

Public Assessment Report

Scientific discussion

Utrogestan (progesterone)

SE/H/2023/01/E/01

This module reflects the scientific discussion for the approval of Utrogestan. The Public Assessment Report was written in October 2015 by the previous RMS UK and is attached at the end of this document. RMS transfer from UK to SE was completed October 2019. For information on changes after this date please refer to the module 'Update'.

Application/Legal Basis	Article 8(3), known active substance
Active substance	progesterone
Pharmaceutical form	vaginal capsule, soft,
Strength	200 mg
Applicant	Besins Healthcare Ireland Limited
EU-Procedure number (original)	UK/H/5838

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the application for Utrogestan, 200 mg, vaginal capsule, soft, could be approved.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/non approval	Summary/Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)



Medicines & Healthcare products
Regulatory Agency



Public Assessment Report

UK PAR

Utrogestan Vaginal 200mg Capsules

(progesterone)

UK Licence No: PL 28397/0005

Besins Healthcare

LAY SUMMARY

Utrogestan Vaginal 200mg Capsules (progesterone)

This is a summary of the Public Assessment Report (PAR) for Utrogestan Vaginal 200mg Capsules (PL 26397/0005, formerly PL 16468/0011). It explains how the application for Utrogestan Vaginal 200mg Capsules was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Utrogestan Vaginal 200 mg Capsules.

For practical information about using Utrogestan Vaginal 200mg Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Utrogestan Vaginal’ in this Lay Summary.

What is Utrogestan Vaginal and what is it used for?

Utrogestan Vaginal is a medicine that can be used to help pregnancy. Utrogestan Vaginal 200mg is used to assist fertility treatment techniques using the patient’s own eggs, such as in-vitro fertilisation (IVF), gamete intra-Fallopian transfer (GIFT) or zygote intra-Fallopian transfer (ZIFT).

Utrogestan Vaginal is not a contraceptive.

How does Utrogestan Vaginal work?

Utrogestan Vaginal contains the active ingredient progesterone, which is a natural, female sex hormone, produced in the body. This medicine works by adjusting the hormonal balance within the body.

How is Utrogestan Vaginal used?

Utrogestan Vaginal is available as vaginal capsules.

This medicine should be used exactly as instructed by the doctor. The patient should read and check with your doctor or pharmacist if you are not sure. The patient should contact the pharmacy if she requires an applicator. The applicator supplied by the pharmacy contains a leaflet. This leaflet includes pictures and describes how to use the applicator.

Using this medicine to help pregnancy

- This medicine should be inserted deep into the vagina.
- The capsule should not be taken by mouth. However, if Utrogestan Vaginal is accidentally taken by mouth it will not cause harm; it will only reduce the chances of becoming pregnant.

How much to use

- Treatment with Utrogestan Vaginal begins on the day of embryo transfer.
- Every day, 200mg of Utrogestan Vaginal should be taken in the morning, at lunchtime and at bedtime, or 200mg in the morning and the evening, as instructed by your doctor.
- If there is laboratory evidence of pregnancy, the same dose regime should continue until the 7th to 12th week of pregnancy, as instructed by your doctor.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

This medicine can only be obtained with a prescription.

What benefits of Utrogestan Vaginal have been shown in studies?

The company, Laboratoires Besins International, provided its own data on efficacy and safety studies. These studies have shown that Utrogestan Vaginal is effective in the proposed indication to assist fertility treatment techniques using the patient's own eggs, such as in-vitro fertilisation (IVF), gamete intra-Fallopian transfer (GIFT) or zygote intra-Fallopian transfer (ZIFT).

In addition, Laboratoires Besins International has provided data from the published literature on progesterone.

What are the possible side effects of Utrogestan Vaginal?

Like all medicines, Utrogestan Vaginal can cause side effects although not everybody gets them.

For the full list of all side effects reported with Utrogestan Vaginal.

What measures are being taken to ensure the safe and effective use of Utrogestan Vaginal?

A risk management plan has been developed to ensure that Utrogestan Vaginal is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Utrogestan Vaginal, 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/healthcare professionals will be monitored/reviewed continuously.

Other information about Utrogestan Vaginal

A Marketing Authorisation for Utrogestan Vaginal 200mg Capsules (PL 16468/0011) was granted in the UK to Laboratoires Besins International on 21 December 2012. Subsequent to a Change of Ownership (COA) procedure, Utrogestan Vaginal (PL 23138/0020) was granted to Marlborough Pharmaceuticals Limited on 29 November 2013. Subsequent to a further COA procedure, Utrogestan Vaginal 200mg Capsules (PL 28397/0005) was granted to Besins Healthcare on 02 December 2013.

The full PAR for Utrogestan Vaginal 200mg Capsules follows this summary.

For more information about treatment with Utrogestan Vaginal 200mg Capsules read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2015.

SCIENTIFIC DISCUSSION

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Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Laboratoires Besins International a Marketing Authorisation for the medicinal product Utrogestan Vaginal 200mg Capsules (PL 16468/0011) on 21 December 2012. This product is a prescription-only medicine (POM) indicated for supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles.

Utrogestan Vaginal 200mg Capsules may be referred to as Utrogestan in this report.

The application was submitted under Article 8(3) of Directive 2001/83/EC, as amended. The application is a line extension representing a new route of administration (vaginal) for Utrogestan 200mg capsules (PL 16468/0007). It seeks to extend the indications and posology for Utrogestan 200mg capsules to include the use vaginally for supplementation of the luteal phase during ART cycles. Utrogestan 200mg capsules (PL 16468/0007) was first authorised in the UK 1997 for oral administration, the first orally administered progesterone product on the UK market. Progesterone is currently licensed in the UK in the form of pessaries, intramuscular injection and as a vaginal gel.

The application was referred to the Commission on Human Medicines (CHM) and Chemistry Pharmacy and Standards Expert Advisory Group (CPS EAG), who met individually in November 2010 and April 2012 for consideration of whether the quality and efficacy of the product was demonstrated. Following consideration of the applicant's responses and further data that were submitted, the approval of the Marketing Authorisation was recommended.

The active ingredient is micronised progesterone, a form of the naturally occurring steroid, chemically identical to progesterone of ovarian origin. The progesterone used in Utrogestan 200mg is obtained by hemisynthesis on the basis of a precursor.

Progesterone is a sex steroid hormone and the only natural progestogen/progestin. Progesterone is produced in the adrenal glands, the gonads (specifically after ovulation in the corpus luteum), the brain, and, during pregnancy, in the placenta. All progestogens have anti-oestrogenic and antigonadotropic properties. Progestogens differ in their potency (affinity for progesterone receptors) and side effects.

Progesterone is an essential regulator of normal female reproductive function. Its effects are mediated by two nuclear progesterone receptor (PR) proteins: PRA and PRB, which are identical except for the N-terminal end of PRB. PRA and PRB are isoforms that may differ functionally. Progesterone, like all other steroid hormones is synthesized from pregnenolone, a derivative of cholesterol. Progesterone is also the precursor of the mineralocorticoid aldosterone, and after conversion to 17-hydroxyprogesterone (another natural progestogen) of cortisol and androstenedione. Androstenedione can be converted to testosterone, oestrone and oestradiol.

No new non-clinical studies were conducted, which is acceptable given that the application is for the known active substance progesterone, for which the pharmacodynamics, pharmacokinetic and toxicological properties are well known.

Ten pharmacokinetic studies and two efficacy studies were submitted to support the application. The applicant has stated that the pharmacokinetics studies were conducted in accordance with the principles laid down in the European Union guidance on pharmacokinetic studies (European Commission 1998). The

efficacy studies are stated to have been carried in accordance with Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of using Utrogestan Vaginal 200mg Capsules outweigh the risks and a Marketing Authorisation was granted.

Subsequent to a Change of Ownership (COA) procedure, Utrogestan Vaginal (PL 23138/0020) was granted to Marlborough Pharmaceuticals Limited on 29 November 2013. Subsequent to a further COA procedure, Utrogestan Vaginal 200mg Capsules (PL 28397/0005) was granted on 02 December 2013 to Besins Healthcare.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a white soft vaginal capsule. Each capsule contains 200mg micronised progesterone, as the active ingredient.

Utrogestan Vaginal 200mg Capsules also contain refined arachis oil, soya lecithin, gelatin, glycerol and titanium dioxide. Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in polyvinylchloride/aluminium blisters contained in cartons, in pack sizes of 15 and 21 capsules.

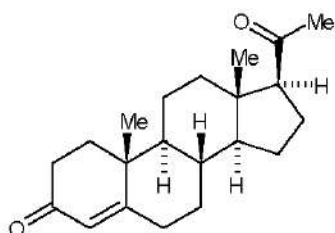
Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Progesterone

INN: Progesterone
 Chemical Name: Pregn-4-ene-3,20-dione
 Molecular Formula: $C_{21}H_{30}O_2$
 Structure



M_r : 314.5
 Appearance: A white or almost white crystalline powder or colourless crystals.

Solubility Practically insoluble in water, freely soluble in ethanol and sparingly soluble in acetone and in fatty oils.

Progesterone is the subject of a European Pharmacopoeia monograph.

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

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, stable soft capsule for vaginal (and oral) use containing 200 mg of progesterone. The product already exists for oral use on the UK market and therefore no further formulation development studies are provided. This is acceptable.

Satisfactory *in-vitro* dissolution profiles considering the vaginal environment have been provided.

All the excipients comply with their respective European Pharmacopoeia monographs, with the exception of soya lecithin, which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data that comply with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with no special storage conditions, has been accepted.

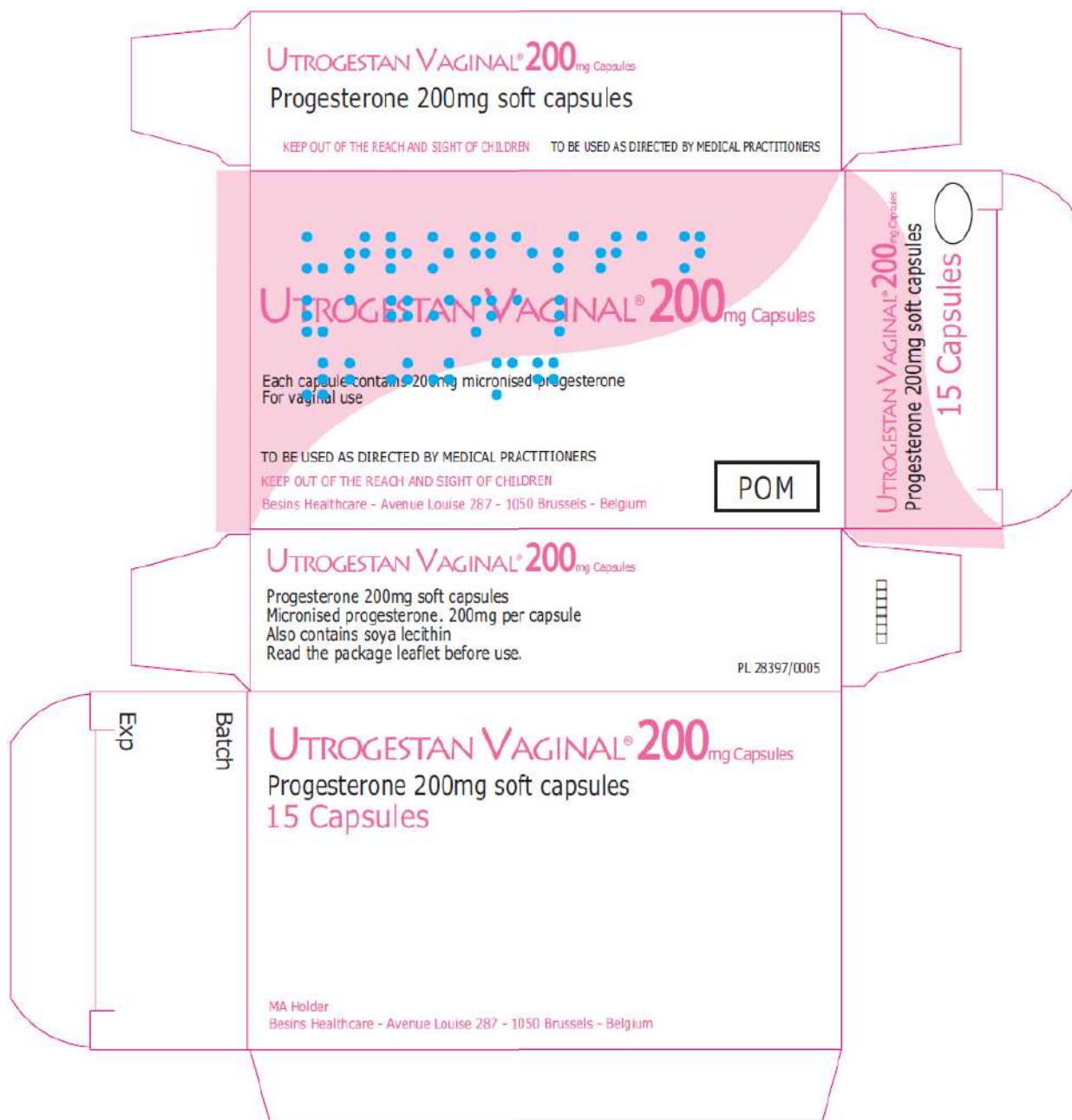
II.4 Discussion on chemical, pharmaceutical and biological aspects

