EMA/CHMP/640071/2022
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Procedure No. EMEA/H/C/005267/II/0009

Invented name: Ryeqo

International non-proprietary name: relugolix / estradiol / norethisterone acetate

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

| Status of this report and steps taken for the assessment | | | | |
|---|---|---|---|---|
| **Current step[1]** | **Description** | **Planned date** | **Actual Date** | **Need for discussion[2]** |
| ☐ | Start of procedure | 02 May 2022 | 02 May 2022 | ☐ |
| ☐ | CHMP Rapporteur Assessment Report | 07 Jun 2022 | 17 Jun 2022 | ☐ |
| ☐ | CHMP members comments | 20 Jun 2022 | 20 Jun 2022 | ☐ |
| ☐ | Updated CHMP Rapporteur Assessment Report | 23 Jun 2022 | n/a | ☐ |
| ☐ | Start of written procedure | 28 Jun 2022 | 28 Jun 2022 | ☐ |
| ☒ | Opinion | 30 Jun 2022 | 30 Jun 2022 | ☐ |

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

| Procedure resources | |
|---|---|
| Rapporteur: | Paula Boudewina van Hennik |
| EMA Product Lead | Name: Rachel Turner |
| Procedure Assistant | Name: Vanessa Moreno |

## Declarations

☒The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report, including in the Product Information, if any.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

# Table of contents

# 1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gedeon Richter Plc. submitted to the European Medicines Agency on 6 April 2022 an application for a variation.

The following changes were proposed:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I and IIIB |

Update of sections 5.3 and 6.6 of the SmPC based on final results from MVT-601-9030_Relugolix_ZEOGRT_Study (Rec); this is a fish, full life cycle test performed in the context of the Environmental Risk Assessment of relugolix.
The Package Leaflet is updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

# 2. Overall conclusion and impact on the benefit/risk balance

For the authorised product Ryeqo, a risk to the aquatic compartment is identified and the Applicant has accordingly proposed to add the appropriate risk phrases be communicated in the SmPC sections 5.3 and 6.6.

The Rapporteur agrees with the updated sentences in the sections 5.3 and 6.6 of the SmPC. The package leaflet is updated accordingly.

The ERA text in the EPAR of Ryeqo, including the summary table, will be updated to reflect the results of the ZEOGRT study.

The benefit-risk balance of Ryeqo, remains positive.

# 3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I and IIIB |

Update of sections 5.3 and 6.6 of the SmPC based on final results from MVT-601-9030_Relugolix_ZEOGRT_Study (Rec); this is a fish, full life cycle test performed in the context of the Environmental Risk Assessment of relugolix.
The Package Leaflet is updated accordingly.

☒is recommended for approval.

### *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

# 4. EPAR changes

### *Summary*

## 4.1.1. Section Ecotoxicity/environmental risk assessment

The Rapporteur notes that the result of the ZEOGRT study was not available at the time Ryeqo was authorised. For this already authorised product, a risk to the aquatic compartment is now identified as well. The text in the EPAR of Ryeqo, including the summary table, will be updated to reflect the results of the ZEOGRT study and the identified risk.

*Conclusions on studies for relugolix*

Relugolix is not PBT, nor vPvB. A risk to the aquatic compartment was identified.

No risk was identified for micro-organisms in the sewage treatment plant (STP), for the groundwater compartment and for the sediment compartment. A risk assessment for the terrestrial compartment was not triggered.

**Summary of main study results**

| | | | |
|---|---|---|---|
| **Substance (INN/Invented Name):** relugolix | | | |
| **CAS-number (if available):** 737789-87-6 | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD107 | log $D_{ow}$ -0.57, 0.85 and 2.7 at pH 5, 7 and 9 | Potential PBT: N |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |
| Bioaccumulation | log $D_{ow}$ | -0.57 at pH 5.1-5.2<br>0.85 at pH 7.1<br>2.7 at pH 9.1 | not B |
| Persistence | ready biodegradability | not ready | |
| | DegT50 parent | $DT_{50,\ water}$ = 3.2/11 d (l/l)<br>$DT_{50,\ sediment}$ = 72/176 d (l/l)<br>$DT_{50,\ system}$ = 70/148 d (l/l) | l=lake. $DT_{50}$ values corrected to 12°C.<br>Conclusion: P |
| | DegT50 metabolites | TP1: $DT_{50,\ system}$ = 17 d (l)<br>TP5: $DT_{50,\ system}$ = 129d (l) | Conclusion: not P<br>Conclusion: P |
| Toxicity | EC10 algae<br>NOEC crustacea<br>NOEC fish | 2.1 mg/L<br>⩾2.5 mg/L<br><0.32 µg/L*<br>EC10 0.103 | T |
| | CMR | not investigated | potentially T |
| **PBT-statement:** | relugolix is considered to be not PBT nor vPvB | | |
| ***Phase I*** | | | |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| $PEC_{surface\ water\ (refined)}$ | 2.66 | µg/L | > 0.01 threshold (Y) |
| Other concerns (e.g. chemical class) | potential reproductive effects on vertebrates and/or lower animals. Action limit does not apply. | | |
| ***Phase II Physical-chemical properties and fate*** | | | |

