ss and dysmenorrhoea was appropriately described by an Emax model with a Hill coefficient. The exposure-response curve approached its maximum at 40 mg. No covariates were investigated.

Considering the substantial food effect of relugolix at doses ≤ 40 mg, simulations were done with an up to 50% reduction of relugolix Ctrough,ss after 40 mg. At 40 mg, there was a 94% (95% CI: -103%, -80%) reduction of the dysmenorrhoea VAS. A 50% reduction of Ctrough,ss resulted in a 79% reduction (95% CI: -94%, -62%).

The relationship between relugolix Ctrough,ss and NMPP was appropriately described by an Emax model without a Hill coefficient. The exposure-response curve approached its maximum at 40 mg. No covariates were investigated.

Considering the substantial food effect of relugolix at doses ≤ 40 mg, simulations were done with an up to 50% reduction of relugolix Ctrough,ss after 40 mg. At 40 mg, there was a 73% (95% CI: -82%, -66%) reduction of the NMPP VAS. A 50% reduction of Ctrough,ss resulted in a 59% reduction (95% CI: -69%, -51%).

Phase 3

The dataset included 635 patients, of whom 212 received placebo. The mean age of the patients was 34.2 years (range 18 to 49 years). Their mean body weight was 70 kg (range 43.8 kg to 155.6 kg). The majority (91.5%) of the patients was White.

In study MVT-601-3101, only 40 mg relugolix were administered. The two co-primary efficacy endpoints were defined as the reduction in the numerical rating scale (NRS) pain scores for dysmenorrhoea and NMPP over the Week 24 pain assessment period.

For both endpoints, no exposure-response relationship, but a difference to placebo was observed. This was more pronounced for dysmenorrhoea than for NMPP.

For both endpoints, baseline age, baseline estradiol, baseline dysmenorrhoea/NMPP score or race had no impact on the response rate. There was a trend of lower response rates in the third and fourth weight quartiles.

The data are in agreement with the phase 2 data and indicate that the plateau of the ER relationship is reached at 40 mg relugolix.

SAFETY

The model describing the relationship between E2 serum concentrations and change in BMD over time applied to the myoma data was applied to a dataset including the studies from the original analysis plus studies MVT-601-3101 and MVT-601-3102 in endometriosis. The model was applied without any modifications and without parameter re-estimation.

The dataset included 6816 BMD observations of 2435 patients. Of these, 3285 BMD measurements and 1136 patients came from studies MVT-601-3101 and MVT-601-3102.

The observed data indicated a decrease of BMD after relugolix monotherapy in Phase 2, which was counteracted by the ABT in Phase 3. The compensatory effect was smaller for delayed ABT.

The results with the endometriosis phase 3 studies included were qualitatively the same as for the previous analysis: The model described the central tendency of the relugolix data reasonably well, but it under-estimated their variability. The model estimated the percentage of subjects with BMD loss from baseline up to 3% reasonably well, but it over-estimated the percentage of subjects with BMD loss > 8%.

Simulations indicated stable BMD data over 36 months after ABT.

Scant data were available for the external qualification of the model, but more data than for the first analysis, and over 24 instead of only 12 months. The model described the central tendency of the data reasonably well, but in this case over-predicted their variability. The model still over-predicted the percentage of subjects with BMD loss >3% for up to 2 years, i.e. the estimates can be regarded as conservative. The observed BMD loss up to 2 years in studies MVT-601-3101 and MVT-601-3102 were small.

5.2 Dose finding and dose recommendation

No new dose-finding study was conducted. The dose investigated was congruent to that already approved for the treatment of hypermenorrhoea associated with uterine fibroids. Since the same pharmacodynamic objective is pursued in both cases, this approach was accepted.

In addition, an active-controlled study was conducted with relugolix monotherapy, in which doses of 10, 20 and 40 mg were compared with leuprorelin. Here, the 40 mg dose produced an effect comparable with that of the active comparator, which also supports the choice of the 40 mg dose for the Phase III studies.

5.3 Efficacy

To confirm efficacy, two pivotal studies, each lasting 24 weeks, were submitted (SPIRIT 1 and 2). A study with relugolix monotherapy is also available from the early development in Japan.

Since the two pivotal studies had an identical design, their data could be pooled. In addition, both studies were followed by a joint open-label 80-week extension phase in which all patients were treated with Ryeqo. Consequently, for those patients who were randomly assigned to active treatment, data are available for a treatment period of up to 104 weeks.

When assessing the data it should be noted that presumably unblinding occurred in some cases, as a result of the effect of relugolix on the bleeding pattern. 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 those taking placebo.

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, whereas in the other group patients received monotherapy with relugolix 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 the efficacy of the preparation 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 and, in particular, BMD loss, can be effectively attenuated by the addition of the add-back therapy.

Premenopausal patients aged 18-50 years who had been diagnosed with endometriosis within the last 10 years, e.g. during a laparoscopy or laparotomy, were included. The presence of moderate to severe pain (dysmenorrhoea and "non-menstrual pelvic pain", NMPP) had to be confirmed during a 5-week run-in phase, and severity of pain was measured on a VAS-like scale. Previous surgical treatment was not required as an inclusion criterion, but ultrasound diagnosis on its own was not sufficient.

Both treatment-naïve patients as well as patients already having received drug treatment were included. However, only limited data are available on the type and duration of medical treatment (and the question as to why it was discontinued). In addition, analgesic therapy on its own was also regarded as "previous medical treatment".