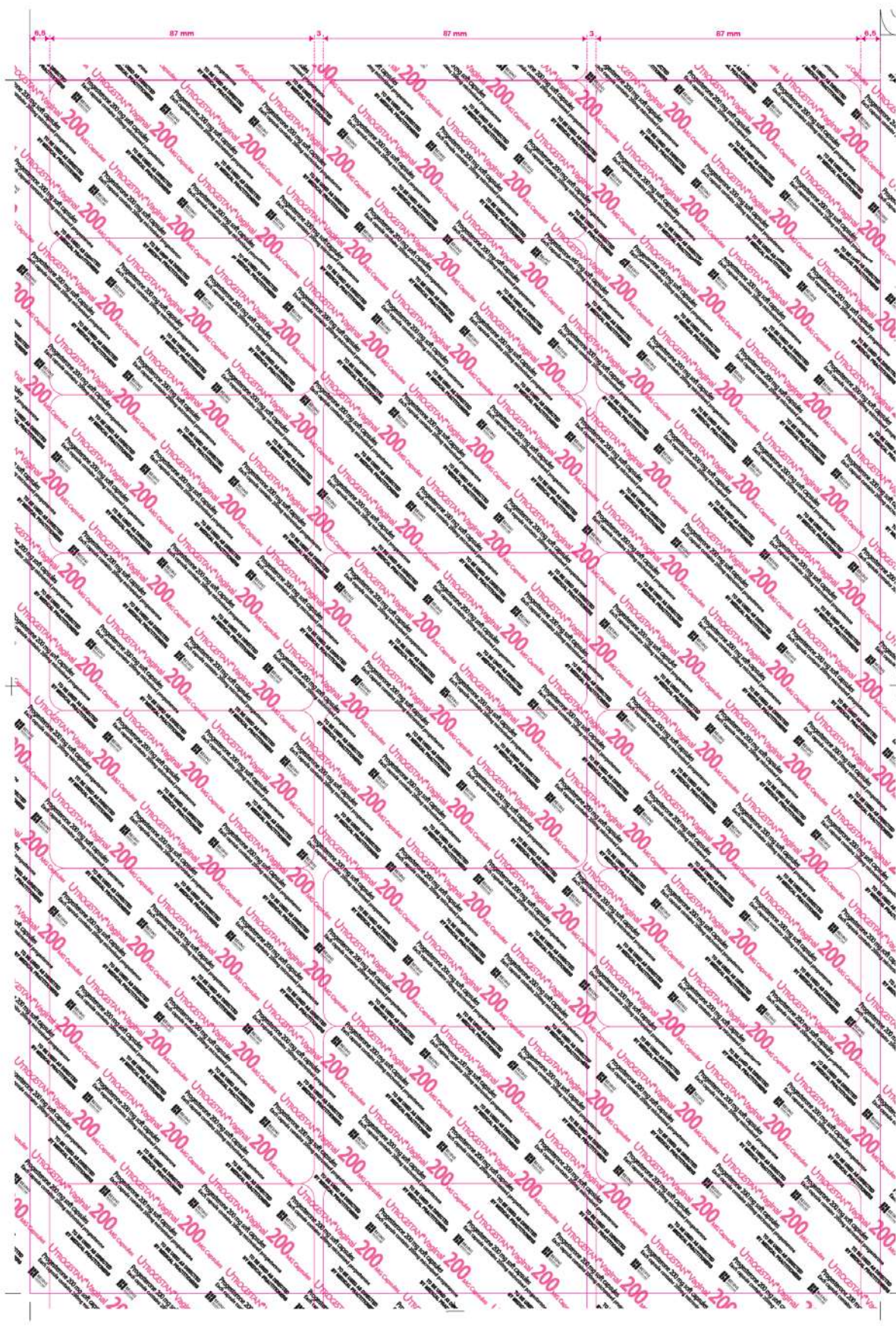
It is recommended that a Marketing Authorisation is granted for Utrogestan Vaginal 200mg Capsules.

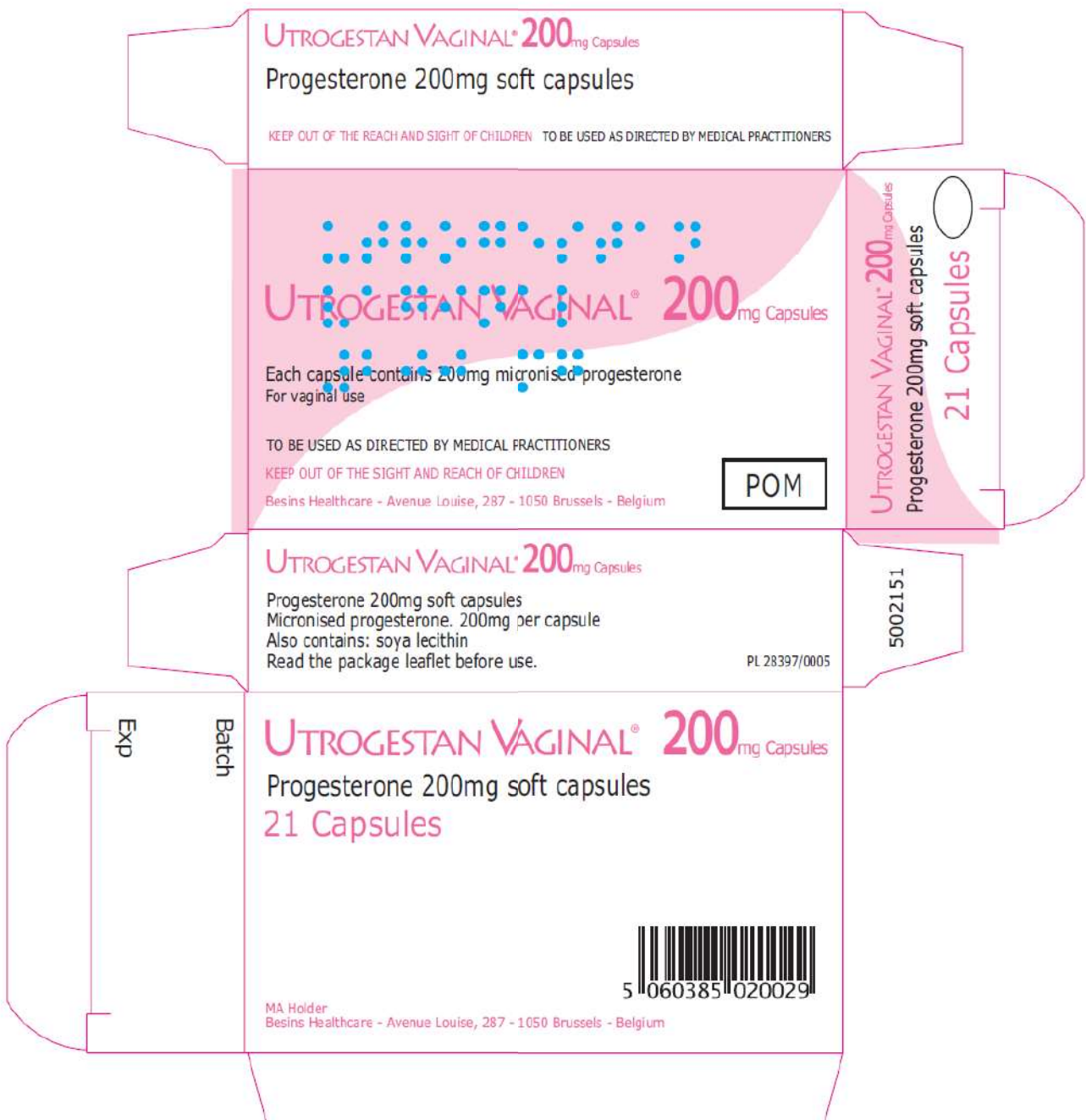
II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

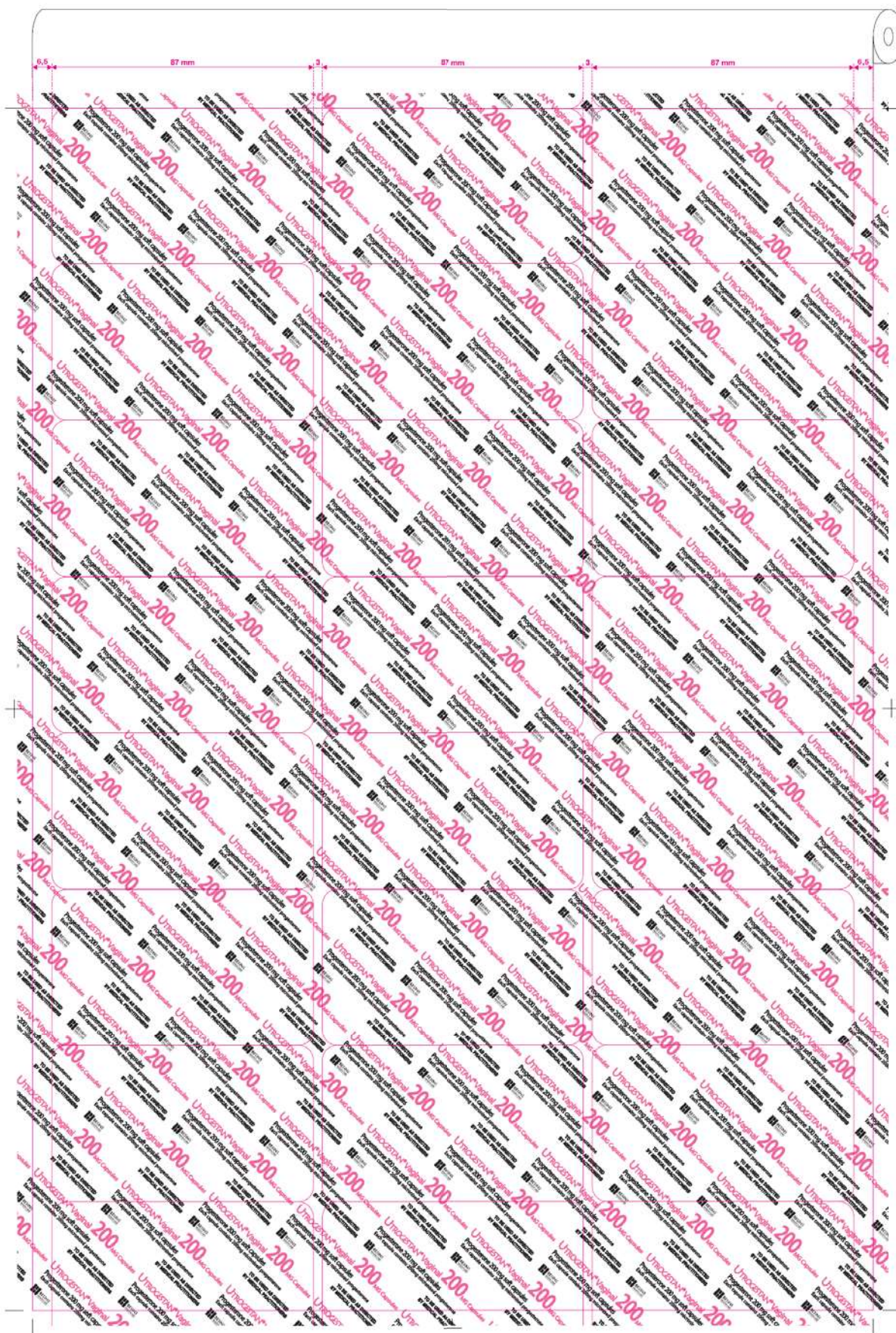
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

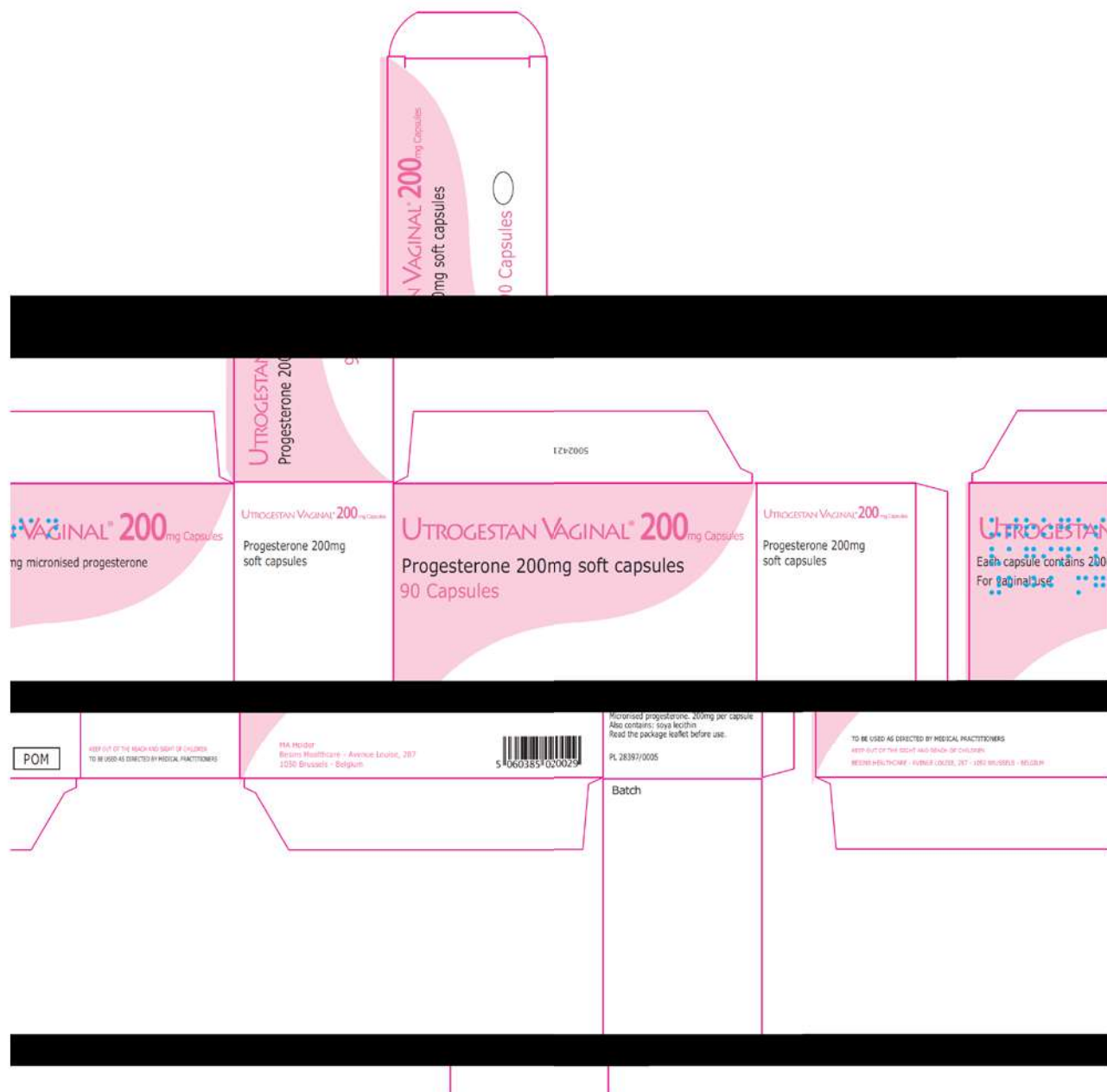
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:

