Public Assessment Report

Decentralised Procedure

Progesterone 400 mg pessaries

Procedure No: UK/H/6113/001/DC

UK Licence No: PL 30306/0693

Actavis Group PTC ehf
LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Progesterone 400 mg pessaries (PL 30306/0693; UK/H/6113/001/DC). It explains how Progesterone 400 mg pessaries were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use this product.

The product will be referred to as Progesterone pessaries throughout the remainder of this PAR.

For practical information about using Progesterone pessaries, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Progesterone pessaries and what are they used for?
Progesterone pessaries contain progesterone which is a natural, female sex hormone, produced in the body.

Progesterone pessaries are for women who need extra progesterone while undergoing treatment in an Assisted Reproductive Technology (ART) programme.

How do Progesterone pessaries work?
Progesterone acts on the lining of the womb helping the woman to become and to stay pregnant when being treated for infertility.

Each pessary contains 400 mg of progesterone.

How are Progesterone pessaries used?
The recommended dose is 400 mg twice a day by vaginal insertion. The administration of the Progesterone pessary should start on the day of egg retrieval. The administration of Progesterone should be continued for 38 days if pregnancy has been confirmed.

What benefits of Progesterone pessaries have been shown in studies?
The clinical data is the same as that submitted for an existing product, Cyclogest 400mg. The clinical data consisted of two studies, the first showed the correct dosage to be taken and the second showed that the product was not clinically poorer than a similar product.

In addition, the company has provided data from the published literature on progesterone use.

What are the possible side effects of Progesterone pessaries?
For information about side effects that may occur when using Progesterone pessaries, please refer to Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

Why are Progesterone pessaries approved?
No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Progesterone pessaries outweigh the identified risks, and the grant of a Marketing Authorisation was recommended.
What measures are being taken to ensure the safe and effective use of Progesterone pessaries?
A Risk Management Plan (RMP) has been developed to ensure that Progesterone pessaries are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Progesterone pessaries
Following the completion of a decentralised procedure, a Marketing Authorisation was granted in the UK on 16 January 2017.

The full PAR for Progesterone pessaries follows this summary.

For more information about treatment with Progesterone pessaries, read the PIL or contact your doctor or pharmacist.

This summary was last updated in March 2017.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th></th>
<th>Introduction</th>
<th>Page 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>Page 7</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>Page 8</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>Page 9</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>Page 19</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and recommendation</td>
<td>Page 19</td>
</tr>
<tr>
<td></td>
<td>Annex 1 - Table of content of the PAR update for MRP and DCP</td>
<td>Page 24</td>
</tr>
</tbody>
</table>
I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Progesterone pessaries (PL 30306/0693; UK/H/6113/001/DC) could be approved.

This is a decentralised application submitted in accordance with Article 8(3) of Directive 2001/83/EC, as amended, for a known active substance. This application is based on the assessment of an existing product, Cyclogest 400mg, which was granted a Market Authorisation in the UK to LD Collings and Company Limited on 08 February 1977 (PL 02343/0002). Following a change of Marketing Authorisation Holder that was granted on 01 September 2000, the current Marketing Authorisation holder is Actavis UK Limited (PL 00142/0508).

Cyclogest 200 and 400mg pessaries have been marketed in the UK for the treatment of pre-menstrual syndrome (including pre-menstrual tension and depression) and for the treatment of puerperal depression for a long time. A variation to add a new therapeutic indication ‘luteal phase support as part of an Assisted Reproductive Technology (ART) treatment for women’ was recently concluded for Cyclogest in November 2015.

The indications of this product are limited to the indications which were originally granted for Cyclogest 400mg in November 2015, namely:

- luteal phase support as part of an Assisted Reproductive Technology (ART) treatment for women

Progesterone is a natural hormone indicated for a number of different women’s health conditions and is available in different pharmaceutical forms.

The United Kingdom acted as RMS and Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Croatia, Hungary, Ireland, Iceland, Italy, Luxembourg, Latvia, Malta, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, and Slovakia were CMSs.

Assisted reproductive techniques (ART), as defined by ICMART (International Society of Monitoring Assisted Reproduction) and World Health Organisation (WHO), are all treatments or procedures that include the in vitro handling of both human oocytes and sperm or of embryos, for the purpose of establishing pregnancy. This includes, but is not limited to, in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) and embryo transfer (ET), gamete intrafallopian transfer, zygote intra-fallopian transfer (ZIFT), tubal ET, gamete and embryo cryopreservation, oocytes and embryo donation, and gestational surrogacy.

In the context of assisted reproduction techniques, luteal phase support (LPS) is the term used to describe the administration of medications with the aim to support the process of implantation. Supplementation of progesterone in the luteal phase and continuance of progesterone therapy during the first trimester has been found in several studies to have benefits in promoting fertility, preventing miscarriages and even preventing pre-term labour.

Progesterone preparations can be divided into two groups: natural progesterone and synthetic preparations. Natural progesterone has no adverse effects on high-density lipoproteins, no teratogenic effects and is more effective than the derivatives in inducing secretory changes at the endometrium.
Traditionally, progesterone was given by means of intramuscular (IM) injections, which makes it unacceptable for long-term treatment. A decrease in the use of IM progesterone has been observed that likely reflects the cumbersomeness of these injections (i.e. not self-administrable) and the possibility of serious local reactions. In this respect, the vaginal route is the preferred way to administer natural progesterone.

The application is for a Prescription-Only Medicine (legal classification POM).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

All Member States agreed to grant Market Authorisations for Progesterone 400 mg pessaries at the end of procedure (Day 209 – 7 January 2017). After a subsequent national phase, the UK granted a Market Authorisation for this product on 16 January 2017 (PL 30306/0693).
II QUALITY ASPECTS

II.1 Introduction
Progesterone pessaries contain 400 mg of progesterone per pessary. The other ingredient is the pharmaceutical excipient hard fat.

The finished product is packed in polyvinylchloride (PVC) / polyethylene (PE) strip packs, in pack sizes of 12 or 15 pessaries.