All patients with contraindications for oestrogen therapy were excluded. Other relevant exclusion criteria were chronic pelvic pain due to another cause (e.g. pelvic inflammatory disease, symptomatic ovarian cysts, etc.), patients with ≥4 previous operations to treat their endometriosis and any form of

surgical endometriosis treatment within the last 3 months. Also excluded were patients who had failed to respond at all to previous therapy with GnRH analogues or GnRH antagonists (as well as with depot MPA) (whereas a partial response was permitted). Other exclusion criteria were factors associated with an increased risk of BMD loss, particularly osteoporosis or other metabolic bone diseases, and all drugs with a possible influence on bone density.

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

As regards analgesics, rescue medication was defined in two stages. In the first stage, only ibuprofen was permitted in single doses of 200 mg (without specifying a maximum daily dose). The second stage involved opiates (tramadol, codeine or hydrocodone) as monotherapy or in fixed combinations with paracetamol. Fixed doses were defined for the opiates. The administration of rescue medication had to be documented in the patient diary.

Both pivotal studies as well as the open-label extension study each had two co-primary endpoints, namely

- the proportion of patients who experienced a reduction in dysmenorrhoea on the NRS of ≥ 2.8 points by week 24
- the proportion of patients who experienced a reduction in NMPP of ≥ 2.1 points by week 24

in each case without a simultaneous increase in analgesic use during the study. The two cut-off scores were determined using anchor-based analyses on the blinded pooled data of the two pivotal studies (taking into account approx. 200 patients per study) and can be accepted.

In addition, there were a total of seven key secondary endpoints also subjected to confirmatory testing, with a hierarchical approach to adjust for multiple testing. In addition to pain parameters, these key secondary endpoints also included a disease-specific health questionnaire and the change in analgesic use.

The comparison between the combination and placebo in the pivotal studies was subjected to confirmatory testing. For the comparison between the delayed group and placebo, descriptive analysis was performed. 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=638 patients were randomised in the SPIRIT 1 study, n=623 patients in the SPIRIT 2 study. The drop-out rates of 16% and 18%, respectively, were relatively low in both studies (and lower than assumed during determination of sample size).

Approx. 60% of patients entered the open-label extension phase after completing the pivotal studies.

The demographic characteristics were well balanced between the three treatment groups in both studies. Overall, mean age was approx. 34 years, and just under half of the patients were ≥35 years old. Mean BMI was approx. 26kg/m^2. Around 91% of the patients were white, followed by just under 6% who were black.

The baseline characteristics also showed only small differences between the treatment groups, which can be considered as not relevant. While the inclusion criteria allowed for a medical history of up to 10 years, the actual mean time since diagnosis was only approx. 4 years, with a median of just over 3 years. In a good two thirds of the patients, the diagnosis had only been confirmed within the last 5 years. This means that a high proportion of patients had been diagnosed with endometriosis only recently. However, due to the delay in diagnosis - several years in many cases - this does not rule out the possibility that the pain symptoms had been present for many years.

The most common sites of the endometriosis lesions were the ovaries, the pouch of Douglas and the peritoneum, which is in line with expectations. More than half of the patients were found to have an endometrioma, around 40% had ovarian adhesions and approx. 25% had tubal adhesions.

The baseline scores were 7.0-7.1 points (corresponding to severe pain) for dysmenorrhoea, 5.6-5.8 points (corresponding to moderate pain) for NMPP and 5.2-5.4 points for dyspareunia. The baseline score for the pain domain of EHP-30 was approx. 56 points, where a score of 55 points or more is considered to represent a significant impairment of daily activities.

A statistically significant advantage for Ryeqo over placebo was found for both co-primary endpoints in both pivotal studies. In the pooled data from both studies, the response rate for dysmenorrhoea was 74.8% for Ryeqo compared to just 28.6% for placebo. The corresponding rates for NMPP were 62.1% vs. 41.0%. The findings for the delayed group were largely comparable with those for the combination group. Various sensitivity analyses showed consistent results.

The findings for the key secondary endpoints were also consistent with those for the co-primary endpoints. The smallest (and in the SPIRIT 2 study only just statistically significant) effect was found for dyspareunia, which is generally known to respond poorly to treatment.

At the end of the studies, over 80% of the patients were opiate-free with the combination (compared to 71% with placebo). The proportion of patients who no longer required any analgesics was significantly higher, at 55%, with Ryeqo than the 27% with placebo.

The efficacy findings in the delayed group were essentially comparable with those in the combination group, indicating that, as had already been shown in the treatment of hypermenorrhoea associated with uterine fibroids, the efficacy of relugolix is not adversely affected to any relevant extent by the add-back therapy. As expected, the pharmacodynamic findings showed a smaller reduction in the E2 concentration in the combination group than in the delayed group.

Overall, in both studies, efficacy of the proposed combination was shown for the treatment of endometriosis-associated pain.

N=802 patients were enrolled in the open-label extension study, at the end of which the response rate was a good 85% for dysmenorrhoea and just under 74% for NMPP. Here too, the findings for the main secondary endpoints were consistent with those for both co-primary endpoints. Overall, the efficacy achieved in the pivotal studies was maintained during the extension phase up to a treatment period of 104 weeks.

Follow-up data after discontinuation of Ryeqo are not available for this indication.