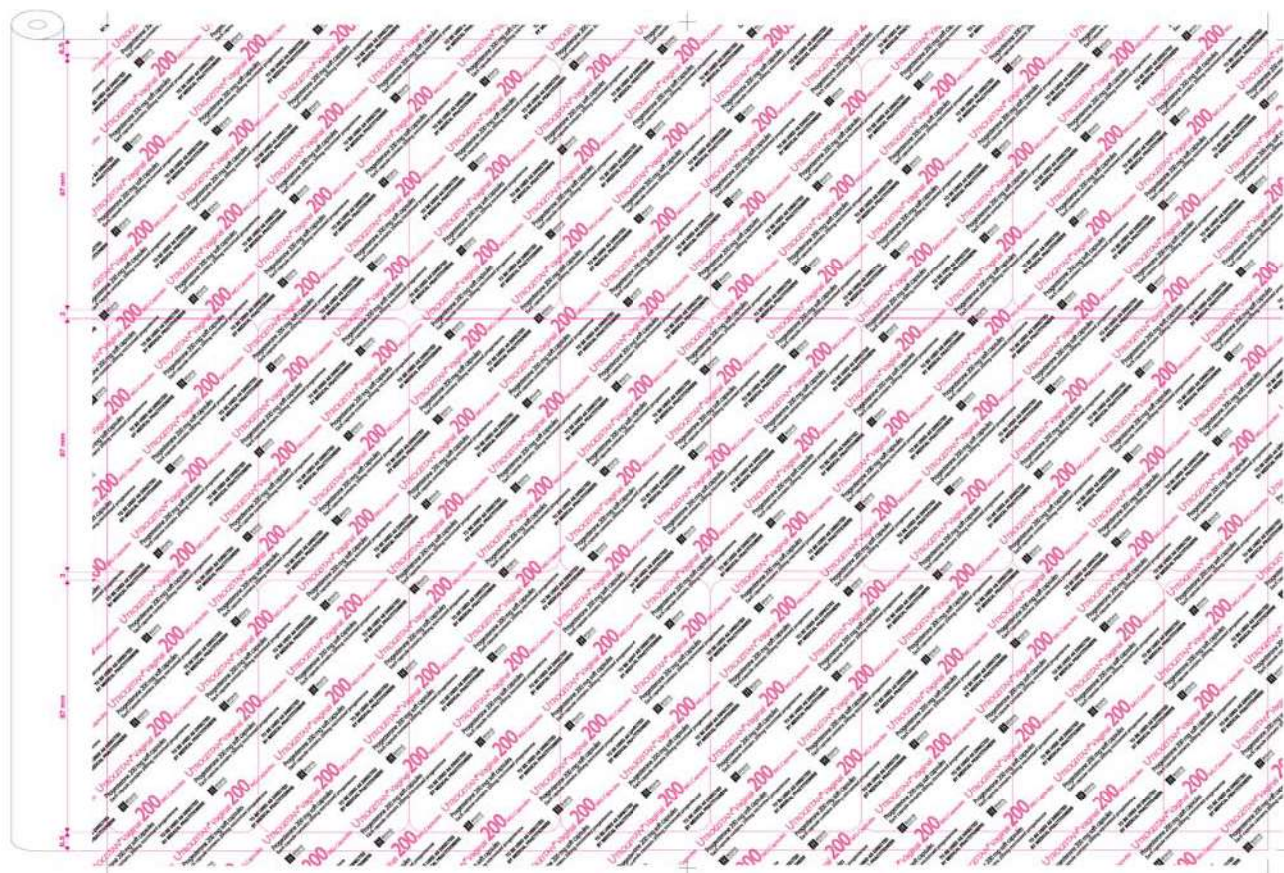












III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of progesterone for both oral and vaginal routes of administration are well-known, no further non-clinical studies have been provided and none are required. The Applicant has submitted data from the literature in support of the application.

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 Pharmacodynamics

Progesterone is a hormone with different actions dependent on the period in the oestrous cycle. Progesterone regulates maturation of the oocytes, ovulation, myometrial quiescence, mammary gland growth and endometrial enzymes.

Progesterone is clinically well-established for both oral and vaginal routes of administration and in view of this no pharmacology data in support of the proposed indication has been provided. However, brief reference is made of the fact that progesterone is used extensively in veterinary medicine for indications including disorders of the reproductive system, for oestrous synchronization and preparation of donor and receptor animals in the case of embryo transfer.

The effects of progesterone on a number of secondary targets were described. The overall effect on the cardiovascular, respiratory and central nervous systems was not discussed; however, given the effects on the secondary targets and/or organ systems and the clinical experience with products containing progesterone, no further information will be requested at this time.

III.3 Pharmacokinetics

The physiological plasma concentration of progesterone in men is approximately 0.3 ng/mL; in women this ranges from 0.23 to 1.2 ng/mL (follicular phase), 8.3 to 25 ng/mL (luteal phase) and 21 to 200 ng/mL (pregnancy). In a publication by Csapo and colleagues, circulating plasma levels of progesterone were measured in 12 nulliparous patients (mean age of 19.5 years) during the last 7 weeks of gestation and spontaneous labour. Plasma progesterone levels were 173 ± 6 ng/mL in the 2-3 weeks prior to the onset of labour, and 146 ± 11 ng/mL at the onset of labour.

The proposed product was administered to healthy women via the vaginal route at a dose of 200 mg progesterone in several clinical studies and during these studies the maximum $C_{\max}$ was within physiological plasma concentrations of progesterone in women. In other clinical investigations involving women undergoing assisted reproductive technology procedures, following the use of the proposed product, peak plasma concentrations of progesterone during the luteal phase ranged from negligible to 160 ng/mL.

In the bloodstream, progesterone is bound mostly to albumin, but some is also bound to transcortin, also known as corticosteroid-binding globulin. Progesterone accumulates in fatty tissue due to its lipophilic properties, and in tissues/organs containing progesterone-receptors.

Progesterone has a half-life of about 5 minutes and following oral administration, is metabolised mainly by the liver to pregnanediol. One clinical study compared the metabolism of progesterone following a single oral vs vaginal administration. The metabolites detected following oral administration of Utrogestan (pregnanedione and pregnanolone) were undetectable or only detected at very low levels following vaginal

administration. This difference is due to the lack of first-pass metabolism when Utrogestan is administered vaginally. This is clinically significant since the predominant pregnanediol metabolite (5 α -dihydroprogesterone) is an active metabolite, as are both 5 α - and 5 β -pregnanolone, which importantly have sedative effects that are avoided with vaginal administration. Other clinical studies have also confirmed that levels of 5 β -pregnanolone are very low following vaginal administration of Utrogestan.

Following intravenous injection of humans, the reported half-lives for progesterone range from 3 to 90 minutes, and excretion is predominantly via urine (50 to 60%). When Utrogestan Capsules were administered to healthy women via the vaginal route at a dose of 200 mg progesterone per day for 5 days, mean terminal elimination half-life of progesterone was 10.8 ± 2.2 hours, while clearance was 1370 ± 465 L/hour.

The pharmacokinetic data provided suggest that exposures of the active substance and/or active metabolites are in line with or lower than that experienced with the previously/currently marketed oral formulations containing progesterone. This provides some reassurance in terms of safety. Overall, the pharmacokinetic aspects of the non-clinical overview are considered adequate.

III.4 Toxicology

In a 26-week subcutaneous toxicity study in rats, organ atrophy (gonads, uterus, prostate) and increased pituitary weight (males only) were observed at the maximum dose of 16 mg/kg/day. However, in a 26-week oral study in the same species, the NOEL was very high (160 mg/kg/day). Treatment of dogs for 1 to 1.5 years with progesterone containing subcutaneous implants (approximately 225, 375, 1125 or 1650 mg progesterone/kg) resulted in a slight degree of mammary enlargement, glandular activity and nodule development at ≥ 375 mg/kg. Treatment of monkeys for 1 year with vaginal rings releasing 235 or 1770 μ g progesterone/day showed effects on organs of the reproductive system at both dose levels.

A report by the International Agency for Research on Cancer (IARC) suggests that progesterone was not genotoxic in a range of *in vitro* and *in vivo* investigations. Studies on transformation in rodent cells *in vitro* were inconclusive with a rat embryo cell study giving a positive result, a mouse cell study giving a weak positive result and a Syrian hamster embryo cell study giving a negative result. The Committee for Veterinary Medicinal Products (CVMP) concluded that progesterone does not exhibit mutagenic activity in most *in vitro* and *in vivo* tests performed and that overall, steroid hormones are devoid of genotoxic activity *in vivo*.

Some evidence of an increased incidence of carcinoma was observed (in reproductive tissues) in mice and pre-neoplastic mammary gland nodules were seen in dogs after chronic treatment. However, progesterone is known to increase the tumour incidence in endocrine target tissues after continuous (parenteral) doses that are clearly above those observed physiologically. The evidence suggests that progesterone is not carcinogenic *per se*, but mechanistically works via an epigenetic mechanism associated with its endocrine activity, i.e. it has the ability to cause a hyperproliferative effect at the cellular levels which is mediated by the steroid-hormone receptor interaction. Treatment with Urogestan Capsules as proposed will produce physiological concentrations of progesterone and not supra-physiological concentrations, such that the overall carcinogenicity risk is not increased by treatment over a relatively short time period (as proposed).

There was no evidence of teratogenicity/embryotoxicity following treatment with natural progesterone. Progesterone administered intramuscularly to rats at 5 mg/day on days 16 to 19 of gestation had no effect, but the same dosage on days 20 to 23 of gestation caused fetal death, which was probably related to the prolonged delay of parturition following progesterone administration. This was not considered to be of

relevance to the proposed use/indications as the product is to be administered up until the 12th week of pregnancy only.

A repeated dose local tolerance study was performed in adult female New Zealand White rabbits; whereby animals (n=6/group) were intravaginally administered with no treatment at all (control group), inert ingredients within the gelatin capsule (vehicle group) or one third of the contents of one capsule via the intravaginal route daily for 29 consecutive days. The daily dose of progesterone administered intravaginally within the gelatin capsule was 33 mg, which is comparable to the maximum clinical dose of 600 mg/day (approx. 60 kg body weight). During the study, there were no treatment-related deaths and no clinical signs of adverse effects. Examination of the vulva revealed no adverse treatment-related local tolerance findings from treatment with Utrogestan capsules, with no treatment-related increases in vulvar erythema. There were no adverse effects on the body weight development or food consumption. There were no macroscopic or microscopic abnormalities attributable to treatment.

There is clinical evidence to suggest that vaginal administration of Utrogestan is generally well-tolerated in healthy, young female volunteers (metrorrhagia, spotting and vaginal discharge observed in some), in women with ovarian failure and in women undergoing assisted reproductive technology procedures. Overall, the data suggest that toxicity profile of Utrogestan capsules following vaginal administration is similar to the oral formulations that were approved previously. Hence, there are no additional safety concerns with the proposed product.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMA/CHMP/SWP/4447/00], the applicant submitted an Environmental Risk Assessment (ERA) for progesterone and this has been updated in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMA/CHMP/SWP/4447/00 corr 2] (see Annex 1). It is concluded that Utrogestan Vaginal 200mg Capsules are of negligible risk to the environment when used in accordance with the product information.

III.6 Discussion of the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the application is for the known active substance progesterone, for which the pharmacodynamics, pharmacokinetic and toxicological properties are well known. A review of the literature is provided and is acceptable.

It is recommended that a Marketing Authorisation is granted for Utrogestan Vaginal 200mg Capsules, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction.

The clinical pharmacology of progesterone is well-known. Several pharmacokinetic and two clinical efficacy studies were submitted to support the application.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

The pharmacokinetic properties of progesterone are well known. Several clinical pharmacokinetic studies were submitted to demonstrate the pharmacokinetics of Utrogestan 200mg Capsules after vaginal administration. Overall, the studies were adequate.

The pivotal pharmacokinetic study, was a comparative study that compared the plasma bioavailability of progesterone from one 200mg Utrogestan capsule and 1.125g of Crinone 8% Gel (containing 90 mg of progesterone per dose), both administered vaginally in healthy women. The study was not designed to demonstrate the bioequivalence of the two products: it was aimed to compare systemic exposure. The other pharmacokinetic studies were supportive. Details of the pivotal pharmacokinetic study are summarised below:

Subjects included were non-pregnant, healthy women (aged 19-38 years) with a normal body weight (Broca's criteria) and on an oral oestradiol analogue/progestin combination contraceptive to ensure suppression of endogenous progesterone secretion; plasma progesterone had to be < 0.3 ng/ml on two different days between Day 4 and 18 in the menstrual cycle prior to the study. Exclusion criteria included evidence of any clinically significant condition that might affect the pharmacokinetics of progesterone, regular use of any medication (except an oral contraceptive) within the previous 8 weeks, and use of any oestrogen or gestagen injection within the previous 6 months. A total of 25 subjects entered the study and 24 completed it (mean $\pm$ SD age 27.8 ± 4.8 years, mean $\pm$ SD weight 63.3 ± 9.6 kg, all Caucasian). The patient who did not complete the study was withdrawn during the washout period after the Crinone arm due to evidence of a pre-existing depressive disorder.

Subjects received one of the two study treatments, in a random order with a washout period of at least 7 days, between Day 4 and 18 of the menstrual cycle (but not before menstrual bleeding had stopped). A blood sample was taken for pharmacokinetic analysis prior to dosing at 0800h (following an overnight fast) and further blood samples were taken over the next 96 hours. The mean $\pm$ SD baseline progesterone level was 0.18 ± 0.35 ng/ml in the Utrogestan arm and 0.11 ± 0.08 ng/ml in the Crinone arm. The main pharmacokinetic results of the study are presented in the table below:

Table 1 Mean($\pm$ SD) Plasma Pharmacokinetic Parameters for Progesterone Following Vaginal Administration of one Utrogestan 200mg Capsule or 1.125 g of Crinone 8% Gel

Parameter	Utrogestan	Crinone	Ratio or *Difference (90% Confidence Interval)
C_{0max} (ng/ml)	6.87 ± 1.80	6.83 ± 2.32	103.4% (92.4-115.8%)
T_{max} (hours)	40.55 ± 29.10	10.08 ± 6.11	*28.73 (17.01-38.88)
AUC_0 (ng.h/ml)†	281.9 ± 120.8	189.4 ± 96.9	146.1% (126.2-169.1%)
$T_{1/2}$ (hours)	14.82 ± 10.00	17.47 ± 9.13	88.2% (67.0-116.3%)

N = 23, † AUC_0 until the last concentration above the limit of quantification

AUC_0 = Area under the net plasma concentration-time curve; C_{0max} = Maximum plasma concentration increase

$T_{1/2}$ = Apparent terminal half-life; T_{max} = Time to maximum plasma concentration

Results and Conclusion

The pharmacokinetic analysis demonstrated that, following the administration of Utrogestan, the maximum plasma concentration increase above baseline (C_{0max}) and terminal half-life of plasma progesterone were comparable to those following the administration of Crinone. However, the AUC for progesterone corrected for baseline levels (AUC_0) until the last concentration above the limit of quantification was almost 50% greater with Utrogestan compared with Crinone, and the T_{max} was 29 hours later with Utrogestan.