Not all pack sizes may be marketed.

All primary product packaging complies with EU legislation concerning materials in contact with foodstuffs.

II.2 DRUG SUBSTANCES
rINN: Progesterone
Chemical Name: Pregn-4-ene-3,20-dione

Structure:

![Molecular Structure of Progesterone](image)

Molecular Formula: C_{21}H_{30}O_{2}

Molecular Weight: 314.5

Appearance: Progesterone is a white or almost white crystalline powder or colourless crystals.

Solubility: practically insoluble in water; freely soluble in dehydrated alcohol and sparingly soluble in acetone and fatty oils.

All aspects of the manufacture and control of the active substance, progesterone, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT
Pharmaceutical development
The objective of the development programme was to formulate safe, efficacious, pessaries containing 400 mg of progesterone per pessary. Suitable product development data have been submitted with this application.
The only excipient ‘hard fat’ complies with its European Pharmacopoeia monograph.

None of the excipients are of human or animal origin and furthermore, none are sourced from genetically modified organisms.

There were no novel excipients used.

**Manufacture of the product**
A description and flow-chart of the manufacturing method has been provided.

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results.

**Finished Product Specification**
The finished product specification is satisfactory. Test methods have been described and are adequately validated. Batch data that comply with the release specification have been provided.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. The results from these studies support a shelf-life of 4 years with the special storage condition, “Do not store above 30°C”.

Suitable post approval stability commitments to continue stability testing on batches of the finished product have been provided.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
It is recommended that a Marketing Authorisation is granted for Progesterone 400 mg pessaries.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**
As the pharmacodynamic, pharmacokinetic and toxicological properties of progesterone are well known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

**III.2 Pharmacology**
Not applicable for this product type. Refer to Section ‘III.1; Introduction’.

**III.3 Primary Pharmacodynamics**
Not applicable for this product type. Refer to Section ‘III.1; Introduction’.

**III.4 Pharmacokinetics**
Not applicable for this product type. Refer to Section ‘III.1; Introduction’.
III.5 Toxicology
Not applicable for this product type. Refer to Section ‘III.1; Introduction’.

III.6 Impurities
The specifications set by the manufacturer comply with the ICH Guideline Q3B(R2) ‘Impurities in New Drug Products’.

III.7 Environmental Risk Assessment (ERA)
Since this product will be used as a substitute for other products that are currently on the market, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary. The applicant has provided suitable information to verify that no increase in the exposure of the environment to the active ingredient is to be expected.

The environmental risk is of progesterone well documented. There are extensive data in the literature in relation to the environmental impact of progesterone. As a result, no further in vivo work is considered necessary and the wording in the product literature (PIL and SmPC) is considered acceptable. Progesterone is an endocrine modulator, therefore, as a precaution a statement regarding the disposal of any unused medicinal product is included in the summary of product characteristics and patient information leaflet.

III.8 Discussion on non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Progesterone 400 mg pessaries.

IV CLINICAL ASPECTS
IV.1 Introduction
This application is a line extension of the existing licence for Cyclogest 400mg (PL 00142/0508), however, the therapeutic indications are restricted to the following that were originally granted for Cyclogest 400mg in November 2015:

- luteal phase support as part of an Assisted Reproductive Technology (ART) treatment for women

In support of the above indication, data from the following studies have been submitted:

1. A pharmacokinetic/pharmacodynamics study to primarily compare the secretory status of the endometrium after 9 days of vaginal application of the test product Cyclogest (100 mg bid, 200 mg bid, 400 mg bid, and 400 mg od) versus the reference product 90mg od Crinone 8% Vaginal Gel (Merck Serono Limited) versus placebo bid.

2. A comparative efficacy study to show the non-inferiority of Cyclogest 400mg bid versus 90mg od Crinone 8% Vaginal Gel (Merck Serono Limited) in the achievement of clinical pregnancy after 38 days of luteal phase support after in vitro fertilisation.

IV.2 Pharmacokinetics
The pharmacokinetic/pharmacodynamic study investigated the single- and multiple-dose pharmacokinetics of the test product Cyclogest (100 mg bid, 200 mg bid, 400 mg bid, and 400 mg od) versus the reference product 90mg od Crinone 8% Vaginal Gel (Merck Serono Limited).

The plasma concentrations and systemic exposure of the 100mg bid dose of Cyclogest was comparable to that of 90mg od Crinone 8% Vaginal Gel (Merck Serono Limited), with a non-linear dose response for the 200mg and 400mg doses of Cyclogest, and the
bioavailability of progesterone after the 200 and 400mg dose Cyclogest was approximately 60% higher than that of 90mg od Crinone 8% Vaginal Gel (Merck Serono Limited).

No specific studies were performed to demonstrate distribution and elimination of progesterone after vaginal administration. However, literature references were provided which suggest that the relative total distribution of Cyclogest 200mg daily given vaginally is 322 l/kg, while the relative total clearance is 21.2 l/min and the mean effective apparent terminal half-life was 9.01 hours. In addition, the results of pharmacokinetics/pharmacodynamics study showed that the terminal half-life (t1/2MD) of Cyclogest 400mg once a day was 18.5 hours in comparison to Crinone which as 25.9 hours [geometric means]). The 1/2MD for Cyclogest 200mg twice a day was 21.2 hours while the T1/2MD for the 400mg twice a day regimen was 14.6 hours. The results from the literature references should be interpreted with caution because the details of analytical methods used for estimation of progesterone are not known. However, it would appear from the literature references provided, that systemic exposure of progesterone metabolites following vaginal administration is low in comparison to after oral administration. It should also be noted that the pharmacokinetics of progesterone is well-known.

IV.3 Pharmacodynamics
The above pharmacokinetic / pharmacodynamic study also compared the secretory status of the endometrium after 9 days of vaginal application of the test product Cyclogest (100 mg bid, 200 mg bid, 400 mg bid, and 400 mg od) versus the reference product 90mg od Crinone 8% Vaginal Gel (Merck Serono Limited) versus placebo bid. Further, the safety and tolerability of the above doses of test product versus the reference product and placebo were also investigated.