5.4 Safety

A total of 56 studies, in which n=4587 patients or test subjects received at least one dose of relugolix or the proposed combination have been completed to date. 2652 patients were exposed for ≥6 months, 1569 patients for ≥12 months. 1381 patients or test subjects received at least one dose of the proposed combination, 912 for ≥6 months, 627 for ≥12 months and 212 for ≥24 months. Overall, the data pool can therefore be considered sufficient for the assessment of safety. The assessment of safety is based primarily on the pooled data from the three Phase III studies.

In the early studies with relugolix monotherapy, dose-dependence was observed for oestrogen deficiency symptoms. In the later studies, only the 40 mg dose was investigated.

In the data pool for the phase III studies, the safety profile corresponded to what would be expected during this kind of hormone therapy and had already been observed in the studies for hypermenorrhoea associated with uterine fibroids. Most of the adverse events (AEs) can be attributed to the pharmacological effects of relugolix or the add-back therapy. No new, unexpected safety signals were observed. Small differences (particularly in the incidence of the individual adverse effects) resulted from the different indications. For hypermenorrhoea associated with fibroids, for example, bleeding disorders were, by definition, present on enrolment in the study, and more bleeding disorders tended to be documented as AEs during the course of the study than in endometriosis.

The overall incidence of AEs was comparable between Ryeqo (76%) and placebo (70%). The incidence in the delayed group was 79%, and was higher particularly during the monotherapy phase compared to the combination.With the combination, the incidence of oestrogen deficiency symptoms was only marginally higher than with placebo.

The most common AEs with the combination were headache (33.0%), hot flushes (12.0%), nasopharyngitis (10.0%) and nausea (6.0%).

Serious adverse events (SAEs) were rare on the whole, with a total of 12 cases with the combination and 9 cases with placebo. In each study, most of the SAEs occurred in one individual case only.

Study discontinuations due to AEs were also rare on the whole, although at 4.5% they were slightly more frequent with the combination than with placebo (2.9%). They were most frequent in the delayed group, at 5.8%, with the majority occurring during the first 12 weeks (i.e. during monotherapy).

The safety profile during the open-label extension phase was comparable with that in the two pivotal studies. No additional safety signals were observed. Only the AE of vulvovaginal dryness, in the majority of cases, occurred only during the extension phase, which is in line with expectations, since this symptom generally develops only with prolonged oestrogen deficiency.

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

The data available to date from the Postmarketing Surveillance for the combination also show no new safety signals that would go beyond what is already known.

Overall, the safety profile of Ryeqo was largely comparable with that of 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 no more frequent, to any relevant extent, than with placebo. This supports the assumption that the oestrogen deficiency caused by the GnRH antagonist can be effectively attenuated by the add-back therapy.

The endometrial safety of the preparation in this indication was also confirmed by endometrial biopsies.

Special safety aspects

BMD loss, which can be expected with monotherapy with a GnRH antagonist, must be considered one of the most relevant risks of such treatment. Therefore, the effect of the combination on the long-term course of bone density was comprehensively investigated during the development programme.

The early studies with relugolix monotherapy and a dose of 40 mg showed a dose-dependent BMD loss that was comparable with that for the active comparator leuprorelin.

In the Phase III studies, regular DXA scans were performed to assess bone density. In order to enable a comparison with an untreated population, an observational study (for both indications) 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. Since they were consistent with the data already known from the indication of hypermenorrhoea associated with fibroids, they will not be described 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 the development of 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, this was designed to identify differences between monotherapy with relugolix (which is associated with a considerable risk of BMD loss) and the proposed combination, i.e. to confirm the benefit of the add-back therapy.

Up to week 12, a decrease in BMD compared to baseline was observed in both active treatment groups, but this was significantly greater in the delayed group (i.e. during relugolix monotherapy) than with the combination. The situation subsequently stabilised, although the absolute values were also lower in the longer term in the group with initial monotherapy than in the group that had received the add-back therapy from the outset. During the extension study, the BMD profile of the patients in the former placebo group corresponded to that observed with the combination treatment during the pivotal studies. In the combination group, however, BMD did not decrease any further and a plateau appears to have been reached. Overall, the BMD loss was less than 2% of the baseline value in the overwhelming majority of cases.

The comparison with the data from the observational study also indicates that the influence of relugolix on bone is mitigated by the add-back therapy.

In addition, follow-up data after discontinuation of Ryeqo were also collected. No relevant findings were identified. However, results are difficult to interpret due to a high rate of missing examinations. In the few cases with persistent BMD loss, this finding was attributed to other risk factors (like vitamin D deficiency, smoking or alcohol abuse).

Whether the relatively small changes in BMD under Ryeqo increase the risk for postmenopausal osteoporosis (and therefore fractures later on) can still not be assessed on the basis of the available data. The relatively high average BMI in both pivotal studies and the lack of data for underweight patients (who have an increased risk of osteoporosis) are critical points.

It should also be noted that, in addition to 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 findings on the return of menstruation after discontinuation of the preparation were also comparable with those in the indication already authorised. The time to onset of the first menstruation was slightly longer after the combination than after placebo. Overall however, the findings can be considered of no concern, and in most cases menstruation returned within two months.

5.5 Final clinical benefit risk assessment

Endometriosis is a common chronic gynaecological disease in women of childbearing age, a complex oestrogen-dependent illness whose exact cause and pathophysiology are still unknown. Endometriosis is defined by the occurrence of endometrium outside the uterine cavity (usually within the peritoneal space, but also in other remote sites).