| Study type | Test protocol | Results | | | Remarks |
|---|---|---|---|---|---|
| Adsorption-Desorption | OECD 106 | $K_{oc\ sludge}$ 353, 233 L/kg<br>$K_{oc\ soil}$ 8781, 28346, 289871 L/kg | | | |
| Ready Biodegradability Test | OECD 301B | not readily biodegradable | | | |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | $DT_{50,\ water}$ = 1.5/5.3 d (l/l)<br>$DT_{50,\ sediment}$ = 34/83 d (l/l)<br>$DT_{50,\ system}$ = 33/70 d (l/l)<br>% shifting to sediment = 9% and 26% | | | l=lake; $DT_{50}$ values at 20°C; Significant shifting to sediment observed. |
| ***Phase IIa Effect studies*** | | | | | |
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/*R. subcapitata* | OECD 201 | EC10 | 2.1 | mg/L | growth rate |
| *Daphnia* sp. Reproduction Test | OECD 211 | NOEC | ≥2.5 | mg/L | reproduction, growth, mortality |
| Fish, Zebrafish extended one generation reproduction test (ZEOGRT) / *Danio rerio* | - | NOEC<br>EC10 | <0.32*<br>0.103** | µg/L | F2, hatching |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | NOEC<br>EC10 | ≥1000<br>>1000 | mg/L | respiration |
| ***Phase IIb Studies*** | | | | | |
| Sediment dwelling organism | OECD 218 | NOEC | 1253 | mg / $kg_{dw}$ | development; normalised to 10% o.c. |

* 18% effect was observed at the lowest test concentration of 0.32 µg/L (mean measured value), a NOEC cannot be derived.
** The EC10 is a factor of 3 below the lowest test concentration.

For more information, please refer to the Summary of Product Characteristics.

# Annex: Rapporteur’s assessment comments on the type II variation

# 5. Non-clinical aspects - Environmental Risk Assessment

## *5.1. Summary of the Applicant's response*

This non-clinical overview addendum is submitted in connection with the completion of PAM REC no.2 as listed in the letter of Recommendations of 19 May 2021: ERA Relugolix: The applicant should submit a fish, full life cycle test conducted as per the adapted test protocol, and updated ERA.

For the study report of the fish full life-cycle test reference is made to M1.6 of this submission (M1.6 MVT-601-9030). A critical assessment of the study has been included in the updated ERA which is also part of M1.6 (M1.6 MVT-601-9038_Relugolix ERA). This is in line with the approach taken for all previously submitted ERA study reports.

## *5.2. Assessment of the ZEOGRT study (MVT-601-9030)*

The report for the Zebrafish Extended One-Generation Reproduction Test (ZEOGRT) study with relugolix was finalized on 12 Aug 2021 and the Applicant has provided a copy of the final study report. The ZEOGRT study has been assessed previously during the Orgovyx procedure (EMEA/H/C/005353/0000) and a copy of the assessment is included below.

The assessor confirms the submission of the requested study. The study has been summarised below and considered acceptable.