The primary endpoints of the study were the proportion of endometrium with adequate transformation to secretory state (both late and early). In addition, endometrial thickness on transvaginal sonography (TVS) and the histology were assessed. The results of the study showed that all doses of Cyclogest culminated in endometrial transformation to early and late secretory states. For the 200mg twice daily and 400mg twice daily, however, transformation occurred in majority of cases (more than 90%).

Bioequivalence
For products that are applied locally and are intended to act without systemic absorption, the approach to determine equivalence on systemic measurements is not applicable. The applicant has submitted a non-inferiority study comparing the test product versus the reference product, Crinone 8% Vaginal Gel, as explained below in Section IV.5, Clinical Safety.

IV.4 Clinical Efficacy
A multi-centre, multi-national, open-label, randomised, parallel-group, non-inferiority Phase III trial was conducted to demonstrate non-inferiority of Cyclogest 400 mg twice daily in comparison to Crinone 8% (90 mg) in the achievement of clinical pregnancy. Premenopausal woman undergoing fresh embryo transfer (ET) during in vitro fertilization (IVF) / intra-cytoplasmic sperm injection (ICSI) treatment aged between 18 and 40 years with BMI ≥18 and ≤30 kg/m² were included in the study.

Primary objective
To evaluate non-inferiority in the achievement of pregnancy rate (foetal heart movement measured by transvaginal ultrasonography [TVUS]) after 38 days of luteal phase support using Cyclogest 400 mg twice daily compared to Crinone 8% (90 mg) once daily.
Secondary objectives

- To compare the safety and tolerability of Cyclogest 400 mg twice daily to Crinone 8% (90 mg) od when used for 10 weeks of luteal phase support.
- To compare the achievement of clinical pregnancy rate (foetal heart movement measured by TVUS) after 10 weeks of luteal phase support using Cyclogest 400 mg twice daily or Crinone 8% (90 mg) once daily.
- To compare patient-rated convenience in the use of Cyclogest 400 mg twice daily to Crinone 8% (90 mg) once daily when used for 10 weeks of luteal phase support.
- To compare biochemical pregnancy rates between Cyclogest 400 mg twice daily and Crinone 8% (90 mg) once daily after 18 days and 38 days relative to oocyte retrieval (OR).
- To compare the clinical implantation rate (embryo with foetal heart movement measured by TVUS) per number of embryos transferred after 38 days of luteal phase support using Cyclogest 400 mg twice daily or Crinone 8% (90 mg) once daily.

Outcomes/endpoints

Primary endpoint
Clinical pregnancy rate after 38 days of luteal phase support (foetal heart movement measured by TVUS).

Secondary endpoints

- Clinical pregnancy rate achieved after 70 days (10 weeks) of luteal phase support (foetal heart movement measured by TVUS).
- Clinical implantation rates per number of embryos transferred after 38 days of luteal phase support (foetal heart movement measured by TVUS).
- Biochemical pregnancy rate at Day 18 and Day 38 after.

Criteria for efficacy analysis were defined as:

- Clinical pregnancy: assessed by TVUS as foetal heart movement
- Biochemical pregnancy: assessed by β-hCG as ≥25 IU/l
- Patient's treatment convenience assessed by questionnaire
- The patient's evaluation of bleeding and leakage assessed by diary

Evaluations of safety were based on the following measures and assessments:

- Adverse events
- Physical and gynaecological examination (including TVUS)
- Vital signs
- Safety laboratory (biochemistry and haematology)

The choice of the non-inferiority margin for this trial was deduced taking into account views on both relative and absolute effect sizes. It was agreed during an investigators meeting with key opinion leaders that combining both clinical and statistical aspects was appropriate. Non-inferiority analysis was based on the absolute difference between proportions (p1 - p2). The non-inferiority margin was defined as -9% (points).

The following hypotheses were supposed to be tested at significance level α=2.5%: H0: π1 - π2 ≤ -9% versus H1: π1 - π2 > -9% i.e. the alternative hypothesis was claiming non-inferiority of Cyclogest to Crinone with a non-inferiority-margin of 9%.
Results

Participant flow

Figure 10-1 Disposition of patients

Baseline data
The mean age of the patients was 33 years (range: 20 to 40). 765 patients were of Caucasian ethnicity (99.6%) and 3 were Asian (0.4%).

Outcomes and estimation
The overall pregnancy rate was 38.3% for Cyclogest and 39.9% for Crinone. Statistical analysis showed non-inferiority of Cyclogest for the Full-Analysis Set (FAS), with corresponding pregnancy rates of 38.3% and 39.9% for Cyclogest and Crinone, respectively. The lower limit of the 97.5% confidence interval (CI) was -8.6% and thus above the pre-defined non-inferiority margin of -9%-points.

With regard to the Per-Protocol (PP) set, pregnancy rates were 38.1% for Cyclogest and 40.4% for Crinone. Non-inferiority was not shown for the PP set; the lower limit of the 97.5% CI was -9.5%, which is below the pre-defined non-inferiority margin of -9%-points.
Although, non-inferiority could not be formally shown for the PP set based on the pre-defined -9% non-inferiority margin, the conclusion for a lack of non-inferiority was very marginal (a lower limit of -9.5% was observed). It should be taken into account that a reference pregnancy rate of 30% was used for deriving the non-inferiority margin of -9%. Since the actual pregnancy reference rate was about 40% a non-inferiority margin of up to -12% appears more appropriate based on historical data. This limit of -12%, as well as others above 9%, have also been used in a previous trial. During the planning of the study, investigators judged an observed difference of 5%-points between pregnancy rates as clinically acceptable. In fact, both analyses (based on FAS and the PP set) showed similar results, i.e. a difference in clinical pregnancy rates of about 2%-points (Cyclogest minus Crinone), which are well below the clinically acceptable difference of 5%. Furthermore, it appears worthwhile to recognize that a difference of 0.5% (i.e. a value of 0.005) corresponds to a difference of only two responses (pregnancy) in the total study population of 713 patients (PP), which is judged as negligible from the clinical point of view. This aspect of the robustness of concluding non-inferiority against marginal, clinically insignificant changes in outcome (only two cases) is addressed in more detail below.