The prevalence of endometriosis in the total population of women during their fertile phase of life is usually stated as approx. 10%, although a much higher figure of 20-50% is quoted for women with fertility problems.

Common symptoms of endometriosis are chronic pelvic pain, primarily in the form of dysmenorrhoea but also pain that is unrelated to menstruation (known as non-menstrual pelvic pain, NMPP), and dyspareunia. The intensity of the pain symptoms is highly variable, but asymptomatic courses are rare. In most cases, the symptoms disappear after menopause.

While in the past, surgical treatment (which is associated with a risk of complications and a high recurrence rate) used to be the gold standard, drug treatment is increasingly viewed as a viable alternative. As the ectopic endometrium is similarly sensitive to the influence of sex hormones as the intrauterine endometrium, hormonal treatment of the symptoms is possible and useful. However, no causal treatment exists.

Medical treatment is aimed at hormone suppression with the induction of amenorrhoea and avoidance of ovulatory cycles, thereby inhibiting the inflammatory process and halting the progression of the disease. The treatment focuses mainly on oestrogen inhibition, since the reduction of oestrogen levels is intended to cause atrophy of the lesions, which usually leads to a reduction in pain. The aim of all hormonal treatments is so-called therapeutic amenorrhoea.

The GnRH analogues used in this indication to date lead to functional ovariectomy and, therefore, to severe oestrogen deficiency symptoms and a risk of BMD loss. In contrast, the new, non-peptide GnRH antagonists, by combining them with an add-back therapy consisting of estradiol (E2) and norethisterone acetate (NETA), aim at achieving an E2 level in a range that ensures good efficacy on the one hand and mitigates the adverse effects on the other. Ryeqo contains the GnRH antagonist relugolix in a fixed combination with the add-back therapy.

Beneficial effects and respective uncertainties

Clinical pharmacology: There were no clinically relevant pharmacokinetic differences between the subjects with endometriosis from study MVT-601-3101 and the previous population consisting of healthy subjects and subjects with myomas.

The exposure-response analyses for efficacy indicated an Emax-type relationship between relugolix exposures and efficacy endpoints, which reached its plateau at exposures following the 40 mg dose.

Simulations with the exposure-response model relating serum oestradiol concentrations and BMD indicated stable BMD data for up to 2 years of relugolix plus ABT. However, this was the same model as in the primary Ryeqo application and the associated uncertainties were similar.

The efficacy of the proposed combination in treating endometriosis-associated pain was demonstrated in two pivotal studies with an identical design. The combination reduced dysmenorrhoea by around 75% and NMPP by around 50%. The observed effects were not only statistically significant compared to placebo, but can also be considered clinically relevant.

In an open-label extension, efficacy of the combination was maintained for up to two years.

Uncertainties regarding benefit

Since patients who had undergone hysterectomy or bilateral oophorectomy were excluded from the pivotal studies, no data are available for the treatment of recurrences of endometriosis after such surgery.

Interpretation of both the efficacy and safety data is somewhat limited by the fact that blinding was very 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 the active treatment.

Unfavourable effects and respective uncertainties

Clinical pharmacology: As in the primary Ryeqo application, simulations using the exposure-response models for efficacy indicated a substantial decrease of efficacy if Ryeqo is administered with a high fat high calorie meal.

The safety profile observed for the proposed combination largely corresponded to what would be expected during this kind of hormonal therapy and was already known from the studies in hypermenorrhoea associated with uterine fibroids. 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.

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 available can be considered as adequate for assessing short-term safety. There were no prohibitive concerns.

Uncertainties regarding risks

Uncertainties exist particularly with regard to the long-term safety of the product, since data are only available for a maximum treatment period of 24 months for a disease that can require decades of treatment.

In particular, the data on the course of BMD (regardless of the indication) have so far been limited to a maximum treatment period of 2 years. The available BMD data primarily 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 also rule out, with adequate certainty, a relevant BMD loss during treatment given for an unlimited period. In particular, it has to be expected that, although the average values for BMD do not give cause for concern, individual outliers may present with much greater BMD loss. Risk factors that might be used to identify such patients beforehand (so that they might then be denied the treatment or subjected to close BMD monitoring) are not known.

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.

Furthermore, the data on the course after discontinuation of treatment are still limited and not sufficient to prove that BMD completely normalises after the end of treatment. This is particularly critical because endometriosis is generally a long-term treatment, since any spontaneous improvement of symptoms is not expected to occur before menopause. In everyday clinical practice, in most cases, the patient will therefore require treatment over a period of more than 24 months.

However, these uncertainties are appropriately acknowledged in the Information for healthcare professionals.

Benefit-risk balance

Overall, the benefit-risk ratio of the proposed combination for the treatment of endometriosis-associated pain can be assessed as positive. However, long-term therapy requires monitoring of the BMD, as has already been specified in the indication of hypermenorrhoea associated with fibroids. DXA scans every two years are recommended. In perimenopausal patients, treatment should be temporarily interrupted every two years to ensure that the onset of menopause can be identified and the preparation then discontinued permanently in order to prevent patients from being exposed to any unnecessary risk of BMD loss.

Taking into account both the efficacy and safety of the available hormonal treatments, Swissmedic concluded that Ryeqo should not be used as first-line treatment, but only in patients who have had an inadequate response to previous progestogen therapy or in whom such therapy is not possible for other reasons.

6 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.

7 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.