**Effect on Fish - Chronic toxicity**

| Substance | Species | Method | T [°C] | pH | Total hardness [mmol/L] | Duration [days] | Criterion | Endpoint | Value [µg/L] | Ri |
|---|---|---|---|---|---|---|---|---|---|---|
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | 21 | NOEC | F0 Wet weight ♂ | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | 21 | NOEC | F0 Wet weight ♀ | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | 21 | NOEC | F0 body length ♂ | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | 21 | NOEC | F0 body length ♀ | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | 21 | NOEC | F0 fecundity | 1.02 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | 21 | NOEC | F0 fertilisation rate | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | 21 | NOEC | F0, OVA-histo. | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | 21 | NOEC | F0, testi-histo | 0.32 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | 21 | NOEC | F0 VTG ♂ | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | 21 | NOEC | F0 VTG ♀ | 3.24 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | 21 | NOEC | F0 E2 | 3.24 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | 21 | NOEC | F0 11-KT | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1,5 | NOEC | F1, hatching | 1.02 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 35 | NOEC | survival | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 35 | NOEC | body length | 1.02 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 63 | NOEC | survival | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 24.5-26.0 | 7.2-7.9 | 0.9-1.2 | F1, 63 | NOEC | body length | 9.91 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 60 | NOEC | Time to 1st spawning | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 119 | NOEC | F1 fecundity | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 119 | NOEC | F1 fertilisation rate | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 133 | NOEC | survival | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 133 | NOEC | body length | 9.91 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 133 | NOEC | body weight | 9.91 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 133 | NOEC | Sex ratio | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 133 | NOEC | F1 VTG ♂ | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 133 | NOEC | F1 VTG ♀ | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 133 | NOEC | F1 E2 | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 133 | NOEC | F1 11-KT | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F1, 133 | NOEC | F1 histo. ♂,♀ | 35 | 1 |
| Relugolix | *Danio rerio* | FT | 26.3-26.6 | 7.89-8.11 | 0.9-1.2 | F2, 4 | EC10 | F2, hatching | 0.16[a] | 2 |

Days in F1 and F2 are based on "days post fertilization"; FT=flow-through.
a The EC10 is below the lowest test concentration.

**Reference**
Ellebrecht, E. 2021. Zebrafish (Dania rerio) Extended one generation reproduction test (ZEOGRT), Flow through conditions Test item: Relugolix. Schmallenberg, Germany. Report number MYO-001/4-49/A

**Guideline**
none

**Description**
A GLP compliant chronic zebrafish (*Danio rerio*) study was performed with nominal relugolix (Batch No.: 1813481; purity: 99.4%) concentrations of 0.32, 1.00, 3.20, 10.0, and 32.0 µg/L and an untreated control in four replicates each under flow through conditions. A primary methanoic stock solution was prepared by adding an appropriate amount of test item. A small amount of the methanoic stock was transferred to a clean glass bottle onto the inner glass surface. After complete evaporation of the solvent, the bottles were filled with dilution water. The glass bottle was placed on a magnetic stirrer and stirred at least overnight. An aliquot ofthis aqueous stock solution for each test concentration was filled up to its final volume with dilution water. These solutions served as application solutions in the flow-through device. To achieve the final concentration in the test vessels, the application solutions was mixed with dilution water in adequate volumes via the dosing pumps. Prior to the test start, 5 male and 5 female spawning fish per replicate were held under test conditions for at least 14 days to record spawning success during the pre-treatment phase. When fish in all test vessels achieved daily spawning of at least 10 eggs per female and fertilization rates equal to or above 80%, the exposure phase was started. Parental fish (F0-generation) were exposed for three weeks. In week 4, fertilized eggs were kept to prepare a F1-generation. The F1 fish were monitored over 5 weeks during their early life stage phase, followed by a juvenile growth phase for a further 4 weeks. After reaching sexual maturity, start of reproduction and spawning success were observed and recorded over a period of approx. 8 weeks. An F2-generation was prepared by keeping eggs from F1 parental animals, and eggs were exposed until hatch. The total duration of the test was approx. 20 - 22 weeks, until hatch of F2 animals. During the test, dissolved oxygen, pH and water temperature were measured in regular intervals in all test vessels of treatment groups and controls. Water temperature was measured at least at each working day. Additionally, water temperature was measured continuously in two control vessels. Oxygen and pH were measured at least twice a week ineach test vessel. The concentrations of relugolix were assessed by chemical analysis using LC-MS/MS. The LOQ was determined to be 0.10 µg/L. At test start, samples were taken from all test vessels inorder to confirm correct dosing. During the course of the study, samples were taken on a weekly basis, alternating between the vessels that were served by the same dosage pump. At test end, samples of all vessels were analysed. The fish were fed once daily ad libitum with commercially available flake food and brine shrimp nauplii *(Artemia salina).*Blood samples (by cardiac puncture) were taken for analysis of Vitellogenin (VTG), E2 and 11-keto testosterone (11-kT) levels. The measurement of VTG, E2 and 11-KT was conducted with ELISA methods. The body of each parental fish was fixed for histopathological evaluation of the gonads and sex determination.