**Secondary endpoints**

**Clinical pregnancy rate at Day 70**
Overall, clinical pregnancy rates were lower on Day 70 compared to Day 38.

<table>
<thead>
<tr>
<th>Analysis Set</th>
<th>Treatment</th>
<th>Pregnancy rate % (n)</th>
<th>Lower limit of 97.5% CI</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS (N=737)</td>
<td>Cyclogest</td>
<td>38.3% (141 / 368)</td>
<td>-1.6%</td>
<td>non-inferiority</td>
</tr>
<tr>
<td></td>
<td>Crinone</td>
<td>39.9% (146 / 366)</td>
<td>-8.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>-1.6%</td>
<td>-9.5%</td>
<td>non-inferiority not shown</td>
</tr>
<tr>
<td>PP (N=713)</td>
<td>Cyclogest</td>
<td>38.1% (136 / 357)</td>
<td>-2.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Crinone</td>
<td>40.4% (144 / 356)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical implantation rate**
The clinical implantation rate per number of embryos transferred assessed after 38 days of luteal phase support were 24.6% for Cyclogest and 26.5% for Crinone. At Day 70, implantation rates per number of embryos transferred were 22.5% for Cyclogest and 24.5% for Crinone.
Biochemical pregnancy rates at Day 18 and Day 38

Biochemical pregnancy rates observed at Day 18 were 46.3% for Cyclogest and 47.6% for Crinone and at Day 38 rates were 40.8% for Cyclogest and 42.9% for Crinone.

Table 11-4: Biochemical pregnancy rate after 18 and 38 days of luteal phase support

With regard to any blood loss occurring until Day 38 and Day 70, no differences in pregnancy rates were observed between patients receiving Cyclogest or Crinone. Different pregnancy rates were seen between patients who had no blood loss until the respective study days: For patients treated with Cyclogest, the pregnancy rate was 51.0%, whereas 61.3% was observed for those patients receiving Crinone (FAS, Day 38).
Subgroup analysis

Subgroup analyses of pregnancy rate were performed according to age group, Body Mass Index (BMI) and number of transferred embryos.

Clinical pregnancy rates at Day 38 were higher for younger patients aged \( \leq 35 \) years (41.4%) compared to older patients >35 years (33.8%). An effect of being overweight (i.e. BMI of 25 to 30 kg/m\(^2\)) on pregnancy rate was not apparent.

Comparable pregnancy rates were observed for Cyclogest and Crinone with regard to the number of transferred embryos. Pregnancy rates were lower in both treatment groups when only a single embryo was transferred.

Higher pregnancy rates were observed for Crinone (46.5%) when embryos in the 2- to 4-cell stage were transferred compared to Cyclogest (36.0%). No difference between patients was seen when embryos in cleavage stages \( \geq 5 \) cells were transferred. Most of the patients underwent Intra-Cytoplasmic Sperm Injection (ICSI) as the method of in-vitro fertilization and no difference in pregnancy rates between the two study treatments was observed.
In order to evaluate statistical significance of the potentially influencing factors (subgroups), a logistic regression model was applied using forward and backward selection. The following factors were identified to have significant impact on the pregnancy rate: age group, number of embryos transferred, and occurrence of bleeding until Day 38.

Post-hoc analyses
Pregnancy rates were highly comparable between Bulgaria, Czech Republic, and Hungary with rates of 40.8%, 40.8%, 39.7% for Cyclogest, respectively, and of 37.0%, 35%, 36.8% for Crinone, respectively, whereas in Serbia the rates differed markedly between Cyclogest (34.8%) and Crinone (50.0%), which was consistently observed across all study sites in this country. In Belgium, Cyclogest (27.3%) had more than twice the rate compared to Crinone (12.5%), although according to the applicant, this could be explained by chance due to the low number of patients included in the country.

Clinical pregnancy rates without Serbia were 39.9% for Cyclogest and 35.2% for Crinone and the respective lower limit of the 97.5% CI was -3.7%, showing non-inferiority of Cyclogest (FAS, Table 14.4.2-1.1). Also, for the PP set non-inferiority was observed with a respective lower limit of the 97.5% CI of -4.9%-points and clinical pregnancy rates of 39.8% for Cyclogest and 36.1% for Crinone.
Overall conclusions on clinical efficacy
This study was conducted to show efficacy of Cyclogest 400 mg b.i.d in comparison to Crinone 8% (90 mg) by demonstrating non-inferiority of Cyclogest 400 mg b.i.d to Crinone in the achievement of clinical pregnancy after 38 days of luteal phase support after *in-vitro* fertilisation. Cyclogest 400mg b.i.d was demonstrated to be non-inferior to Crinone for the FAS in terms of clinical pregnancy rate after 38 days of luteal phase support (the primary endpoint). For the PP analysis set, however, non-inferiority to Crinone was not demonstrated. Post-hoc analyses conducted by the applicant showed pregnancy rates were found to differ significantly in Serbia. The applicant has provided a satisfactory discussion and justification regarding the non-demonstration of non-inferiority in the PP population and suggests widening the non-inferiority margin to 10%, as historical data suggest that Crinone is better than no treatment by an absolute margin of 16.9% with the lower limit of the 95% CI being 13.7%. This acceptable, especially since pregnancy rates in the study were higher than anticipated.

With regards to the noted differences in pregnancy rates observed between Serbia and other countries, the MAH has tried to investigate the reasons for the noted differences and it would appear that:

- No irregularities were found in the central web-based system used for randomisation
- The study was apparently monitored and no signs of fraudulent conduct was detected
- There was no apparent difference in compliance between patients treated with Cyclogest or Crinone. In addition, compliance according to the diary and drug accountability showed no apparent difference.
- There were no issues with the storage conditions of the investigational medicinal products. The same batches were used for all the study sites.