IV.3 Pharmacodynamics

The effect of progesterone is well established and known. There are no particular requirements for pharmacodynamic studies and none have been carried out.

IV.4 Clinical Efficacy

To demonstrate efficacy, two studies were submitted. Only the data of the pivotal study was considered relevant as the second study (a Phase I/II study) was an uncontrolled one-arm study and it did not provide comparative evidence of efficacy. The pivotal study is discussed below:

Study (Pivotal)

A multi-centre, open label randomised active-controlled parallel group study comparing the efficacy and safety of vaginal Utrogestan 200mg Capsules and Crinone 8% Gel (a vaginal administration of progesterone gel) in providing luteal phase support to women undergoing in-vitro fertilisation (IVF), with or without intracytoplasmic sperm injection (ICSI).

Objectives

The aim of the study was to demonstrate the efficacy and tolerability of Utrogestan 200mg vaginally for luteal phase support during assisted reproduction, with Crinone 8% Gel (containing 90 mg of progesterone per dose) used as comparison. Crinone 8% Gel has a UK Marketing Authorisation and is established in the indication of progesterone supplementation as part of an assisted reproductive technology treatment.

Study Design

430 patients were recruited and randomised before embryo transfer took place. Patients were randomised to receive, vaginally, either one Utrogestan 200mg Capsule 3 times per day or two doses of Crinone 8% Gel per day. Each patient was to receive treatment daily beginning on the evening of the transfer day up to the 12th week of gestation, if pregnant.

Patients were followed up at Visit T1 (12 – 14 days after embryo transfer when pregnancy was confirmed), visit T2 (27 to 29 days after embryo transfer) and visit T3 (35-42 days after embryo transfer and visit T4 (63-70 days after embryo transfer.) The primary outcome measure was the ongoing pregnancy rate at week 12.

Main inclusion criteria

- Indication for IVF/ICSI
- Successful transfer of 2 or 3 embryos
- First treatment cycle
- Age ≥ 18 years and ≤ 35 years
- Normal cytological smear within the past 12 months

Main exclusion criteria

- Severe acute and chronic liver disease
- Rotor or Dubin-Johnson syndrome
- Hepato-cellular tumours
- Known hypersensitivity to one of the active constituents or excipients contained in the investigational medication

Primary endpoint

The primary endpoint was ongoing pregnancy rate at the end of study (≥ 12 th week of gestation).

Secondary endpoints

The secondary endpoints included amongst others:

- Number of implantations/living foetus
- Miscarriage rates

Statistical methods

The primary goal was to demonstrate non-inferiority of the test medication Utrogestan 200mg Capsule to the reference medication Crinone 8% Gel. The intent-to-treat population was used as the primary analysis population, with the per-protocol population providing a secondary analysis.

Hence, non-inferiority was to be declared if the lower limit of the 90% confidence interval for the difference between arms (treatment) was above -0.1 (i.e., a 10% non-inferiority margin). The applicant has provided an adequate justification for the use of the 10% non-inferiority margin.

Results

Disposition of Subjects

The patient disposition table is shown below:

Table 2: Patients withdrawing and patients remaining in the trial

	UTROGEST® 200		CRINONE® 8 %		Total	
Patients screened					583	
Patients enrolled					430	
Patients randomised	218		212		430	
Patients prematurely withdrawn	163	74.8 %	165	77.8 %	328	76.3 %
up to or at T 1	137	62.8 %	138	65.1 %	275	64.0 %
up to or at T 2	17	7.8 %	20	9.4 %	37	8.6 %
up to or at T 3	6	2.8 %	6	2.8 %	12	2.8 %
after T 3 till end of trial	3	1.4 %	1	0.5 %	4	0.9 %
Patients remaining in the study up to the 12 th week of gestation	55	25.2 %	47	22.2 %	102	23.7 %

Most withdrawals occurred up to or at visit T1 due to lack of β HCG increase and vaginal bleeding, which pertained to about two thirds of the study population (Table 2). Pregnancy failure was accountable for 93.9% and 90.9% of discontinuations in the Utrogestan 200mg Capsule and Crinone 8% Gel groups, respectively. The reasons for withdrawal are shown in Table 3. The reasons and rates for discontinuations appeared similar in both groups.

Table 3: Reasons for discontinuation

Withdrawal reason	UTROGEST® 200		CRINONE® 8 %	
	N	% of study group	N	% of study group
Pregnancy failure	153	70.2 %	150	70.8 %
Vaginal bleeding, no biochemical pregnancy	143	65.6 %	141	66.5 %
Abortion	3	1.4 %	6	2.8 %
Missed abortion	7	3.2 %	3	1.4 %
Other reasons for withdrawal	10	4.6 %	15	7.1 %
Adverse event	1	0.5 %	2	0.9 %
Local intolerance	1	0.5 %	3	1.4 %
Unallowed hormone therapy	4	1.8 %	3	1.4 %
Withdrawal of consent			2	0.9 %
Patient did not return	3	1.4 %	2	0.9 %
Other	1	0.5 %	3	1.4 %
Total	163	74.8 %	165	77.8 %

Primary efficacy analysis

Pregnancy rates

Confirmatory analysis of efficacy was based on the ongoing pregnancy rate at or beyond 12 weeks gestation as the primary outcome measure of this study.

The results for the analysis for the intent-to treat (ITT) and per-protocol (PP) populations are shown below:

Table 2: Analysis of data sets
Table 2 : Analysis of Data Sets

	Utrogestan	Crinone	Difference
ITT	25.2% (55/218)	22.2% (47/212)	3.1% (95%CI:[-6.5%;12.5%])
PP	26.4% (55/208)	23.9% (47/197)	2.6% (95%CI:[-7.2%; 12.3%])
ITT Sensitivity analysis: includes early withdrawals with confirmed pregnancy	28.0% (61/218)	26.9% (57/212)	1.1% (95%CI:[-8.4%; 10.6%])

Conclusion on efficacy

Suitable justification has been provided for the dose regimen of Utrogestan 200mg Capsule and Crinone 8% Gel used in the study. The data from the study demonstrated that Utrogestan 200mg Capsule was statistically non-inferior to Crinone 8% Gel for supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles.

Number of implantation/living fetuses

Multiplicity of pregnancies was recorded at visits T3 (8th week of gestation) and T4 (12th week of gestation). 71% of pregnancies in the Utrogestan group and 79% in the Crinone8% Gel group were singleton pregnancies. 83 and 72 fetuses were detected at T3 and T4 respectively in the Utrogestan 200 mg Capsule group and 64 and 58 fetuses in the Crinone8% Gel group. The Mann-Whitney statistic amounted to 0.5468 (0.4622 to 0.6361) at visit T3 ($p=0.3268$) and to 0.5432 (0.4600 to 0.6263 at visit 4 ($p=0.3268$).

Miscarriage rate (rate of abortions/missed abortions

In the Utrogestan 200mg Capsule group 10/218 women experienced an abortion or missed abortion. For the Crinone 8% Gel group, 9/212 women (4.2%) experienced an abortion or missed abortion. The rate difference was 0.0034 ($p=0.990$), a very similar rate of abortion in each group.

Clinical safety

The frequency of adverse events in the pivotal efficacy study is given in the table below:

Table 3: Patients with adverse events (overall and specific visits, percentage of patients with available data)

	UTROGEST [®] 200 (N = 218)				CRINONE [®] 8 % (N = 212)			
	yes	no	data missing		yes	no	data missing	
Visit T 1	13	6.1 %	199	6	14	6.7 %	195	3
Visit T 2	3	4.1 %	70	145	7	10.8 %	58	147
Visit T 3	7	11.3 %	55	156	5	9.4 %	48	159
Visit T 4	6	11.1 %	48	164	7	14.6 %	41	164
at any time	21	9.7 %	196	1	21	9.9 %	191	0

The detailed description and the summary tables provided (see below) indicate that there were no significant serious adverse events in patients treated with Utrogestan 200mg Capsules in the pivotal efficacy study and the adverse events were comparable in the Utrogestan and Crinone groups. The overall frequency of adverse events in the Utrogestan and Crinone groups were 11.0% and 12.3% respectively.

TABLE 4 : Comparative Table of Treatment-Emergent Adverse Events in the Pivotal Efficacy Study.

	UTROGESTAN 200 mg (N = 218)			CRINONE 8% (N = 212)		
	Total R/NR		Total	Total R/NR		Total
	R	NR	All - n (%)	R	NR	All - n (%)
Ovarian hyperstimulation syndrome		7	7 (3.2)		9	9 (4.2)
Vaginal bleeding/spotting	1	2	3 (1.4)	1	2	3 (1.4)
Nausea/Emesis		2	2 (0.9)		1	1 (0.5)
Vaginal candidiasis/infection		1	1 (0.5)	1		1 (0.5)
Cervical dysplasia (PAP III D)		1	1 (0.5)			0 (0.0)
Varicella infection		1	1 (0.5)			0 (0.0)
ET associated inflammation		1	1 (0.5)			0 (0.0)
Diarrhoea	1		1 (0.5)			0 (0.0)
Exanthema	1		1 (0.5)			0 (0.0)
Acute urinary retention		1	1 (0.5)			0 (0.0)
Jugular vein thrombosis	1		1 (0.5)			0 (0.0)
Ovarian cyst		1	1 (0.5)			0 (0.0)
Bloating	1		1 (0.5)			0 (0.0)
Vaginal discharge	1		1 (0.5)	6		6 (2.8)
Local itching/burning/irritation	1		1 (0.5)	4		4 (1.9)
Pregnancy hypertonus			0 (0.0)		1	1 (0.5)
Cervical ectopia with bleeding			0 (0.0)		1	1 (0.5)
Total - n (%)	7 (3.2)	17 (7.8)	24 (11.0)	12 (5.7)	14 (6.6)	26 (12.3)

TABLE 5 : Comparative Table of Treatment-Emergent Local Adverse Events in the Pivotal Efficacy Study.

	UTROGESTAN 200 mg (N = 218)			CRINONE 8% (N = 212)		
	Total R/NR		Total	Total R/NR		Total
	R	NR	All - n (%)	R	NR	All - n (%)
Erythema	11	3	14 (6.4)	14	2	16 (7.5)
Burning	5	1	6 (2.7)	6		6 (2.8)
Vaginal discharge	3	2	5 (2.3)	1	1	2 (0.9)
Itching	3		3 (1.4)	7		7 (3.3)
Total - n (%)	22 (10.1)	6 (2.8)	28 (12.8)	28 (13.2)	3 (1.4)	31 (14.6)

TABLE 6 : Comparative Table of Withdrawals Due to an Adverse Event in the Pivotal Efficacy Study

	UTROGESTAN 200 mg (N = 218)	CRINONE 8% (N = 212)
	n (%)	n (%)
Adverse Event	1 (0.5)	2 (0.9)
Local Tolerance	1 (0.5)	3 (1.4)

IV.5 Clinical Safety

The safety profile of progesterone administered via the vaginal route is well known. The safety of Utrogestan Vaginal 200mg Capsules was demonstrated primarily through the pivotal efficacy study. No new or unexpected safety concerns arose from this application.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, 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 Utrogestan Vaginal 200mg Capsules.

Routine pharmacovigilance and routine risk minimisation activities are acceptable to monitor the safety concerns described in the Risk Management Plan.

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Utrogestan Vaginal 200mg Capsules.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet has been performed on the basis of a bridging report making reference to the Patient Information Leaflet for the product Utrogestan 200mg Capsules (PL 16468/0007). The bridging report submitted by the applicant has been found to be acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION QUALITY

The important quality characteristics of Utrogestan Vaginal 200mg Capsules 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

No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of progesterone are well-known, no additional data were required.

EFFICACY

With the exception of the efficacy study, no new data were submitted and none are required for this type of application.

The applicant's Utrogestan Vaginal 200mg Capsules has been demonstrated to be non-inferior to Crinone 8% Gel in the supplementation of luteal phase during assisted reproductive technology (ART).

SAFETY

The safety profile of progesterone is well-known. No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Utrogestan Vaginal 200mg Capsules have been demonstrated to be non-inferior to Crinone 8% Gel in the supplementation of luteal phase during assisted reproductive technology (ART). The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION

The grant of a Marketing Authorisation is recommended.

Utrogestan Vaginal 200mg Capsules

(progesterone)

STEPS TAKEN AFTER AUTHORISATION-SUMMARY

The following table lists a non-safety update to the Marketing Authorisation for this product that has been approved by the MHRA since the product was first licensed. The table includes an update that has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Scope	Outcome
09 July 2015	Type IB	To update the Environmental Risk Assessment.	Approved on 15 September 2015

Annex 1

Our Reference: PL 28397/0005- 0016
Product: Utrogestan Vaginal 200mg Capsules
Marketing Authorisation Holder: Besins Healthcare
Active Ingredient(s): Progesterone.

Type of Procedure: National
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable):

Reason:
 To update the Environmental Risk Assessment.

Linked / Related Variation(s) or Case(s):
 None

Supporting Evidence

- Module 1.6.1 Environmental Risk Assessment.
- Published literature

Evaluation

The applicant has used published literature to assess the environmental risk of the drug substance, in accordance with CHMP guideline EMEA/CHMP/SWP/4447/00 corr 2.

A summary of results is provided below:

PBT screening		Result	Conclusion
Bioaccumulation potential- logK _{ow}		LogK _{ow} 3.87	Potential PBT No
PBT-statement:		The log K _{ow} value for Pregn-4-ene-3, 20-dione (progesterone) is < 4.5, therefore screening for PBT is not required as this does not meet the criteria for classification as a PBT compound.	
Phase I			
Calculation	Value	Unit	Conclusion
PEC _{surfacewater, refined}	0.117	µg/L	>0.01 threshold Yes
Other concerns (e.g. chemical class)	Pregn-4-ene-3, 20-dione (progesterone) is considered to be a potential endocrine disruptor.		Yes
Outcome of Phase I :	Since the PEC _{sw} value is > 0.01 µg/L action limit and pregn-4-ene-3, 20-dione (progesterone) is considered to be potential endocrine disruptor, a Phase II environmental fate and effects analysis is required.		