**Results**
The measured concentrations did not remain within 80-120% of the nominal concentration, with single measured values ranging from 65.0 % to 142 % of the nominal values. The mean measured concentrations per treatment during the course of the study, however, were between 99.1 % (at 10.0 µg relugolix/L) and 109 % (at 32.0 µg relugolix/L) of the nominal concentrations. The mean measured concentrations were calculated to be 0.32 µg/L; 1.02 µg/L; 3.24 µg/L; 9.91 µg/L; and 35.0 µg/L, which were used for expressing the effect concentrations. A significant difference between control and treatments in fecundity was observed in the top three concentrations starting at a concentration of 3.24 µg/L. Fertilisation rate was 92.1% in the controls and 78, 80, 77, 79 and 81% in treatments with 0.32

µg/L; 1.02 µg/L; 3.24 µg/L; 9.91 µg/L; and 35.0 µg/L, respectively. A significant difference in fertilization rate was observed only for the treatment at the concentration of 3.24 µg/L. This effect was not concentration dependent and the NOEC was considered to be 35 µg/L for fertilization rate. No difference was observed for body weight and length in F0. An increase in female plasma VTG and E2 levels was observed at the concentrations of 9.91 and 35 µg/. No difference in plasma VTG and 11-KT was observed between control and treatment groups for males. Hatch in F1 was completed at 5 dpf. A significant difference in hatching success was observed at three high concentrations of 3.24 µg/L; 9.91 µg/L; and 35.0 µg/L. No differences for post hatch survival were found until 21, 35, 63, 133 dpf in F1 between the control and the treatment groups. An increase in body length at day 35 was observed at concentrations of ≥ 3.24 µg/L. It is suggested that this growth effect may also result from a reduced number of larvae at higher concentrations. At 63 dpf, an increase in body length was found at the highest test concentration of 35.0 µg/L. At the termination of F1 generation, the body length and wet weight were determined separately for males and females. An increase in body weight and length for both males and females was observed at the highest test concentration of 35.0 µg/L. First spawning was recorded within a 5-day span between 57 and 62 dpf in all vessels. No difference in F1 fecundity, fertilization rate and sex ratio was observed. No difference in plasma VTG, 11-KT and E2 was observed between control and treatment groups. The mean hatching success in the controls of F2 was 91.3%, which is comparable to that of F1. A concentration dependent, significant (Williams multiple t-test, $p \leq 0.05$) decrease in the mean hatching success was observed in all treatment groups: 75%, 56%, 50%, 65% and 10% hatching at 0.32, 1.0, 3.2, 9.1 and 35 µg/L, respectively. A NOEC cannot be determined statistically as the lowest test concentration shows effect. NOEC, determined as NOEC=LOEC/2 = 0.16 µg/L. The EC10 for F2 hatching was calculated to be 0.16 µg/L.

**Remarks**

The applicant derived a 'NOEC' using the REACH R.10 guidance rule of NOEC = LOEC/2 for endpoints showing a LOEC >10 and <20% effect. The LOEC meets this criterion. The EC10 estimate equals this estimate and can be used for the risk assessment. The finding that the lowest test concentration already shows 18% effect and the EC10 needs to be extrapolated makes this result less reliable, Ri = 2. The remainder of the study is considered reliable and meets validity criteria. Results are used for conclusions, Ri=1.

**Conclusion**

The ZEOGRT study is considered acceptable and the data are used to update the ERA.

## *5.3. Updated ERA*

With respect to the ERA assessment for relugolix, the Applicant has committed to providing an updated ERA for relugolix. Because relugolix is an active substance in multiple medicinal products (ie, Orgovyx (EMEA/H/C/005353/0000) and Ryeqo), used across multiple indications (120 mg for advanced prostate cancer or 40 mg [in combination with oestradiol 1 mg and norethisterone acetate 0.5 mg] approved for uterine fibroids and under development for endometriosis), a single ERA for the combined use of relugolix was requested and has been provided previously with the Applicant’s responses to Day 180 questions of the Orgovyx procedure (EMEA/H/C/005353/0000). The current updated report ((MVT-601-9038, version 3, dated 03-01-2022)), which contains the final environmental risk assessment for relugolix including results from the ZEOGRT study, was already assessed during this Orgovyx procedure and an updated copy of the previous assessment is included below.