▼ 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

Ryeqo is indicated in adult women before the onset of menopause for:

- Treatment of fibroid associated hypermenorrhea
- Treatment of moderate to severe endometriosis-associated pain in women which have had an inadequate response to progestogen therapy or if progestogen therapy is not possible

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

Treatment with Ryeqo must be initiated and supervised by a doctor experienced in the diagnosis and treatment of uterine fibroids and/or endometriosis.

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. For patients in the perimenopause a withdrawal attempt should be made every two years. Treatment should be discontinued after the onset of the menopause

For patients with myomatosus uterus the fibroid(s) size should be monitored according to standard clinical practice, but at least every two years as well.

Forgotten intake

If a tablet is missed out, the missed tablet 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.

Dose adjustment for use with P-glycoprotein (P-gp) inhibitors

The concomitant use of Ryeqo with oral P-gp inhibitorsis not recommended. If concomitant use with once or twice daily oral P-gp inhibitor (e.g. azyhtromycin) is unavoidable, take Ryeqo first, followed by administration of the P-gp inhibitor at least 6 hours thereafter and monitor patients more frequently for adverse reactions (see "Interactions").

Dose adjustment when used with combined P-gp and strong CYP3A inducers

The concomitant use of Ryeqo with combined P-gp and strong cytochrome P450 (CYP)3A inductors is not recommended.

Special dosage instructions

Children and young people

Ryeqo is not authorized for use in children and adolescents (see also “Warnings and precautions”). The safety and efficacy of Ryeqo have only been studied in adults. Ryeqo has no indication in girls before menarche.

Older patients

Ryeqo has only been studied in premenopausal patients. There is generally no indication after the 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 Gonadotropin-Releasing-Hormon-(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. After an initial, in most case clinically irrelevant decrease in BMD, a plateau was reached after 24 weeks of treatment, after that, the BMD remained largely stable (as measured up to 2 years). The average decrease in BMD during the first year of treatment with Ryeqo was 0.69%.
However, decreases in BMD by > 3% were observed in 21% of patients. Therefore, a DXA scan is recommended after the first 52 weeks of treatment to rule out the presence of clinically relevant BMD loss. If Ryeqo is used for a longer period of time, this examination should be repeated every two years. Depending on the extent of the BMD changes, a new individual risk-benefit assessment may be necessary.
Data on the influence of Ryeqo on BMD are only available for a duration of use of up to 2 years. It is not known whether long-term therapy (e.g. over 10 or more years) could lead to a greater loss of BMD.
Data on the course of BMD after discontinuation of Ryeqo are also only available for a maximum observation period of 12 months (see ‘Properties / Effects’). It is not known whether BMD recovers after discontinuation of therapy when used for more than two years. In particular, it is not known whether a reduction in BMD of the small magnitude as observed with Ryeqo could have an effect on the subsequent fracture risk (particularly in the postmenopausal period).
Patients with risk factors for osteoporosis or other metabolic bone diseases were excluded from the clinical studies, and co-medications that could affect BMD (like corticosteroids or anticonvulsants) were not allowed during the studies. A particularly careful risk-benefit assessment should therefore be conducted in patients with such risk factors (such as smoking, excessive alcohol consumption, positive family history of osteoporosis, previous low trauma fractures, metabolic bone disease or use of

medications known to be associated with a risk of decreased BMD). 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.
Due to the low number of underweight patients in the clinical trials, it is also not possible to say whether being underweight (especially in severe cases) could lead to increased BMD loss when using Ryeqo. The presence of anorexia nervosa was an exclusion criterion in the pivotal studies due to the increased risk of osteoporosis in these patients.
BMD loss is of particular importance in adolescents and young adults, as this is the crucial phase for bone growth. Limited data is available on the use of Ryeqo before the age of reaching final skeletal maturity and subsequently the potential risk of future osteoporotic fractures.
The use of Ryeqo in young adults before reaching final skeletal maturity (i.e. up to the age of 25) therefore requires a strict risk-benefit assessment and subsequently any risk factors (see above) should be taken into account before the use of Ryeqo.
As Ryeqo has only been studied in patients aged 18 years and over, no data are available that would allow an assessment of the risk of clinically relevant BMD loss in adolescents. Ryeqo must therefore not be used in adolescents <18 years of age due to the unknown long-term risks for the bone.

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 of the 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 for the treatment of fibroids, the amenorrhea rate was around 50% after 24 weeks of treatment and around 70% after 12 months of therapy and around 58% after 24 months of therapy. In Clinical studies on endometriosis, 65.2% of patients had amenorrhoea after 6 months of therapy, 76.6% after 12 months and 82.3% after 2 years.
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.

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 active ingredients.

Pharmacokineitc interactions

Influence of other drugs on the pharmacokinetics of relugolix

The effects of concomitantly applied medicinal products on relugolix exposure observed in clinical studies and resulting recommendations are summarised in Table 1.