Phase II Tier A Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	Not reported	Adsorption Coefficient $K_{oc} = 8,248$			Value quoted from Smolenski, 2008.
Phase II Tier A Effect studies					
Study type	Test protocol	Endpoint	Value	Unit	Remarks
<i>Daphnia</i> sp. Reproduction Test	Not reported	NOEC (14d)	0.1	mg/L	<i>Daphnia magna</i>
$PNEC_{water}$ $PEC_{surfacewater}/$ $PNEC_{water}$			0.001 0.117	mg/L	Unlikely to represent a risk to the aquatic environment
$PEC_{groundwater}$ $PNEC_{groundwater}$ $PEC/PNEC_{groundwater}$			2.93×10^{-5} 0.001 0.0293	mg/L	Unlikely to represent a risk to the aquatic environment

PBT	Persistent, Bioaccumulative and Toxic
$PEC_{surfacewater}$	Predicted Environmental Concentration _{surfacewater}
$PEC_{groundwater}$	Predicted Environmental Concentration _{groundwater}
$PNEC_{water}$	Predicted No Effect Concentration _{water}
$PNEC_{groundwater}$	Predicted No Effect Concentration _{groundwater}

Estimation of exposure of the environment to progesterone has shown that: screening for persistence, bioaccumulation and toxicity (PBT) of progesterone is not required since the log n-octanol/water partition coefficient ($\log K_{ow}$) value (3.87) is below the guidance lower limit value of 4.5.

In the Phase I assessment, the PEC_{sw} value for progesterone was above the action limit of 0.01 µg/L and the active compound is also considered to be a potential endocrine disruptor, resulting in Phase II analysis being performed.

PEC/PNEC analysis in the Phase IIA assessment showed that no further refinement of the PEC_{sw} and PEC_{gw} was required for Phase IIB and that further assessment of the terrestrial compartment was not required.

The Applicant has quoted a reference by Yotis and Stanke (1966) which found that progesterone exerted an antimicrobial action only on gram-positive bacteria at concentrations, *in vitro*, of 10 µg/ml or greater. The $PEC_{surfacewater}$ concentration of progesterone arising from the use of Utrogestan Vaginal 200mg Capsules has been calculated to be 0.117 µg/l. Since there is an extensive margin between the quoted progesterone concentration that has antimicrobial action and the $PEC_{surfacewater}$ concentration of progesterone, it is agreed that Utrogestan Vaginal 200mg Capsules are unlikely to represent a risk to environmental microorganisms.

Although the $\log K_{ow}$ value of 3.87 is below the threshold of 4.5 for screening of persistence, bioaccumulation and toxicity, the K_{ow} value is 7413 (inverse log of 3.87). According to EMEA/CHMP/SWP/4447/00 corr 2, if the n-octanol/water partition coefficient indicates the transfer of the drug substance from the aquatic environment into organisms and a potential to bioaccumulate (i.e. $K_{ow} > 1000$), then the bioconcentration factor should be considered in Tier B studies. However, an increase in environmental exposure to progesterone is deemed unlikely since this is a generic product and there is already extensive literature data on the environmental impact of this class of compound and therefore further screening is not required.

Proposals for Labelling

The Applicant has concluded that the environmental risk, as a result of the prescribed usage of Utrogestan Vaginal 200mg capsules, is negligible and therefore the following statement can be used in the product literature:

“Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.”

The proposed environmental statement for labelling is acceptable.

Conclusions:

Based on the review of the data on safety, the variation for Utrogestan Vaginal 200mg Capsules, to update the environmental risk assessment, could be approved.

Decision – Approved on 17 September 2015.



Medicines & Healthcare products
Regulatory Agency



Public Assessment Report

UK PAR

Utrogestan Vaginal 200mg Capsules

(progesterone)

UK Licence No: PL 28397/0005

Besins Healthcare

LAY SUMMARY

Utrogestan Vaginal 200mg Capsules (progesterone)

This is a summary of the Public Assessment Report (PAR) for Utrogestan Vaginal 200mg Capsules (PL 26397/0005, formerly PL 16468/0011). It explains how the application for Utrogestan Vaginal 200mg Capsules was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Utrogestan Vaginal 200 mg Capsules.

For practical information about using Utrogestan Vaginal 200mg Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Utrogestan Vaginal’ in this Lay Summary.

What is Utrogestan Vaginal and what is it used for?

Utrogestan Vaginal is a medicine that can be used to help pregnancy. Utrogestan Vaginal 200mg is used to assist fertility treatment techniques using the patient’s own eggs, such as in-vitro fertilisation (IVF), gamete intra-Fallopian transfer (GIFT) or zygote intra-Fallopian transfer (ZIFT).

Utrogestan Vaginal is not a contraceptive.

How does Utrogestan Vaginal work?

Utrogestan Vaginal contains the active ingredient progesterone, which is a natural, female sex hormone, produced in the body. This medicine works by adjusting the hormonal balance within the body.

How is Utrogestan Vaginal used?

Utrogestan Vaginal is available as vaginal capsules.

This medicine should be used exactly as instructed by the doctor. The patient should read and check with your doctor or pharmacist if you are not sure. The patient should contact the pharmacy if she requires an applicator. The applicator supplied by the pharmacy contains a leaflet. This leaflet includes pictures and describes how to use the applicator.

Using this medicine to help pregnancy

- This medicine should be inserted deep into the vagina.
- The capsule should not be taken by mouth. However, if Utrogestan Vaginal is accidentally taken by mouth it will not cause harm; it will only reduce the chances of becoming pregnant.

How much to use

- Treatment with Utrogestan Vaginal begins on the day of embryo transfer.
- Every day, 200mg of Utrogestan Vaginal should be taken in the morning, at lunchtime and at bedtime, or 200mg in the morning and the evening, as instructed by your doctor.
- If there is laboratory evidence of pregnancy, the same dose regime should continue until the 7th to 12th week of pregnancy, as instructed by your doctor.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

This medicine can only be obtained with a prescription.

What benefits of Utrogestan Vaginal have been shown in studies?

The company, Laboratoires Besins International, provided its own data on efficacy and safety studies. These studies have shown that Utrogestan Vaginal is effective in the proposed indication to assist fertility treatment techniques using the patient's own eggs, such as in-vitro fertilisation (IVF), gamete intra-Fallopian transfer (GIFT) or zygote intra-Fallopian transfer (ZIFT).

In addition, Laboratoires Besins International has provided data from the published literature on progesterone.

What are the possible side effects of Utrogestan Vaginal?

Like all medicines, Utrogestan Vaginal can cause side effects although not everybody gets them.

For the full list of all side effects reported with Utrogestan Vaginal.

What measures are being taken to ensure the safe and effective use of Utrogestan Vaginal?

A risk management plan has been developed to ensure that Utrogestan Vaginal is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Utrogestan Vaginal, 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/healthcare professionals will be monitored/reviewed continuously.

Other information about Utrogestan Vaginal

A Marketing Authorisation for Utrogestan Vaginal 200mg Capsules (PL 16468/0011) was granted in the UK to Laboratoires Besins International on 21 December 2012. Subsequent to a Change of Ownership (COA) procedure, Utrogestan Vaginal (PL 23138/0020) was granted to Marlborough Pharmaceuticals Limited on 29 November 2013. Subsequent to a further COA procedure, Utrogestan Vaginal 200mg Capsules (PL 28397/0005) was granted to Besins Healthcare on 02 December 2013.

The full PAR for Utrogestan Vaginal 200mg Capsules follows this summary.

For more information about treatment with Utrogestan Vaginal 200mg Capsules read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2015.

SCIENTIFIC DISCUSSION

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Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Laboratoires Besins International a Marketing Authorisation for the medicinal product Utrogestan Vaginal 200mg Capsules (PL 16468/0011) on 21 December 2012. This product is a prescription-only medicine (POM) indicated for supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles.

Utrogestan Vaginal 200mg Capsules may be referred to as Utrogestan in this report.

The application was submitted under Article 8(3) of Directive 2001/83/EC, as amended. The application is a line extension representing a new route of administration (vaginal) for Utrogestan 200mg capsules (PL 16468/0007). It seeks to extend the indications and posology for Utrogestan 200mg capsules to include the use vaginally for supplementation of the luteal phase during ART cycles. Utrogestan 200mg capsules (PL 16468/0007) was first authorised in the UK 1997 for oral administration, the first orally administered progesterone product on the UK market. Progesterone is currently licensed in the UK in the form of pessaries, intramuscular injection and as a vaginal gel.

The application was referred to the Commission on Human Medicines (CHM) and Chemistry Pharmacy and Standards Expert Advisory Group (CPS EAG), who met individually in November 2010 and April 2012 for consideration of whether the quality and efficacy of the product was demonstrated. Following consideration of the applicant's responses and further data that were submitted, the approval of the Marketing Authorisation was recommended.

The active ingredient is micronised progesterone, a form of the naturally occurring steroid, chemically identical to progesterone of ovarian origin. The progesterone used in Utrogestan 200mg is obtained by hemisynthesis on the basis of a precursor.

Progesterone is a sex steroid hormone and the only natural progestogen/progestin. Progesterone is produced in the adrenal glands, the gonads (specifically after ovulation in the corpus luteum), the brain, and, during pregnancy, in the placenta. All progestogens have anti-oestrogenic and antigonadotropic properties. Progestogens differ in their potency (affinity for progesterone receptors) and side effects.

Progesterone is an essential regulator of normal female reproductive function. Its effects are mediated by two nuclear progesterone receptor (PR) proteins: PRA and PRB, which are identical except for the N-terminal end of PRB. PRA and PRB are isoforms that may differ functionally. Progesterone, like all other steroid hormones is synthesized from pregnenolone, a derivative of cholesterol. Progesterone is also the precursor of the mineralocorticoid aldosterone, and after conversion to 17-hydroxyprogesterone (another natural progestogen) of cortisol and androstenedione. Androstenedione can be converted to testosterone, oestrone and oestradiol.

No new non-clinical studies were conducted, which is acceptable given that the application is for the known active substance progesterone, for which the pharmacodynamics, pharmacokinetic and toxicological properties are well known.

Ten pharmacokinetic studies and two efficacy studies were submitted to support the application. The applicant has stated that the pharmacokinetics studies were conducted in accordance with the principles laid down in the European Union guidance on pharmacokinetic studies (European Commission 1998). The

efficacy studies are stated to have been carried in accordance with Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of using Utrogestan Vaginal 200mg Capsules outweigh the risks and a Marketing Authorisation was granted.

Subsequent to a Change of Ownership (COA) procedure, Utrogestan Vaginal (PL 23138/0020) was granted to Marlborough Pharmaceuticals Limited on 29 November 2013. Subsequent to a further COA procedure, Utrogestan Vaginal 200mg Capsules (PL 28397/0005) was granted on 02 December 2013 to Besins Healthcare.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a white soft vaginal capsule. Each capsule contains 200mg micronised progesterone, as the active ingredient.

Utrogestan Vaginal 200mg Capsules also contain refined arachis oil, soya lecithin, gelatin, glycerol and titanium dioxide. Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in polyvinylchloride/aluminium blisters contained in cartons, in pack sizes of 15 and 21 capsules.

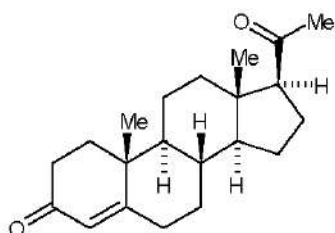
Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Progesterone

INN: Progesterone
 Chemical Name: Pregn-4-ene-3,20-dione
 Molecular Formula: $C_{21}H_{30}O_2$
 Structure



M_r : 314.5
 Appearance: A white or almost white crystalline powder or colourless crystals.

Solubility Practically insoluble in water, freely soluble in ethanol and sparingly soluble in acetone and in fatty oils.

Progesterone is the subject of a European Pharmacopoeia monograph.

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

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, stable soft capsule for vaginal (and oral) use containing 200 mg of progesterone. The product already exists for oral use on the UK market and therefore no further formulation development studies are provided. This is acceptable.

Satisfactory *in-vitro* dissolution profiles considering the vaginal environment have been provided.

All the excipients comply with their respective European Pharmacopoeia monographs, with the exception of soya lecithin, which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data that comply with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with no special storage conditions, has been accepted.

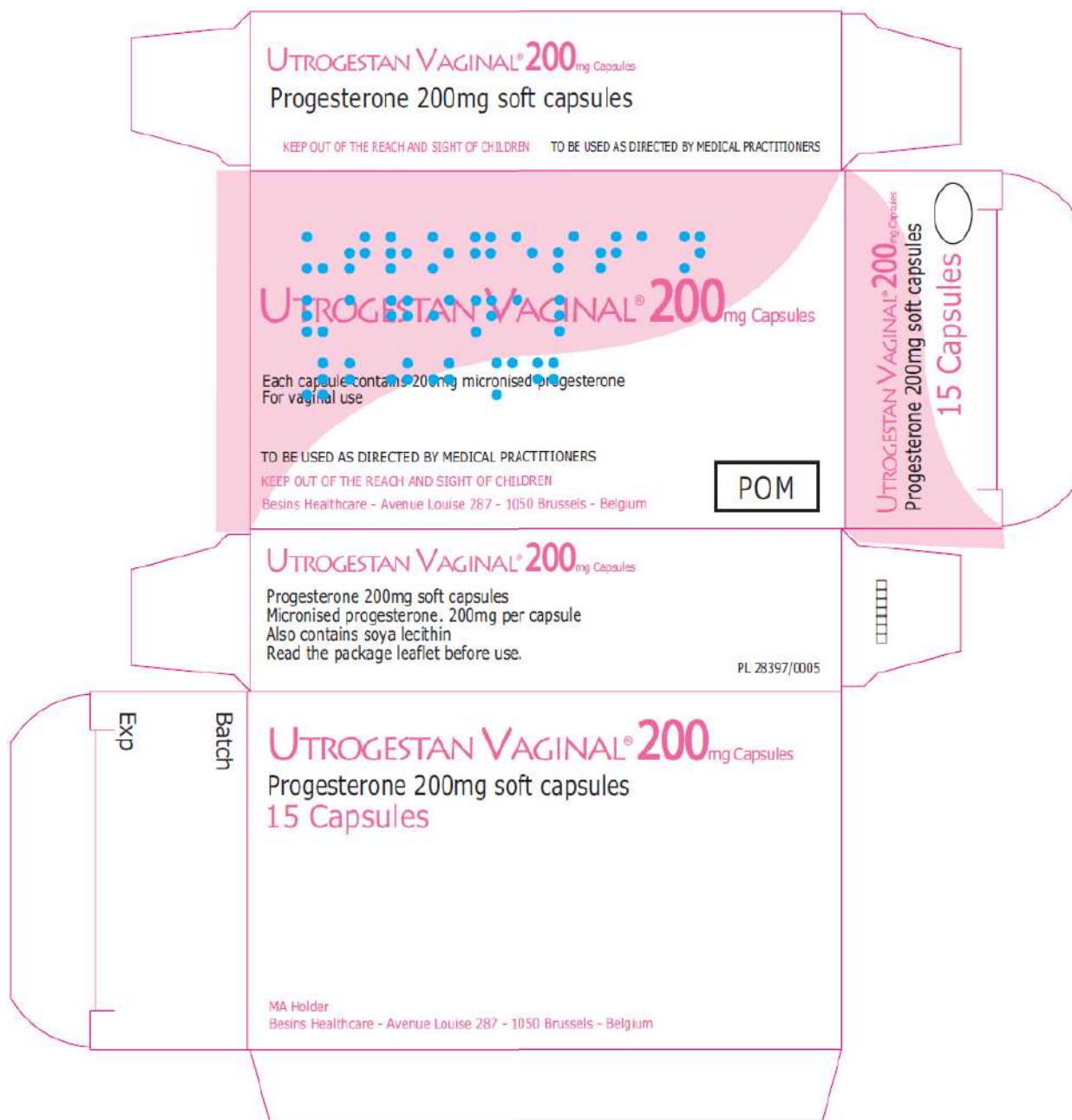
II.4 Discussion on chemical, pharmaceutical and biological aspects