A post- study questionnaire on the ART procedures and patients’ medical backgrounds to further investigate the observed differences was sent to all the participating sites. None of the variables investigated appeared to have been responsible for difference in results between Serbia and the other countries. A logistic regression analysis was also conducted which
indicated that whilst some of the variables investigated did affect the pregnancy rate, even after adjusting for these factors, there was still a significant interaction between country and treatment suggesting that some unknown factor could be affecting the results.

Overall, the reasons for the disparity in results between Serbia and the rest of the sites remain unknown, but will not be further pursued.

IV.5 Clinical Safety

With regards to the data submitted during the pharmacokinetic/pharmacodynamic study, no new or unexpected safety issues were raised during this study.

With regards to the clinical efficacy study, the incidence of adverse events (AEs) was found to be comparable between Cyclogest (43.6%) and Crinone (44.6%). Drug-related adverse events were observed in 58 patients (15.1%) receiving Cyclogest and in 55 patients (14.4%) receiving Crinone. Most of the patients reported AEs of mild or moderate intensity (43.6% of the patients). The most frequently drug-related AEs were ‘reproductive system and breast disorders’ including breast discomfort, breast tenderness, vaginal haemorrhage, metrorrhagia, and vaginal discharge 4.7% in the Cyclogest group and 6.8% in the Crinone group. The frequency reported gastrointestinal disorders were comparable in both groups (Cyclogest: 4.9% and Crinone: 5.2%). For ‘nervous system disorders’ the frequency was also similar (Cyclogest: 5.2%; Crinone: 5.0%).

Table 12-2 Overview of treatment emergent AEs, safety set (N=768)

<table>
<thead>
<tr>
<th></th>
<th>Cyclogest N=385</th>
<th>Crinone N=383</th>
<th>Total N=768</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with any AE</td>
<td>168 (43.6%)</td>
<td>171 (44.6%)</td>
<td>339 (44.1%)</td>
</tr>
<tr>
<td>Number of patients with any SAE</td>
<td>6 (1.6%)</td>
<td>13 (3.4%)</td>
<td>19 (2.5%)</td>
</tr>
<tr>
<td>Number of patients with drug-related AEs</td>
<td>58 (15.1%)</td>
<td>55 (14.4%)</td>
<td>113 (14.7%)</td>
</tr>
<tr>
<td>Number of patients with drug-related SAEs</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Number of patients who discontinued due to AE</td>
<td>19 (4.9%)</td>
<td>12 (3.1%)</td>
<td>31 (4.0%)</td>
</tr>
</tbody>
</table>

Intensity

<table>
<thead>
<tr>
<th></th>
<th>Cyclogest N=385</th>
<th>Crinone N=383</th>
<th>Total N=768</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with mild AEs</td>
<td>126 (32.7%)</td>
<td>133 (34.7%)</td>
<td>259 (33.7%)</td>
</tr>
<tr>
<td>Number of patients with moderate AEs</td>
<td>40 (10.4%)</td>
<td>36 (9.4%)</td>
<td>76 (9.9%)</td>
</tr>
<tr>
<td>Number of patients with severe AEs</td>
<td>2 (0.5%)</td>
<td>2 (0.5%)</td>
<td>4 (0.5%)</td>
</tr>
</tbody>
</table>

Related to study drug

<table>
<thead>
<tr>
<th></th>
<th>Cyclogest N=385</th>
<th>Crinone N=383</th>
<th>Total N=768</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with mild AEs</td>
<td>58 (15.1%)</td>
<td>55 (14.4%)</td>
<td>113 (14.7%)</td>
</tr>
<tr>
<td>Number of patients with moderate AEs</td>
<td>40 (10.4%)</td>
<td>42 (11.0%)</td>
<td>82 (10.7%)</td>
</tr>
<tr>
<td>Number of patients with severe AEs</td>
<td>17 (4.4%)</td>
<td>13 (3.4%)</td>
<td>30 (3.9%)</td>
</tr>
<tr>
<td>Number of patients with severe AEs</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>

Source: Table 14.3.2-3

In total 385 subjects were exposed to Cyclogest 400mg pessaries for the proposed indication of ‘luteal phase support as part of an Assisted Reproductive Technology (ART) treatment for women’ in the study. The most frequency adverse drug events were ‘reproductive system and breast disorders’ for which the incidence was similar in the Cyclogest 400mg pessaries and Crinone 8% Vaginal Gel (Merck Serono Limited) group. Overall, the adverse event profile for Cyclogest 400mg pessaries and Crinone 8% Vaginal Gel (Merck Serono Limited) were comparable and similar. No significant adverse events were identified in either group. In conclusion, there are no major issues with regards to safety of Cyclogest (progesterone) 400mg pessaries for the proposed indication.
IV.6  Risk Management Plan (RMP)
The marketing authorisation holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Progesterone pessaries.

A summary of safety concerns, as approved in the RMP are listed below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
<td>None identified</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>Birth defects</td>
</tr>
<tr>
<td>Missing information</td>
<td>Long term effects in children exposed in utero</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and risk minimisation are proposed for all safety concerns.

IV.7  Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for Progesterone 400 mg pessaries.

V    USER CONSULTATION
A user consultation with target patient groups on the PIL has been performed and the results provided are acceptable.

VI. OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Progesterone 400mg pessaries are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
There are no objections to the authorisation of this product on non-clinical grounds.

CLINICAL
For products that are applied locally and are intended to act without systemic absorption, the approach to determine equivalence on systemic measurements is not applicable.

A pharmacokinetic/pharmacodynamic study was submitted and the results showed that Cyclogest 400mg pessaries twice daily culminated in the endometrial transformation in early and late secretory states in the majority of cases (more than 90%).

In a clinical efficacy study, Cyclogest 400 mg pessaries demonstrated non-inferiority to Crinone 8% Vaginal Gel in the supplementation of luteal phase during assisted reproductive technology (ART).
The applicant has provided an extensive literature review to support the application. No new or unexpected safety concerns were observed during the pharmacokinetic/pharmacodynamic study, or the efficacy study.