Table 1: Effects of co-administered medicinal products on relugolix exposure ($AUC_{0-\infty}$, C_{max}) from clinical trials and resulting recommendations

Dosing scheme of the interacting medicinal product	Dosing scheme of Relugolix	Change in the $AUC_{0-\infty}$ of relugolix (Ratio of geometric mean values (%) and 90% confidence interval)	Change in the C_{max} of relugolix (Ratio of geometric mean values (%) and 90% confidence interval)	Recommendation

Erythromycin 500 mg QID, multiple doses	40 mg single dose	406.31 (324.47, 508.79)	382.09 (293.71, 497.06↑	The concomitant use of Ryeqo with erythromycin or other oral P-gp inhibitors is not recommended. If concomitant use with once- or twice-daily oral P-gp inhibitors (e.g. azithromycin) is unavoidable, take Ryeqo first, followed by administration of the P-gp inhibitor at least 6 hours thereafter ; monitor patients more frequentlyfor adverse events.
Azithromycin 500 mg single dose	120 mg single dose**	147.05 (103.65, 208.63)	162.16(94.87, 277.18)	
Azithromycin 500 mg single dose 6 hours after taking Relugolix		143.14 (97.00, 211.23)↑	131.05 (71.68, 239.59)↑	
Voriconazole 200 mg BID, multiple doses	40 mg single dose	151.15 (124.58, 183.39)	81.85 (42.61, 157.24)↑	No dose modifications recommended for coad-ministration of relugolix and CYP3A4 inhibitors devoid of P-gp inhibition.
Fluconazole 200 mg QD, multiple doses	40 mg single dose	118.85 (106.18, 133.03)↑	143.95 (113.01, 183.35)↑	
Atorvastatin 80 mg QD, multiple doses	40 mg single dose	94.76 (76.57, 117.27)	↓382.09 (293.71, 497.06	
Rifampicin 600 mg QD, multiple doses	40 mg single dose	45.4 (33.45, 61.59)↓	77.2 (55.98, 106.46)↓	Coadministration of Ryeqo with rifampicin or other combined P-gp and strong CYP3A4 induc-ersis not recommended as the efficacy of the relugolix component of Ryeqo could be re-duced.[12]

The effect on the 40 mg dose has not been studied but is likely to be higher.
AUC = area under curve; C_{max} = maximum concentration; QD = once daily; BID = twice daily; QID = four times daily.

Other examples of P-gp inhibitors are clarithromycin, gentamicin, tetracycline, ketoconazole, itracona-zole, carvedilol, verapamil, amiodarone, dronedarone, propafenone, quinidine, ranolazine, ciclosporin, protease inhibitors of the human immunodeficiency virus (HIV) or the hepatitis C virus (HCV) (e.g. ritonavir, telaprevir).

Examples of strong CYP3A4 and/or P-gp inducers are anticonvulsants (e.g. carbamazepine, topiramate, phenytoin, phenobarbital, primidone, oxcarbazepine, felbamate), anti-infectives (e.g. rifampicin, rifabutin, griseofulvin); St John's wort (Hypericum perfora-tum); bosentan and HIV or HCV protease inhibitors (e.g. ritonavir, boceprevir, telaprevir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz). Ritonavir, boceprevir, telaprevir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz)
Due to possible interactions with estradiol and/or norethisterone acetate (see below), long-term co-medication with CYP3A4 inducers is generally not recommended, regardless of whether they are also P-gp inducers.

Influence of other drugs on the pharmacokinetics of estradiol (E2) and norethisterone 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.

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

Table 2: Effects of Relugolix on the exposure (Cmax, AUC0-inf) of concomitantly administered drugs from clinical studies and resulting recommendations

Dosing scheme of the interacting medicinal product	**Relugolix-dosing scheme**	**Change in the $AUC_{0-\infty}$ (Ratio of geometric mean values (%) and 90% confidence interval)**	**Change in the C_{max} (Ratio of geometric mean values (%) and 90% confidence interval)**	**Recommendation**
Midazolam 5 mg single dose	40 mg QD till Steady State	82.34 (69.88, 97.02)	74.32 (60.62, 91.12)	No dose modification for CYP3A4-Substrate necessary.
Rosuvastatin 10 mg single dose	40 mg QD till Steady State	87.21 (74.23, 102.47)	76.53 (65.24, 89.77)	No dose modification for Rosuvastatin necessary. The influence of Relugolix on other BCRP substrates has not been investigated and the significance for other BCRP substrates is unknown.
Dabigatranetexilat 150 mg single dose	120 mg single dose	117.27 (91.49, 150.32)	118.52 (89.98, 156.11)	The effect of 40 mg relugolix on the ex-position of dabigatran is unknown. Caution should be exercised with P- gp substrates with a narrow therapeutic index and the corresponding product information should be consulted.

In vitro studies

Cytochrome P450 (CYP) enzymes

Relugolix is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4, nor an inducer of CYP1A2 or CYP2B6 at clinically relevant plasma concentrations.

Transporter systems

Relugolix is not an inhibitor of OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT2, MATE1, MATE2-K or BSEP at clinically relevant plasma concentrations.

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 see below) 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.

With simultaneous administration of lamotrigine together with combined hormonal contraceptives, but also with simultaneous use of hormone replacement therapy, a clinically relevant increase in lamotrigine clearance with a corresponding significant decrease in lamotrigine plasma levels was observed due to an induction of glucuronidation. Such a decrease in plasma concentrations may be associated with reduced seizure control. It is expected that oestrogen-progestogen combinations, such as those contained in Ryeqo, have a comparable interaction risk. When initiating therapy with Ryeqo, monitoring with possible adjustment of the lamotrigine dose is required. After discontinuation of Ryeqo, lamotrigine levels rise again, so that the patient must also be monitored in this phase and the lamotrigine dose reduced if necessary.