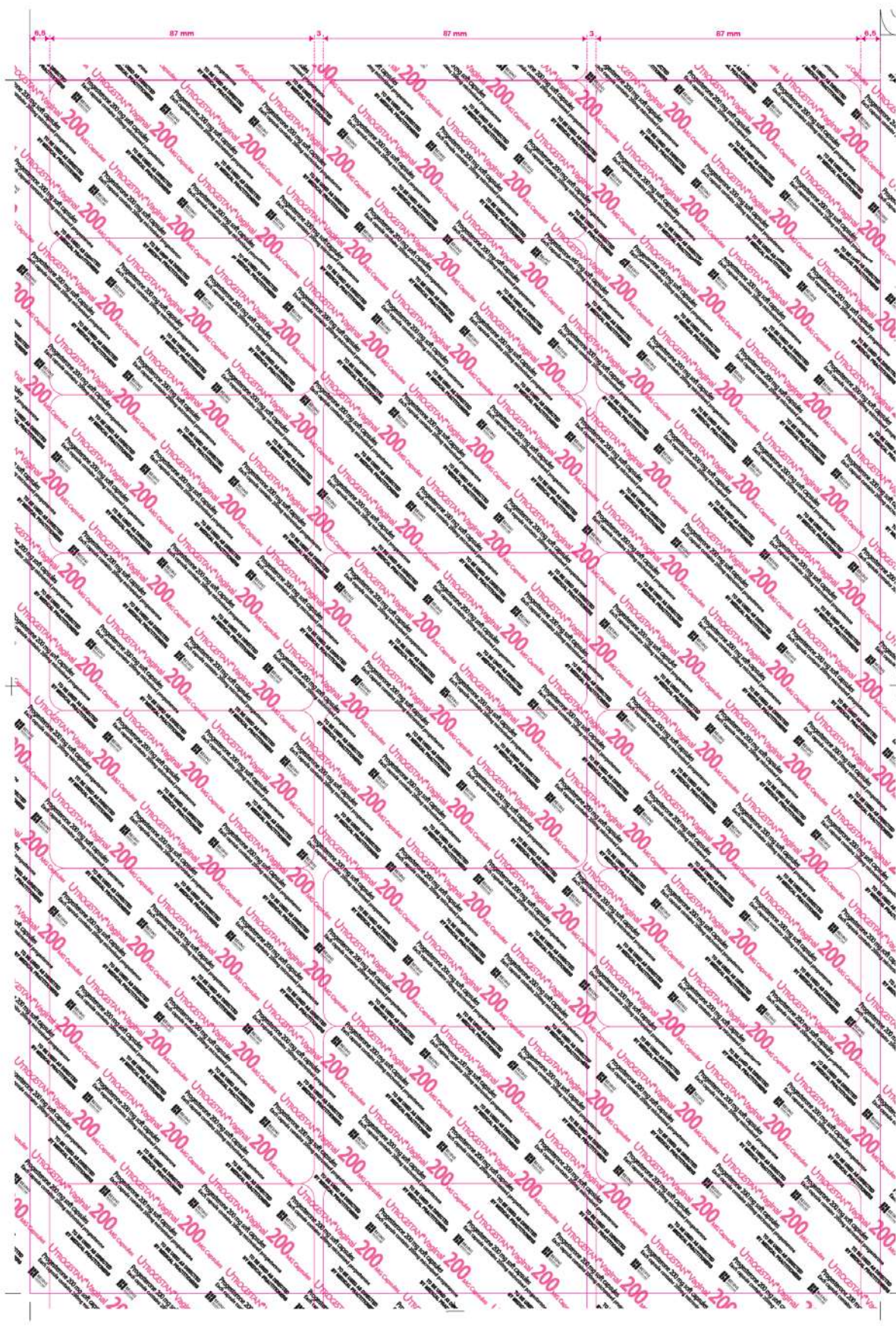
It is recommended that a Marketing Authorisation is granted for Utrogestan Vaginal 200mg Capsules.

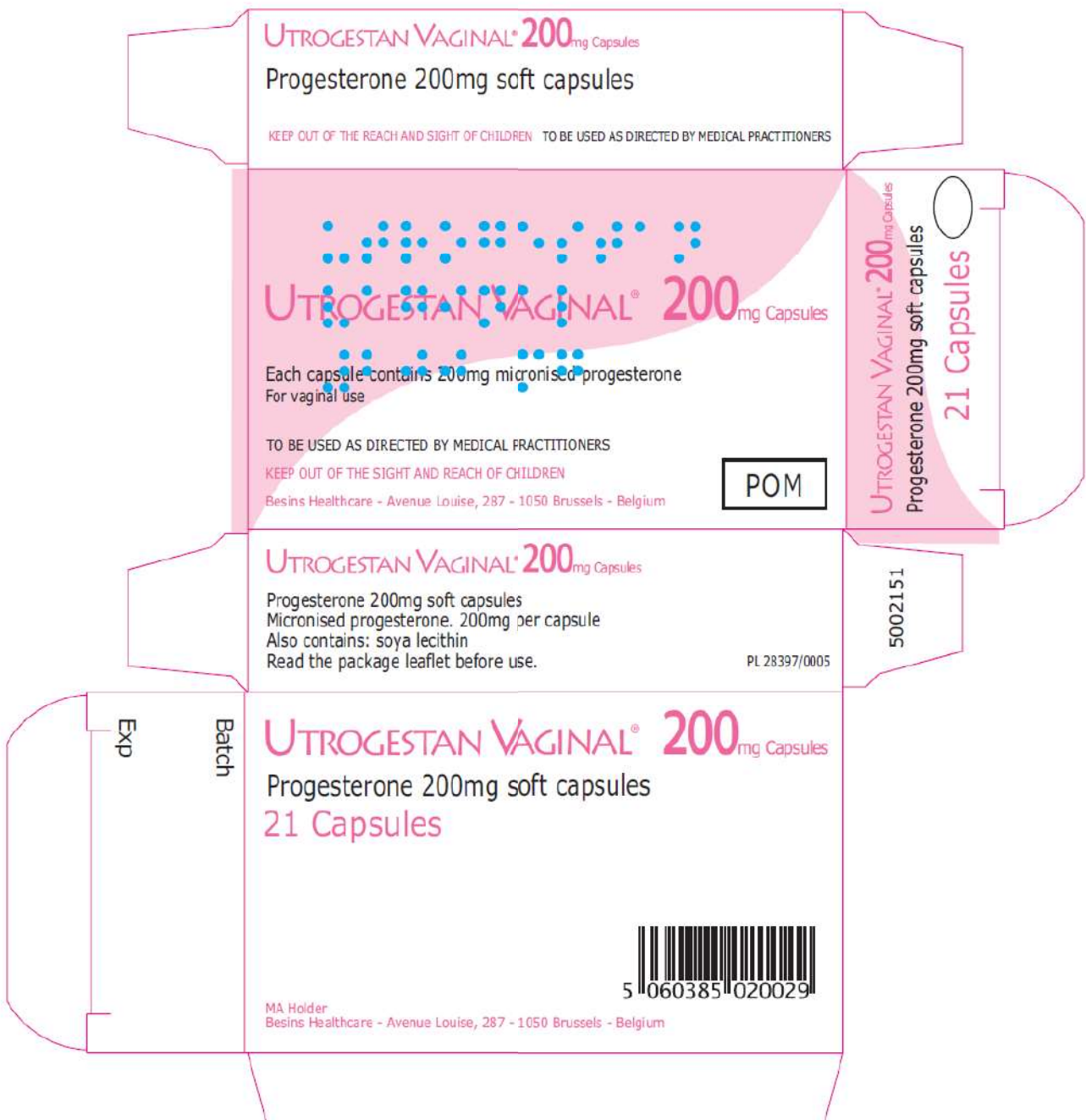
II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

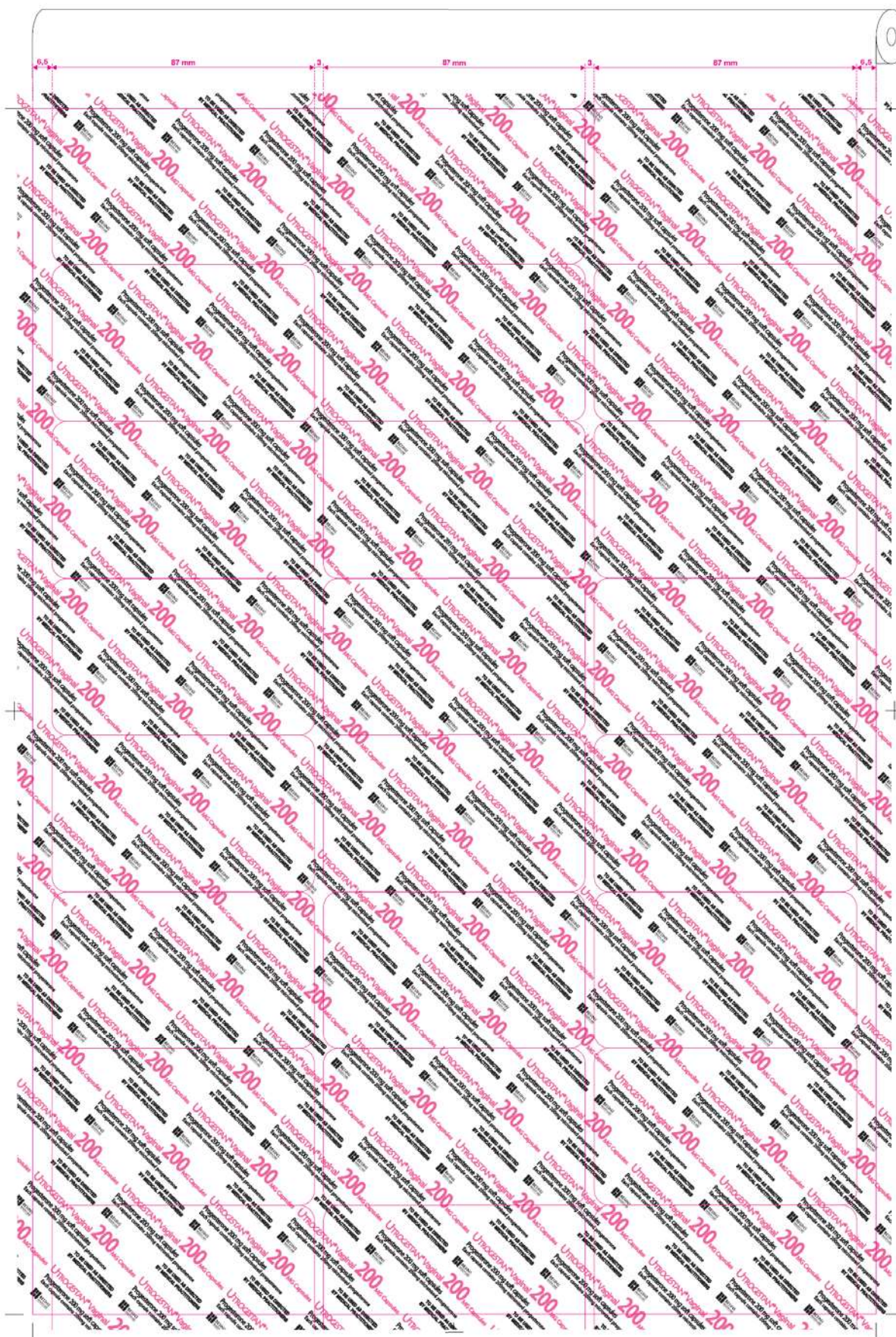
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