**RISK-BENEFIT ASSESSMENT**

The quality of the product is acceptable and any non-clinical or clinical safety concerns have been fully resolved. The risk benefit is, therefore, considered to be positive.

**PRODUCT LITERATURE**

In accordance with Directive 2010/84/EU, the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for a product granted a Marketing Authorisation at a national level are available on the MHRA website.

The following text is the approved label text for this medicine agreed at the end of the decentralised procedure; no label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the labelling mock-ups has been obtained.
**LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

<table>
<thead>
<tr>
<th>CARTON</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Progesterone 400 mg pessaries

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each pessary contains 400 mg progesterone

3. **LIST OF EXCIPIENTS**

hard fat. Please see the enclosed leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Pessary
12 pessaries
15 pessaries

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Vaginal use
Please read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

   Actavis Group PTC ehf, Reykjavikurvegi 76-78, Hafnarfjördur 220, Iceland

12. **MARKETING AUTHORISATION NUMBER(S)**

   PL 30306/0693

13. **BATCH NUMBER**

   Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   POM

15. **INSTRUCTIONS ON USE**

   Use as directed by the doctor

16. **INFORMATION IN BRAILLE**

   Progesterone 400 mg pessaries

17. **UNIQUE IDENTIFIER – 2D BARCODE**

   <2D barcode carrying the unique identifier included>

   <Not applicable>

18. **UNIQUE IDENTIFIER – HUMAN READABLE DATA**

   - **FC**: (number) [product code]
   - **SN**: (number) [serial number]
   - **NN**: (number) [national reimbursement number or other national number identifying the medicinal product]

   <Not applicable>
**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**STRIP**

1. **NAME OF THE MEDICINAL PRODUCT**

   Progesterone 400 mg pessaries

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

   Actavis Group PTCEhf, Reykjavíkurvegi 76-78, Hafnarfjörður 220, Iceland

3. **EXPIRY DATE**

   EXP

4. **BATCH NUMBER**

   Lot

5. **OTHER**
## Annex 1 - Table of content of the PAR update for MRP and DCP

**Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report**

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td>To address the end points of Fish Full Life-Cycle Test (FFLC) and impact of Progesterone to the environment.</td>
<td>UK/H/6113/001/IB/001</td>
<td>None</td>
<td>28 July 2017</td>
<td>26 October 2017</td>
<td>Approval</td>
<td>Yes</td>
</tr>
</tbody>
</table>
ANNEX 1.1

Our Reference: PL 30306/0693, Application 0003
Product: Progesterone 400 mg pessaries

Marketing Authorisation Holder: Actavis Group PTC ehf
Active Ingredient(s): Progesterone

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number: UK/H/6113/001/IB/001

Reason:
To address the end points of Fish Full Life-Cycle Test (FFLC) and impact of Progesterone to the environment.

Supporting Evidence
The applicant submitted an Environmental Risk Assessment based on bibliographic data to address the end points of Fish Full Life-Cycle Test (FFLC) and impact of Progesterone to the environment.

Evaluation:
Recommendation
Based on the review of the literature data provided, the RMS considers that the variation application UK/H/6113/001/IB/001 for Progesterone 400 mg pessaries is approvable.

Executive Summary
Scope of the variation
Following submission of the original Marketing Authorisation Application, it was agreed at Day 180 that as there are extensive information regarding the impact of progesterone on the environment, and toxicity is very well defined, no further non-clinical (in vitro or in vivo) need be conducted by the Applicant. Thus, the Applicant could provide literature data on the fish life-cycle as a post approval commitment (variation).

Data previously provided indicated that based on the standard Phase I environmental risk calculation, using default parameters, the Predicted Environmental Concentration (PEC_{surface water}, 4 \, \mu g/L) exceeded the action limit of 0.01 \, \mu g/L.

A comprehensive assessment of the literature has been performed to address the end points of Fish Full Life-Cycle Test (FFLC) in order to further evaluate the environmental impact of progesterone.

Scientific Discussion
Non-clinical aspects
The Applicant has reviewed several publications and proposed that the main endpoints of a Fish Full Life-Cycle Test (FFLC) have been addressed in the studies on progesterone by one set of investigators (2012), with additional endpoints evaluated by other investigators (one 2011 publication, two 2015 publications). A summary is provided below.
Investigations were performed to evaluate the effects of exposure to different concentrations of progesterone on reproduction and embryonic development in the fathead minnow (*Pimephales promelas*) (2012).

For the reproduction assay, groups of reproductively mature 5-month old fathead minnows were exposed for 21 days to nominal concentrations of 0, 10, 100 or 1000 ng/L progesterone in a flow-through system. Forty groups of adult fish (2 females and 1 male per group) were assessed during a 15-day pre-exposure period for reproductive maturity based on the presence of key secondary sexual characteristics (e.g., fat pad, coloration, presence of nuptial tubercles, and ovipositor) and fecundity estimates. At the end of the 15-day pre-exposure period, 24 reproductive groups that showed the most consistent spawning and egg production were selected for the 21 day progesterone exposure study.

In the main 21 day study, 24 groups of fish (2 females and 1 male per group) were allocated to one of four treatments (0, 10, 100, and 1000 ng/L), and to prevent bias in egg production, the treatment groups were balanced according to their pre-exposure egg production. Data on fecundity and fertility were collected daily. Fecundity was defined as the total egg production. The eggs were assessed for fertilization by observing embryonic development under a dissecting microscope. After the 21-day exposure, all fish were killed using buffered inquels. Each fish of either sex was weighed and scored for the presence of secondary sexual characteristics (including colouring, presence and size of tubercles, and ovipositor). Blood was collected from the caudal vein with heparinised capillary tubes. The gonads were collected and weighed to determine the gonadosomatic index (GSI). Female gonads were analysed for ovarian cortisol content by a validated enzyme-linked immunoassay. Livers were collected from the male fish and one randomly selected female from each tank and were then frozen in liquid nitrogen for subsequent vitellogenin (Vtg) mRNA expression using a validated quantitative real-time polymerase chain reaction assay. The results were analysed using appropriate statistical analyses.