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

Women of childbearing age

Before starting treatment with Ryeqo, all hormonal contraceptives must be discontinued (see "Contraindications"). Non-hormonal contraceptive methods should be used during treatment and for at least 1 month after discontinuation of Ryeqo. The patient should be counselled regarding a suitable contraceptive method.

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=672 patients, who were given Ryeqo for the treatment of heavy bleeding due to uterine fibroids and endometriosis-associated pain in the four pivotal studies.
The most frequent adverse effects in patients treated for fibroids or endometriosis were headache (13%), hot flushes (10%) and uterine bleeding (5%).

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
Very common: Headache
Common: Vertigo
Uncommon: Migraine

Vascular disorders
Very common: Hot flushes (13%)
Common: Blood pressure changes

Disorders of the gastrointestinal tract
Common: Stomach pain, nausea
Uncommon: Dyspepsia

Skin and the subcutaneous tissue disorders
Common: Alopecia, hyperhidrosis

Uncommon:	Urticaria, angioedema

Skeletal muscle, connective tissue and bone disorders

Common:	Arthralgia
Uncommon:	Decrease in BMD by < 2% (not clinically relevant)
Rare:	Clinically relevant BMD loss (see “Warnings and precautions)

Reproductive system and breast disorders

Common:	Bleeding disorders (e.g. menorrhagia, metrorrhagia, irregular periods), abdominal pain, vulvovaginal dryness
Uncommon:	Breast tenderness, cystic changes in the breast expulsion of submucosal fibroids

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 induced by Relugolix (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 patients with fibroids at about 33 pg/mL and patients with endometriosis at about 38 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 extensions of the four 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) over an application period of up to 104 weeks

The effect of Ryeqo on BMD was evaluated in four pivotal studies (Liberty 1 and 2 in myoma-associated hypermenorrhoea, SPIRIT 1 and 2 in endometriosis) using DXA over a treatment period of up to 2 years. A total of 1279 women with uterine fibroids and endometriosis who completed the 24 week pivotal studies were also treated in extension study, where they were exposed to Ryeqo for a total of up to 12 months (endometriosis) or up to 24 months (fibroids)

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 extension studies.

By week 52, the average decrease in BMD at the lumbar spine from baseline was 0.69% in those originally receiving Ryeqo compared to 0.30% in those originally receiving placebo. By week 104, the average decrease in BMD was 0.40% in those originally receiving Ryeqo and 0.18% in those originally receiving placebo. The decrease in BMD was lower in patients taking Ryeqo than in those in the so-called ‘delayed’ group (see ‘Clinical efficacy’ below for a definition)
In addition, BMD measurements were carried out in an observational study on n=714 untreated patients of comparable age with uterine fibroids and endometriosis and were compared with those for patients treated with Ryeqo in the pivotal studies and their extension. During the 52-week observation period, there were minimal changes in BMD under Ryeqo compared to an age-matched cohort of premenopausal women with fibroids and endometriosis.

The course of BMD was also studied, in both indications over a period of 12 months after cessation of Ryeqo, Patients who had BMD loss at the lumbar spine from baseline at the time of follow-up had a complete or partial recovery of BMD by month 12.

Effects on endometrium

In the pivotal studies and their open extensions, endometrial biopsies were performed on a subgroup of patients after 24 and 52 weeks (and in some cases additionally after 104 weeks). Biopsis are available for n=267 patients after 52 weeks of treatment. Only one case of endometrial hyperplasia and no cases of endometrial carcinoma were observed.

Clinical efficacy

Fibroids-associated hypermenorrhoea

The efficacy of Ryeqo for the treatment of fibroids-associated hypermenorrhoea 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. 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 treatment groups 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.

Endometriosis-associated pain

The efficacy of Ryeqo in patients with endometriosis was investigated in two pivotal, multinational, randomised, double-blind, placebo-controlled studies with identical designs (SPIRIT 1 and 2) each lasting 24 weeks in a total of n=1261 patients aged 18 to 50 years. Patients were required to have endometriosis confirmed by direct visualisation during surgery (e.g. laparoscopy) and/or histological evidence, which was accompanied by moderate to severe pain. The pain intensity was assessed using an 11-point numerical rating scale (NRS).
The presence of moderate to severe menstrual-dependent and menstruation-independent pain had to be confirmed during a run-in phase (in which all patients received placebo) over at least two menstrual cycles.
Patients who had undergone hysterectomy and/or bilateral oophorectomy as well as those who had either undergone surgical treatment for endometriosis within the last 3 months or who had already undergone a total of 4 or more surgical treatments were excluded from participation in the study. A lack of response to previous treatment with GnRH analogues or GnRH antagonists was also considered an exclusion criterion.
Patients were randomised 1:1:1 to 3 treatment groups and received either relugolix 40 mg + estradiol 1 mg and norethisterone acetate 0.5 mg (E2/NETA) (Ryeqo) or placebo in the morning on an empty stomach 1 hour before breakfast 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 (so called “delayed” groups). The average age of the included patients was 34 years, and the mean body mass index was 26 kg/m^2. Approximately 91% of the women were white.
22% of the included patients had only received surgical pretreatment for their endometriosis, with the rest either receiving exclusively medical pre-treatment (including analgesics) or both surgical and medical therapy. Overall, 41% of the patients had previously received hormonal therapy for their endometriosis with 24% of the patients having previously been treated with progestins (most commonly

dienogest). 93% of patients were taking analgesics to treat endometriosis-associated pain at the beginning of the study, with opioids (also) used in 29% and 48% of patients in the two studies, respectively.