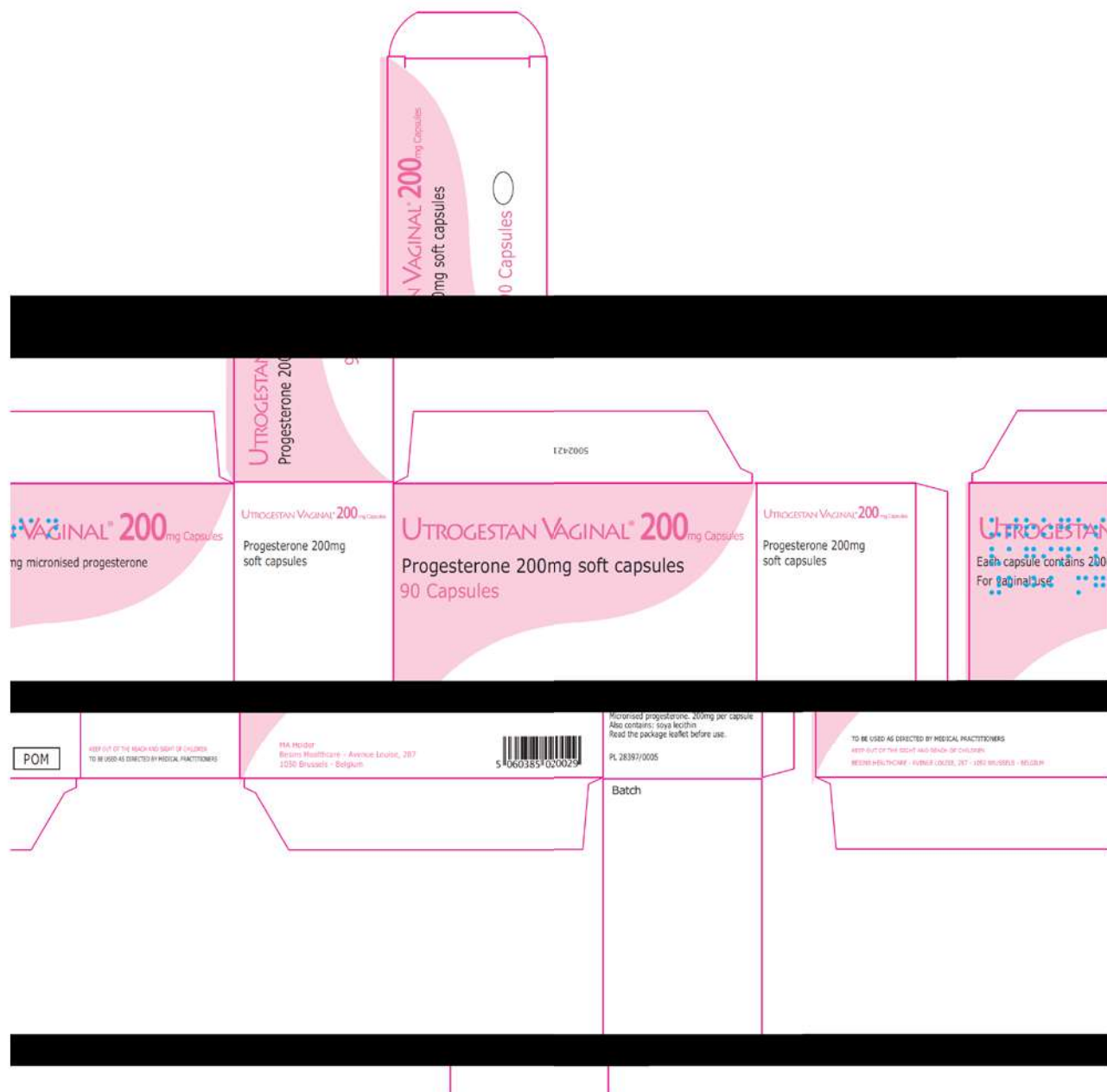
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:

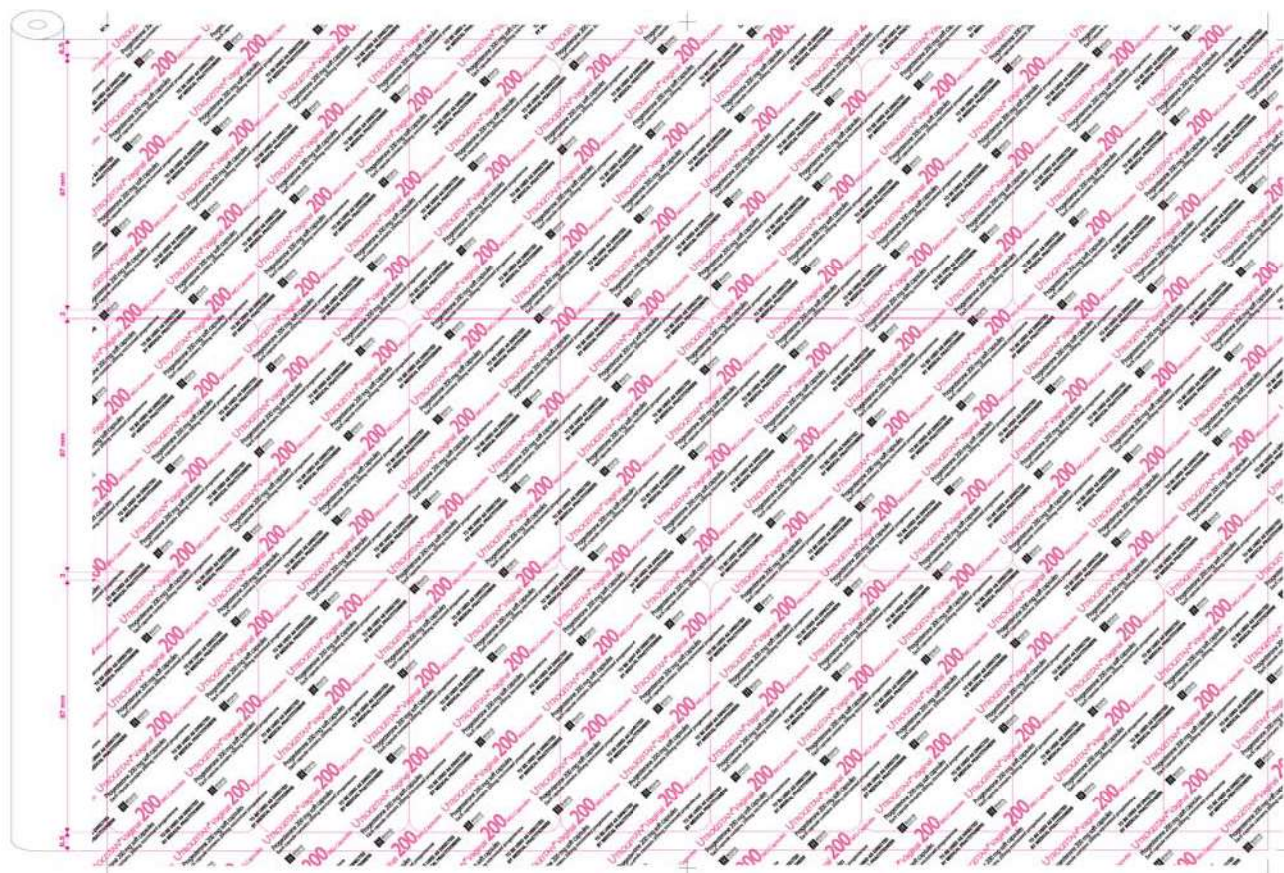












III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of progesterone for both oral and vaginal routes of administration are well-known, no further non-clinical studies have been provided and none are required. The Applicant has submitted data from the literature in support of the application.

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 Pharmacodynamics

Progesterone is a hormone with different actions dependent on the period in the oestrous cycle. Progesterone regulates maturation of the oocytes, ovulation, myometrial quiescence, mammary gland growth and endometrial enzymes.

Progesterone is clinically well-established for both oral and vaginal routes of administration and in view of this no pharmacology data in support of the proposed indication has been provided. However, brief reference is made of the fact that progesterone is used extensively in veterinary medicine for indications including disorders of the reproductive system, for oestrous synchronization and preparation of donor and receptor animals in the case of embryo transfer.

The effects of progesterone on a number of secondary targets were described. The overall effect on the cardiovascular, respiratory and central nervous systems was not discussed; however, given the effects on the secondary targets and/or organ systems and the clinical experience with products containing progesterone, no further information will be requested at this time.

III.3 Pharmacokinetics

The physiological plasma concentration of progesterone in men is approximately 0.3 ng/mL; in women this ranges from 0.23 to 1.2 ng/mL (follicular phase), 8.3 to 25 ng/mL (luteal phase) and 21 to 200 ng/mL (pregnancy). In a publication by Csapo and colleagues, circulating plasma levels of progesterone were measured in 12 nulliparous patients (mean age of 19.5 years) during the last 7 weeks of gestation and spontaneous labour. Plasma progesterone levels were 173 ± 6 ng/mL in the 2-3 weeks prior to the onset of labour, and 146 ± 11 ng/mL at the onset of labour.

The proposed product was administered to healthy women via the vaginal route at a dose of 200 mg progesterone in several clinical studies and during these studies the maximum C_{max} was within physiological plasma concentrations of progesterone in women. In other clinical investigations involving women undergoing assisted reproductive technology procedures, following the use of the proposed product, peak plasma concentrations of progesterone during the luteal phase ranged from negligible to 160 ng/mL.

In the bloodstream, progesterone is bound mostly to albumin, but some is also bound to transcortin, also known as corticosteroid-binding globulin. Progesterone accumulates in fatty tissue due to its lipophilic properties, and in tissues/organs containing progesterone-receptors.

Progesterone has a half-life of about 5 minutes and following oral administration, is metabolised mainly by the liver to pregnanediol. One clinical study compared the metabolism of progesterone following a single oral vs vaginal administration. The metabolites detected following oral administration of Utrogestan (pregnanedione and pregnanolone) were undetectable or only detected at very low levels following vaginal

administration. This difference is due to the lack of first-pass metabolism when Utrogestan is administered vaginally. This is clinically significant since the predominant pregnanediol metabolite (5 α -dihydroprogesterone) is an active metabolite, as are both 5 α - and 5 β -pregnanolone, which importantly have sedative effects that are avoided with vaginal administration. Other clinical studies have also confirmed that levels of 5 β -pregnanolone are very low following vaginal administration of Utrogestan.

Following intravenous injection of humans, the reported half-lives for progesterone range from 3 to 90 minutes, and excretion is predominantly via urine (50 to 60%). When Utrogestan Capsules were administered to healthy women via the vaginal route at a dose of 200 mg progesterone per day for 5 days, mean terminal elimination half-life of progesterone was 10.8 ± 2.2 hours, while clearance was 1370 ± 465 L/hour.

The pharmacokinetic data provided suggest that exposures of the active substance and/or active metabolites are in line with or lower than that experienced with the previously/currently marketed oral formulations containing progesterone. This provides some reassurance in terms of safety. Overall, the pharmacokinetic aspects of the non-clinical overview are considered adequate.

III.4 Toxicology

In a 26-week subcutaneous toxicity study in rats, organ atrophy (gonads, uterus, prostate) and increased pituitary weight (males only) were observed at the maximum dose of 16 mg/kg/day. However, in a 26-week oral study in the same species, the NOEL was very high (160 mg/kg/day). Treatment of dogs for 1 to 1.5 years with progesterone containing subcutaneous implants (approximately 225, 375, 1125 or 1650 mg progesterone/kg) resulted in a slight degree of mammary enlargement, glandular activity and nodule development at ≥ 375 mg/kg. Treatment of monkeys for 1 year with vaginal rings releasing 235 or 1770 μ g progesterone/day showed effects on organs of the reproductive system at both dose levels.

A report by the International Agency for Research on Cancer (IARC) suggests that progesterone was not genotoxic in a range of *in vitro* and *in vivo* investigations. Studies on transformation in rodent cells *in vitro* were inconclusive with a rat embryo cell study giving a positive result, a mouse cell study giving a weak positive result and a Syrian hamster embryo cell study giving a negative result. The Committee for Veterinary Medicinal Products (CVMP) concluded that progesterone does not exhibit mutagenic activity in most *in vitro* and *in vivo* tests performed and that overall, steroid hormones are devoid of genotoxic activity *in vivo*.

Some evidence of an increased incidence of carcinoma was observed (in reproductive tissues) in mice and pre-neoplastic mammary gland nodules were seen in dogs after chronic treatment. However, progesterone is known to increase the tumour incidence in endocrine target tissues after continuous (parenteral) doses that are clearly above those observed physiologically. The evidence suggests that progesterone is not carcinogenic *per se*, but mechanistically works via an epigenetic mechanism associated with its endocrine activity, i.e. it has the ability to cause a hyperproliferative effect at the cellular levels which is mediated by the steroid-hormone receptor interaction. Treatment with Urogestan Capsules as proposed will produce physiological concentrations of progesterone and not supra-physiological concentrations, such that the overall carcinogenicity risk is not increased by treatment over a relatively short time period (as proposed).

There was no evidence of teratogenicity/embryotoxicity following treatment with natural progesterone. Progesterone administered intramuscularly to rats at 5 mg/day on days 16 to 19 of gestation had no effect, but the same dosage on days 20 to 23 of gestation caused fetal death, which was probably related to the prolonged delay of parturition following progesterone administration. This was not considered to be of

relevance to the proposed use/indications as the product is to be administered up until the 12th week of pregnancy only.

A repeated dose local tolerance study was performed in adult female New Zealand White rabbits; whereby animals (n=6/group) were intravaginally administered with no treatment at all (control group), inert ingredients within the gelatin capsule (vehicle group) or one third of the contents of one capsule via the intravaginal route daily for 29 consecutive days. The daily dose of progesterone administered intravaginally within the gelatin capsule was 33 mg, which is comparable to the maximum clinical dose of 600 mg/day (approx. 60 kg body weight). During the study, there were no treatment-related deaths and no clinical signs of adverse effects. Examination of the vulva revealed no adverse treatment-related local tolerance findings from treatment with Utrogestan capsules, with no treatment-related increases in vulvar erythema. There were no adverse effects on the body weight development or food consumption. There were no macroscopic or microscopic abnormalities attributable to treatment.

There is clinical evidence to suggest that vaginal administration of Utrogestan is generally well-tolerated in healthy, young female volunteers (metrorrhagia, spotting and vaginal discharge observed in some), in women with ovarian failure and in women undergoing assisted reproductive technology procedures. Overall, the data suggest that toxicity profile of Utrogestan capsules following vaginal administration is similar to the oral formulations that were approved previously. Hence, there are no additional safety concerns with the proposed product.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMA/CHMP/SWP/4447/00], the applicant submitted an Environmental Risk Assessment (ERA) for progesterone and this has been updated in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMA/CHMP/SWP/4447/00 corr 2] (see Annex 1). It is concluded that Utrogestan Vaginal 200mg Capsules are of negligible risk to the environment when used in accordance with the product information.

III.6 Discussion of the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the application is for the known active substance progesterone, for which the pharmacodynamics, pharmacokinetic and toxicological properties are well known. A review of the literature is provided and is acceptable.

It is recommended that a Marketing Authorisation is granted for Utrogestan Vaginal 200mg Capsules, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction.

The clinical pharmacology of progesterone is well-known. Several pharmacokinetic and two clinical efficacy studies were submitted to support the application.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

The pharmacokinetic properties of progesterone are well known. Several clinical pharmacokinetic studies were submitted to demonstrate the pharmacokinetics of Utrogestan 200mg Capsules after vaginal administration. Overall, the studies were adequate.