Progesterone exposure significantly (*p* ≤0.05) decreased fecundity at 100 and 1000 ng/L. The inhibitory effects of progesterone on egg production became apparent in the treatments 7 to 11 days after the start of the exposure. Over the 21-day exposure period, 87% of the eggs laid at 1000 ng/L treatment were laid before day 8, with 62% of the eggs laid on day 2. There was a single death in the study (one female at 10 ng/L died on day 18).

Progesterone effects on fertilization success (percent fertilization) were analysed in three groups, including eggs laid on the spawning tiles, dropped eggs (defined as eggs found in or on the tray/screen apparatus), and total eggs (tile and dropped eggs). A significant reduction in fertilization success was observed at 1000 ng/L treatment for eggs laid directly on the spawning tile, and this end-point was considered the most biologically relevant result regarding fertilization success. The investigators considered that the fertilization success, which was decreased in the 1000 ng/L treatment, could be a function of progesterone effects on male reproductive capacity i.e. decreased sperm motility.

No significant treatment effect was evident regarding dropped eggs. Though, a significant decrease in fertilization success was present at 10 ng/L progesterone treatment when fertilization success of the eggs on the tile and tray were analyzed together. However, a treatment relationship was not apparent based on the control data and data for all 3 concentrations, and fertilization success that includes dropped eggs (eggs on tray) is not considered a good end-point due to the potential for eggs to succumb to pathogens (bacteria or fungus) on the tray compared to the spawning tile. Including dropped eggs in fecundity estimates reduced the variance between reproductive groups.
The GSI of females was significantly (p ≤0.05) increased at 1000 ng/L relative to controls. Progesterone exposure had no effect on male GSI at any concentration.

There were no effects of progesterone exposure on male or female secondary sexual characteristics. No ov–testes were observed at the gross morphological level in any fish. Progesterone significantly (p ≤0.05) inhibited Vtg mRNA expression in females in the 10 and 100 ng/L treatment groups (not in a concentration-related fashion), but not at 1000 ng/L. Progesterone had no effect on Vtg mRNA expression in males at any concentration. There was no concentration-related effect of progesterone over the concentration range (10-1000 ng/L) on ovarian cortisol concentrations.

As discussed in the study (2012), progesterone is not generally considered to be an important reproductive steroid in fish, although it has been shown to have some binding affinity for the progestin receptors (e.g., mαPR) that mediate gamete maturation and sperm motility, and thus could potentially have direct effects on fathead minnow reproduction. Progesterone is an intermediate in production of reproductive steroids, including androgens, estrogens, cortisol, and other progestins. However, in the study (2012), there were no signs of masculinized females or signs of decreased or increased masculinization in the males.

In the embryonic development static culture study from the same publication (2012), fertilized eggs from the control fish were collected from the spawning tiles in the main 21 day fathead minnow study. Embryos at the same developmental stage (stage 9 or 10) were placed in wells of a microplate and incubated at 27 °C in 500 mL of egg water (60 μg/L salt solution and 300 μg/L methylene blue) containing 0, 10, 100, or 1000 ng/L progesterone (n =12). The developing embryos were observed daily for 5 days or until hatch, and ranked as 1 = normal, 2 = slightly deformed (discoloration, early signs of necrotic tissue, pericardial oedema, cloudy perivitelline space), 3 = severely deformed (expansive necrotic tissue, abnormal development, slowed/erratic blood circulation or heart rate, extreme oedema), 4 = dead. There were no effects of progesterone on early fathead minnow development or hatching success at any of the concentrations tested (10, 100 and 1000 ng/L progesterone).

In another study (2015), the effects of 14-days flow-through exposure to progesterone at 34 ± 4.1 ng/L (mean concentration, based on analyses at days 0, 4, 11 and 14) or norethindrone at 168 ± 7.5 ng/L on steroidogenesis in adult non-spawning female fathead minnows were examined. The solvent control was 0.0042% dimethylformamide. Only the results for progesterone are discussed. Therwere 16 fish exposed to 34 ± 4.1 ng/L (100 ng/L nominal) progesterone, and 19 fish exposed to solvent control. Progesterone exposure reduced expression (non-significant) of luteinizing hormone (LHβ) levels in the brain, without any effect on FSHβ expression of brain. There was significant down-regulation of both isoforms of membrane progesterone receptor, mPRα and mPRβ, in ovary tissue, but there were no significant effects on nuclear estrogen receptors, ERα and ERβ, in ovary tissue.

No effects of progesterone exposure on the steroid receptor expressions in the brain were observed. Progesterone exposure induced down-regulation of 11β-hydroxysteroid dehydrogenase (11β-HSD), and up-regulation of 3β-HSD. In vitro exposure of ovary tissue to progesterone resulted in significantly elevated pregnenolone (1 and 10 μM), 17α-hydroxyprogesterone (10 μM), and 17α,20β-dihydroxyprogrenone (10 μM) and testosterone (0.1 μM) production.
Investigators (2011) reported that a one-week (7-day) flow-through exposure of adult (approximately 12-month old) male fathead minnows (Pimephales promelas) to progesterone caused a significant inhibition of sperm motility (curvilinear velocity; velocity average path; straight line velocity; where n = 4 per treatment for these parameters) at an analysed progesterone concentration of 339.3 ng/L, with no effects observed at an analysed concentration of 25.6 ng/L (nominal concentrations were 30 and 300 ng/L progesterone). The individual males (7 per treatment group) were each paired with 2 females per tank, in a 1 week acclimatisation period prior to exposure to progesterone. The males were killed at the end of the exposure period, and their testes were surgically removed, and sperm prepared for evaluation. The rationale for focusing on sperm motility was that certain progestins have been shown to bind to surface membrane receptors on fish spermatozoa and increase sperm swimming velocity. It was hypothesised, therefore, that sperm swimming velocity might be a useful indicator of progestin exposure in fish. Sperm were video recorded and analysed.