**Assessment of the Applicant's Response (Orgovyx procedure)**

Per recommendations, the final ERA for relugolix was updated to include a table of all relugolix-containing medicinal products (ie, Ryeqo and Orgovyx) describing all approved, pending, and planned indications for each product as well as the active pharmaceutical ingredients present in each product. Additionally, PECsurfacewater was calculated for each product and approved and planned indication with relugolix use for 1) each individual indication alone, 2) the total combined use of Ryeqo for treatment of uterine fibroids or endometriosis, and 3) the total combined use across all intended indications for Ryeqo and Orgovyx. Therefore, PEC/PNEC ratios were assessed for each indication alone and combined to evaluate the risk to the aquatic environment.

The Applicant has updated the ERA (January 2022, report MVT-601-9038) with the outcome of the ZEOGRT (zebrafish extended one generation reproduction test) study as requested. The Applicant has not taken into account the Orgovyx Day 150 assessment, in which it was clarified that the REACH guidance for NOEC derivation (NOEC = LOEC/2 when LOEC > 10 and < 20% effect) is not applicable in EMA ERA framework. The NOEC derived for that endpoint is unbounded: <0.32 µg/L. The Rapporteur put forward an EC10 value that can be used in the risk assessment. The EC10 value is indicative since effects were observed below the lowest test concentration and the EC10 itself was therefore extrapolated below the lowest test concentration.

In the updated ERA, the Applicant included clear tables with the three indications, indicating which product+indication is authorised, under review or planned to be authorised. The table also contained the respective refined $F_{pen}$ values for the indications and the PECs, PNECs and risk quotients per indication and per product (Orgovyx and Ryeqo).

A summary table is provided below, including the critical risk quotients, i.e. for the aquatic compartment. Risk quotients provided are based on the PNECs for the aquatic compartment, derived using the lowest endpoint obtained for all tested aquatic species, which was obtained for F2 hatching of fish in the ZEOGRT and application of an assessment factor of 10. The indicative EC10 of 0.103 µg/L (see above) is used, yielding an indicative PNEC of 0.0103 µg/L.

The risk quotients relevant for the already authorised products Ryeqo and Orgovyx are displayed below: the RQ for the Ryeqo and previously assessed Orgovyx application are 95 and 8.2, respectively, and the summed PEC of the Ryeqo plus Orgovyx amount to 103. The Applicants' RQs were 61, 5.3 and 67, respectively.

| Product+indication | Status | single PEC (µg/L) | RQ | Σ PEC (µg/L) | RQ |
|---|---|---|---|---|---|
| Ryeqo; Heavy menstrual bleeding associated with uterine fibroids | authorised | 0.98 | 95 | - | - |
| Orgovyx; Advanced prostate cancer | authorised | 0.084 | 8.2 | 1.06 | 103 |
| Ryeqo; Endometriosis-associated pain | envisaged | 1.6 | 155 | 2.66 | 259 |

A risk to the aquatic compartment is identified based on the use of Ryeqo and Orgovyx as indicated in the SmPC.

The Applicant has updated the ERA to also include the envisaged marketing authorisation of Ryeqo with the additional indication 'endometriosis-associated pain'.

**Conclusion for Ryeqo**

A risk to the aquatic compartment is identified based on the use of Ryeqo as indicated in the SmPC. The identified risk for relugolix upon the use of Ryeqo should be communicated in the EPAR as well as in the SmPC sections 5.3 and 6.6.

### *5.4. Discussion*

For the authorised product Ryeqo, a risk to the aquatic compartment is identified and the Applicant has accordingly proposed to add the appropriate risk phrases be communicated in the SmPC sections 5.3 and 6.6.

The Rapporteur agrees with the, using track changes, updated sentences in the sections 5.3 and 6.6 of the SmPC and the revision to the package leaflet.

The ERA text in the EPAR of Ryeqo, including the summary table, will be updated to reflect the results of the ZEOGRT study.

## 6. Changes to the Product Information

As a result of this variation, due to the outcome of the update ERA, section(s) 5.3 and 6.6 of the SmPC are being updated to include the identified risk of relugolix for the aquatic compartment. The package leaflet is updated accordingly.