The two studies had two co-primary endpoints (defined as response rate) which were each analysed after 24 weeks and took into account the symptoms in the last 35 days of treatment: firstly the proportion of patients with a reduction in dysmenorrhoea of at least 2.8 points compared to the baseline value and secondly the proportion of patients with a reduction in the NRS score in non-menstrual abdominal of at least 2.1 points compared to the baseline value. In addition, the definition as responders of the analgesic consumption (ibuprofen or opioid) must not have increased compared to the run-in phase.
In addition, a total of 7 secondary endpoints were also tested confirmatory, including not only pain parameters but also a health questionnaire and the change in analgesic consumption.
In both studies, a statistically significantly higher response rate was found for both co-primary endpoints with Ryeqo compared to placebo ($p<0.0001$ in each case):
Dysmenorrhoea: 74.5% vs. 26.9% and 75.2% vs. 30.4% respectively
Menstruation-independent pain: 58.5% vs. 39.6% and 66.0% vs. 42.6% respectively
A clinically relevant reduction in pain intensity was already observed during the first 8-12 weeks of treatment.

The findings for the most relevant secondary endpoints were consistent in this regard.
The dyspareunia score on the NRS also decreased by 2.4 points by week 24 with Ryeqo, but only by 1.7 and 1.9 points with placebo ($p<0.05$). There was also a significantly greater improvement in the pain domain of the EHP-30 (endometriosis-specific health questionnaire) in both studies with Ryeqo compared to the baseline values than with placebo.
The proportion of patients who no longer required any analgesics at week 24 was also significantly higher (in study SPIRIT 1) with Ryeqo than with placebo (56.1% vs. 30.7%; $p<0.0001$). In addition, significantly fewer patients in the Ryeqo group still required opioid therapy at the end of the study than with placebo (16-18% vs. 29%; $p<0.0005$).

In addition, 56.7% of patients on Ryeqo developed amenorrhoea by week 24, compared to only 1.9% of patients on placebo. During the open-label extension, the proportion of amenorrhoeic patients increased further.

After completion of the two studies, the patients were able to continue treatment in a total of 80 weeks of open-label extension, in which all patients received Ryeqo. In this study, the efficacy of Ryeqo in reducing endometriosis-associated pain was maintained up to a treatment duration of 2 years.

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 4.

Table 4. 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*h/mL or pg*h/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} (h)	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 $t_{1/2}$ (h)	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*h/mL for relugolix and NET and in pg*h/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 5.

Table 5. 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*h/mL or pg*h/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} (h)	3 (0.5, 6)	3 (0.50, 12.00)	4 (1, 8.08)	1 (1, 2)

	Relugolix	**Estradiol (E2)**	**Unconjugated Estrone (E1)**	**Norethisterone (NET)**
Effective $t_{1/2}$ (h)	~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 h); 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*h/mL for relugolix and NET and in pg*h/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.*

The steady-state of Relugolix is reached after 12 to 13 days of once-daily administration. The degree of accumulation of Relugolix with once-daily administration is approximately 2-fold.

The accumulation for E2 and NET with once-daily administration is stated to be 33-47%. When used concomitantly with relugolix, a weak inducer of intestinal (presystemic) CYP3A-mediated metabolism, a similar or slightly lower accumulation for E2 is expected.

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 average maximum concentrations were reached 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. However no clinical relevant effects of concomitant food intake were observed on the exposure to estradiol, estrogen metabolites or norethisterone.

Distribution

Relugolix: Relugolix is 68% to 71% bound to human plasma proteins with a mean whole blood-to-plasma ratio of 0.78. 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 and Norethisterone: 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 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. 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.

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, following single-dose administration of the Ryeqo tablet are 61.5 hours. Based on the time to reach steady state and accumulation (see above), the effective half-life of Relugolix is approximately 25 hours.

Estradiol/norethisterone acetate: Estrogens are subject to an enterohepatic cycle and are mainly excreted in the urine in a biologically inactive form.
The metabolites of norethisterone acetate are mainly excreted in the urine as sulphate or glucuronide conjugates. The mean terminal elimination half-life (t1/2) of estradiol and norethisterone after administration of a single dose of the Ryeqo tablet is 16.6 hours and 10.9 hours respectively.

Linearity/Non-linearity

Relugolix exhibits a disproportionate increase in exposure relative 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.

Paediatric patients
The pharmacokinetics of Relugolix have been studied exclusively in adults.

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. Store the container in the outer carton to protect the contents from light and moisture.
To be kept out of reach of children.

Instructions for use

This medicinal product may present a hazard to the environment and in particular to the aquatic environment Unused medicinal product or waste materials derived from it must be disposed of in accordance with local regulations.
The patient must be made aware that the desiccant contained in the pack should not be swallowed.

Marketing authorisation number

68495 (Swissmedic)

Packaging

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]
Box with 28 film-coated tablets (2 blisters of 14 film-coated tablets). [B]

Box with 84 film-coated tablets (6 blisters of 14 film-coated tablets). [B]

Ryeqo tablets are packaged in high-density polyethylene (HDPE) bottles with desiccant and closed with an induction-sealed child-resistant polypropylene cap.
The blisters are made of PVC/aluminium and individually packed in a PET/aluminium/polyethylene film bag with desiccant.

Marketing authorisation holder

Gedeon Richter Schweiz AG, Geneva

Information valid at

January 2025