In another study (2015), the aim was to investigate the effects of progestins on the sex differentiation of zebrafish by measuring the sex ratio and transcriptions of genes related to sex differentiation (Amh, Dmrt1, Figa, Sox9a and Sox9b genes) as well as sex hormone levels and transcriptional expression profiles along the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal (HPA) axes in juvenile zebrafish. There were 20 fish per replicate of 4 per concentration (3 concentrations and solvent control; 0.001% v/v ethanol was solvent). The test system used was semi-static. Exposure (average measured concentrations) of the juvenile zebrafish to 4 ng/L, 33 ng/L and 63 ng/L progesterone or 4 ng/L, 34 ng/L and 77 ng/L norgestrel commenced at 20 days post fertilization (dpf) and ended at 60 dpf. Progesterone was not detected in the solvent control test solution. Only the results for progesterone are discussed in this summary. Exposure to progesterone had no significant effects on survival rates (>85% in all groups), body length, wet weight and K-factor in any treatment group. The results showed that exposure to progesterone caused a significant increase in proportion of females at 63 ng/L, as well as significant down-regulation of Amh gene and up-regulation of Figa mRNA expression at a concentration of 63 ng/L. The sex hormones in exposed fish were measured with estrone being detected only in the fish exposed to the highest progesterone concentration (63 ng/L). Estradiol, androstenedione and testosterone were not altered by any concentration of progesterone. Up-regulation of several key genes controlling the synthesis of sex hormones (i.e., Cyp17, Cyp19a1a and Hsd3b) was observed following exposure to 63 ng/L progesterone, along with induced expression of Pgr mRNA at 63 ng/L. Expression levels of Cyp11b mRNA were decreased at 33 and 63 ng/L progesterone. Progesterone had no effect on expression of Vtg1 mRNA or Cyp11a1 mRNA at any concentration. Progesterone also had no significant effects on expression levels of hypothalamic and pituitary hormones. Only a very limited concentration-related finding (Cyp11b mRNA reduction) was observed at 33 ng/L, and this is not considered to impact upon the NOEC of 10 ng/L progesterone for fish.

**Evaluation:**
In summary, the studies cover only a part of the life cycle, exposure is relatively short, and some of the endpoints are affected. There is also a limitation in the test design. Based on fish toxicity end-points covering reproductive, embryo developmental through to hatching success and relevant endocrinial end-points in the studies summarised and discussed above, the fish The No-Observed-Effect Concentration (NOEC) for progesterone was determined to be 10 ng/L based on toxicologically relevant in vivo effects observed at concentrations >10 ng/L. Using a NOEC of 10 ng/L and a default assessment factor of 10, the Predicted No-Effect Concentration (PNEC) was calculated as is 1 ng/L. This is 10 times lower than the standard action limit of 10 ng/L.
Since the ratio PEC\textsubscript{surface water}:PNEC\textsubscript{water} was above 1 (based on the PEC\textsubscript{surface water} value as provided in the original ERA), further evaluation of the exposure and fate of progesterone in the aquatic environment was performed by the Applicant in accordance with the principles of the ERA Phase II Tier B process. Specifically, the PEC\textsubscript{surface water} was recalculated: Market penetration (F\text{pen}) was recalculated using total annual consumption values (kg) for progesterone based on EU sales of all progesterone containing products for years 2013, 2014, 2015 and 2016 (IMS data; from International Medical Statistics Health PADDS, August 2016). For the Year to August 2016, total annual consumption was 24,083.2 kg for all progesterone medicinal products.

\[
F_{\text{pen}} \% = \frac{\text{Consumption [mg/year]} \times 100}{\text{DOSE}_{\text{ad}} \text{ (mg/day)} \times \text{EU population} (2016) \times 365}
\]

\[
F_{\text{pen}} \% = \frac{24,083,200,000 \text{ mg/year} \times 100}{800 \text{ mg/day} \times \sim 510,100,000 \times 365}
\]

\[
F_{\text{pen}} \% = 0.016
\]

\[
F_{\text{pen}} = 0.00016
\]

Using the refined F\text{pen} value, the PEC\textsubscript{surface water} is reduced from 4 μg/L to 0.064 μg/L; however, this still exceeds the action limit of 0.01 μg/L.

As progesterone is extensively metabolised and an assessment of a wastewater treatment works showed, that despite progesterone being the most abundant steroid hormone in the influent, it is broken down by biodegradation during water treatment, with a high efficiency of removal (98% ±2%) (2014). Therefore, the Applicant theorises that PEC\textsubscript{surface water} for progesterone, based on 98% wastewater removal, equals 1.28 ng/L and has concluded that the ratio of PEC\textsubscript{surface water}:PNEC\textsubscript{water} is 0.064 and hence is below 1 (>15 times lower) for progesterone. Thus, the Applicant considers that the impact of use of the proposed product on the environment, using fish as the optimal test species for assessment of environmental risk for progesterone, is low and further assessment/testing is not considered to be necessary.

The Applicant has included the following statement in the PIL:

‘Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment’

The bibliographic data presented provide some support for the disposal information provided in the PIL. The Applicant is requested to update the section 6.6 of the SPC in line with the disposal information in the PIL when the SmPC is next updated.

**Overall Conclusion**

The available aquatic toxicity data on progesterone lack specific information on effects on fertility, reproduction and other physiological endpoints. However, it is agreed that based on these no observed effect level (NOEL) values and the PEC\textsubscript{surface water} of 64 ng/L, the risk calculation expressed as the Predicted Environmental Concentration/Predicted No-Effect Concentration (PEC/PNEC) ratio clearly indicates a potential risk for the aquatic compartment (PEC/PNEC ratio exceeds 1), and more specific for fish. Additional information that can be obtained from a FFLC will no doubt result in the same conclusion of
the current ERA. The justification to not conduct further toxicology studies, which would involve the use of numerous vertebrates whilst not impacting on the risk:benefit profile of the proposed product, is therefore considered acceptable.

This variation is considered approvable.

**Decision**
Approved on 26 October 2017.