The pivotal pharmacokinetic study, was a comparative study that compared the plasma bioavailability of progesterone from one 200mg Utrogestan capsule and 1.125g of Crinone 8% Gel (containing 90 mg of progesterone per dose), both administered vaginally in healthy women. The study was not designed to demonstrate the bioequivalence of the two products: it was aimed to compare systemic exposure. The other pharmacokinetic studies were supportive. Details of the pivotal pharmacokinetic study are summarised below:

Subjects included were non-pregnant, healthy women (aged 19-38 years) with a normal body weight (Broca's criteria) and on an oral oestradiol analogue/progestin combination contraceptive to ensure suppression of endogenous progesterone secretion; plasma progesterone had to be < 0.3 ng/ml on two different days between Day 4 and 18 in the menstrual cycle prior to the study. Exclusion criteria included evidence of any clinically significant condition that might affect the pharmacokinetics of progesterone, regular use of any medication (except an oral contraceptive) within the previous 8 weeks, and use of any oestrogen or gestagen injection within the previous 6 months. A total of 25 subjects entered the study and 24 completed it (mean $\pm$ SD age 27.8 ± 4.8 years, mean $\pm$ SD weight 63.3 ± 9.6 kg, all Caucasian). The patient who did not complete the study was withdrawn during the washout period after the Crinone arm due to evidence of a pre-existing depressive disorder.

Subjects received one of the two study treatments, in a random order with a washout period of at least 7 days, between Day 4 and 18 of the menstrual cycle (but not before menstrual bleeding had stopped). A blood sample was taken for pharmacokinetic analysis prior to dosing at 0800h (following an overnight fast) and further blood samples were taken over the next 96 hours. The mean $\pm$ SD baseline progesterone level was 0.18 ± 0.35 ng/ml in the Utrogestan arm and 0.11 ± 0.08 ng/ml in the Crinone arm. The main pharmacokinetic results of the study are presented in the table below:

Table 1 Mean($\pm$ SD) Plasma Pharmacokinetic Parameters for Progesterone Following Vaginal Administration of one Utrogestan 200mg Capsule or 1.125 g of Crinone 8% Gel

Parameter	Utrogestan	Crinone	Ratio or *Difference (90% Confidence Interval)
C_{0max} (ng/ml)	6.87 ± 1.80	6.83 ± 2.32	103.4% (92.4-115.8%)
T_{max} (hours)	40.55 ± 29.10	10.08 ± 6.11	*28.73 (17.01-38.88)
AUC_0 (ng.h/ml)†	281.9 ± 120.8	189.4 ± 96.9	146.1% (126.2-169.1%)
$T_{1/2}$ (hours)	14.82 ± 10.00	17.47 ± 9.13	88.2% (67.0-116.3%)

N = 23, † AUC_0 until the last concentration above the limit of quantification

AUC_0 = Area under the net plasma concentration-time curve; C_{0max} = Maximum plasma concentration increase

$T_{1/2}$ = Apparent terminal half-life; T_{max} = Time to maximum plasma concentration

Results and Conclusion

The pharmacokinetic analysis demonstrated that, following the administration of Utrogestan, the maximum plasma concentration increase above baseline (C_{0max}) and terminal half-life of plasma progesterone were comparable to those following the administration of Crinone. However, the AUC for progesterone corrected for baseline levels (AUC_0) until the last concentration above the limit of quantification was almost 50% greater with Utrogestan compared with Crinone, and the T_{max} was 29 hours later with Utrogestan.

IV.3 Pharmacodynamics

The effect of progesterone is well established and known. There are no particular requirements for pharmacodynamic studies and none have been carried out.

IV.4 Clinical Efficacy

To demonstrate efficacy, two studies were submitted. Only the data of the pivotal study was considered relevant as the second study (a Phase I/II study) was an uncontrolled one-arm study and it did not provide comparative evidence of efficacy. The pivotal study is discussed below:

Study (Pivotal)

A multi-centre, open label randomised active-controlled parallel group study comparing the efficacy and safety of vaginal Utrogestan 200mg Capsules and Crinone 8% Gel (a vaginal administration of progesterone gel) in providing luteal phase support to women undergoing in-vitro fertilisation (IVF), with or without intracytoplasmic sperm injection (ICSI).

Objectives

The aim of the study was to demonstrate the efficacy and tolerability of Utrogestan 200mg vaginally for luteal phase support during assisted reproduction, with Crinone 8% Gel (containing 90 mg of progesterone per dose) used as comparison. Crinone 8% Gel has a UK Marketing Authorisation and is established in the indication of progesterone supplementation as part of an assisted reproductive technology treatment.

Study Design

430 patients were recruited and randomised before embryo transfer took place. Patients were randomised to receive, vaginally, either one Utrogestan 200mg Capsule 3 times per day or two doses of Crinone 8% Gel per day. Each patient was to receive treatment daily beginning on the evening of the transfer day up to the 12th week of gestation, if pregnant.

Patients were followed up at Visit T1 (12 – 14 days after embryo transfer when pregnancy was confirmed), visit T2 (27 to 29 days after embryo transfer) and visit T3 (35-42 days after embryo transfer and visit T4 (63-70 days after embryo transfer.) The primary outcome measure was the ongoing pregnancy rate at week 12.

Main inclusion criteria

- Indication for IVF/ICSI
- Successful transfer of 2 or 3 embryos
- First treatment cycle
- Age ≥ 18 years and ≤ 35 years
- Normal cytological smear within the past 12 months

Main exclusion criteria

- Severe acute and chronic liver disease
- Rotor or Dubin-Johnson syndrome
- Hepato-cellular tumours
- Known hypersensitivity to one of the active constituents or excipients contained in the investigational medication

Primary endpoint

The primary endpoint was ongoing pregnancy rate at the end of study (≥ 12 th week of gestation).

Secondary endpoints

The secondary endpoints included amongst others:

- Number of implantations/living foetus
- Miscarriage rates

Statistical methods

The primary goal was to demonstrate non-inferiority of the test medication Utrogestan 200mg Capsule to the reference medication Crinone 8% Gel. The intent-to-treat population was used as the primary analysis population, with the per-protocol population providing a secondary analysis.

Hence, non-inferiority was to be declared if the lower limit of the 90% confidence interval for the difference between arms (treatment) was above -0.1 (i.e., a 10% non-inferiority margin). The applicant has provided an adequate justification for the use of the 10% non-inferiority margin.

Results

Disposition of Subjects

The patient disposition table is shown below:

Table 2: Patients withdrawing and patients remaining in the trial

	UTROGEST [®] 200		CRINONE [®] 8 %		Total	
Patients screened					583	
Patients enrolled					430	
Patients randomised	218		212		430	
Patients prematurely withdrawn	163	74.8 %	165	77.8 %	328	76.3 %
up to or at T 1	137	62.8 %	138	65.1 %	275	64.0 %
up to or at T 2	17	7.8 %	20	9.4 %	37	8.6 %
up to or at T 3	6	2.8 %	6	2.8 %	12	2.8 %
after T 3 till end of trial	3	1.4 %	1	0.5 %	4	0.9 %
Patients remaining in the study up to the 12 th week of gestation	55	25.2 %	47	22.2 %	102	23.7 %

Most withdrawals occurred up to or at visit T1 due to lack of β HCG increase and vaginal bleeding, which pertained to about two thirds of the study population (Table 2). Pregnancy failure was accountable for 93.9% and 90.9% of discontinuations in the Utrogestan 200mg Capsule and Crinone 8% Gel groups, respectively. The reasons for withdrawal are shown in Table 3. The reasons and rates for discontinuations appeared similar in both groups.

Table 3: Reasons for discontinuation

Withdrawal reason	UTROGEST® 200		CRINONE® 8 %	
	N	% of study group	N	% of study group
Pregnancy failure	153	70.2 %	150	70.8 %
Vaginal bleeding, no biochemical pregnancy	143	65.6 %	141	66.5 %
Abortion	3	1.4 %	6	2.8 %
Missed abortion	7	3.2 %	3	1.4 %
Other reasons for withdrawal	10	4.6 %	15	7.1 %
Adverse event	1	0.5 %	2	0.9 %
Local intolerance	1	0.5 %	3	1.4 %
Unallowed hormone therapy	4	1.8 %	3	1.4 %
Withdrawal of consent			2	0.9 %
Patient did not return	3	1.4 %	2	0.9 %
Other	1	0.5 %	3	1.4 %
Total	163	74.8 %	165	77.8 %

Primary efficacy analysis

Pregnancy rates

Confirmatory analysis of efficacy was based on the ongoing pregnancy rate at or beyond 12 weeks gestation as the primary outcome measure of this study.

The results for the analysis for the intent-to treat (ITT) and per-protocol (PP) populations are shown below:

Table 2: Analysis of data sets
Table 2 : Analysis of Data Sets

	Utrogestan	Crinone	Difference
ITT	25.2% (55/218)	22.2% (47/212)	3.1% (95%CI:[-6.5%;12.5%])
PP	26.4% (55/208)	23.9% (47/197)	2.6% (95%CI:[-7.2%; 12.3%])
ITT Sensitivity analysis: includes early withdrawals with confirmed pregnancy	28.0% (61/218)	26.9% (57/212)	1.1% (95%CI:[-8.4%; 10.6%])

Conclusion on efficacy

Suitable justification has been provided for the dose regimen of Utrogestan 200mg Capsule and Crinone 8% Gel used in the study. The data from the study demonstrated that Utrogestan 200mg Capsule was statistically non-inferior to Crinone 8% Gel for supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles.

Number of implantation/living fetuses

Multiplicity of pregnancies was recorded at visits T3 (8th week of gestation) and T4 (12th week of gestation). 71% of pregnancies in the Utrogestan group and 79% in the Crinone8% Gel group were singleton pregnancies. 83 and 72 fetuses were detected at T3 and T4 respectively in the Utrogestan 200 mg Capsule group and 64 and 58 fetuses in the Crinone8% Gel group. The Mann-Whitney statistic amounted to 0.5468 (0.4622 to 0.6361) at visit T3 ($p=0.3268$) and to 0.5432 (0.4600 to 0.6263 at visit 4 ($p=0.3268$).

Miscarriage rate (rate of abortions/missed abortions

In the Utrogestan 200mg Capsule group 10/218 women experienced an abortion or missed abortion. For the Crinone 8% Gel group, 9/212 women (4.2%) experienced an abortion or missed abortion. The rate difference was 0.0034 ($p=0.990$), a very similar rate of abortion in each group.

Clinical safety

The frequency of adverse events in the pivotal efficacy study is given in the table below:

Table 3: Patients with adverse events (overall and specific visits, percentage of patients with available data)

	UTROGEST [®] 200 (N = 218)				CRINONE [®] 8 % (N = 212)			
	yes	no	data missing		yes	no	data missing	
Visit T 1	13	6.1 %	199	6	14	6.7 %	195	3
Visit T 2	3	4.1 %	70	145	7	10.8 %	58	147
Visit T 3	7	11.3 %	55	156	5	9.4 %	48	159
Visit T 4	6	11.1 %	48	164	7	14.6 %	41	164
at any time	21	9.7 %	196	1	21	9.9 %	191	0

The detailed description and the summary tables provided (see below) indicate that there were no significant serious adverse events in patients treated with Utrogestan 200mg Capsules in the pivotal efficacy study and the adverse events were comparable in the Utrogestan and Crinone groups. The overall frequency of adverse events in the Utrogestan and Crinone groups were 11.0% and 12.3% respectively.

TABLE 4 : Comparative Table of Treatment-Emergent Adverse Events in the Pivotal Efficacy Study.

	UTROGESTAN 200 mg (N = 218)			CRINONE 8% (N = 212)		
	Total R/NR		Total	Total R/NR		Total
	R	NR	All - n (%)	R	NR	All - n (%)
Ovarian hyperstimulation syndrome		7	7 (3.2)		9	9 (4.2)
Vaginal bleeding/spotting	1	2	3 (1.4)	1	2	3 (1.4)
Nausea/Emesis		2	2 (0.9)		1	1 (0.5)
Vaginal candidiasis/infection		1	1 (0.5)	1		1 (0.5)
Cervical dysplasia (PAP III D)		1	1 (0.5)			0 (0.0)
Varicella infection		1	1 (0.5)			0 (0.0)
ET associated inflammation		1	1 (0.5)			0 (0.0)
Diarrhoea	1		1 (0.5)			0 (0.0)
Exanthema	1		1 (0.5)			0 (0.0)
Acute urinary retention		1	1 (0.5)			0 (0.0)
Jugular vein thrombosis	1		1 (0.5)			0 (0.0)
Ovarian cyst		1	1 (0.5)			0 (0.0)
Bloating	1		1 (0.5)			0 (0.0)
Vaginal discharge	1		1 (0.5)	6		6 (2.8)
Local itching/burning/irritation	1		1 (0.5)	4		4 (1.9)
Pregnancy hypertonus			0 (0.0)		1	1 (0.5)
Cervical ectopia with bleeding			0 (0.0)		1	1 (0.5)
Total - n (%)	7 (3.2)	17 (7.8)	24 (11.0)	12 (5.7)	14 (6.6)	26 (12.3)

TABLE 5 : Comparative Table of Treatment-Emergent Local Adverse Events in the Pivotal Efficacy Study.

	UTROGESTAN 200 mg (N = 218)			CRINONE 8% (N = 212)		
	Total R/NR		Total	Total R/NR		Total
	R	NR	All - n (%)	R	NR	All - n (%)
Erythema	11	3	14 (6.4)	14	2	16 (7.5)
Burning	5	1	6 (2.7)	6		6 (2.8)
Vaginal discharge	3	2	5 (2.3)	1	1	2 (0.9)
Itching	3		3 (1.4)	7		7 (3.3)
Total - n (%)	22 (10.1)	6 (2.8)	28 (12.8)	28 (13.2)	3 (1.4)	31 (14.6)

TABLE 6 : Comparative Table of Withdrawals Due to an Adverse Event in the Pivotal Efficacy Study

	UTROGESTAN 200 mg (N = 218)	CRINONE 8% (N = 212)
	n (%)	n (%)
Adverse Event	1 (0.5)	2 (0.9)
Local Tolerance	1 (0.5)	3 (1.4)

IV.5 Clinical Safety

The safety profile of progesterone administered via the vaginal route is well known. The safety of Utrogestan Vaginal 200mg Capsules was demonstrated primarily through the pivotal efficacy study. No new or unexpected safety concerns arose from this application.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, 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 Utrogestan Vaginal 200mg Capsules.

Routine pharmacovigilance and routine risk minimisation activities are acceptable to monitor the safety concerns described in the Risk Management Plan.

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Utrogestan Vaginal 200mg Capsules.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet has been performed on the basis of a bridging report making reference to the Patient Information Leaflet for the product Utrogestan 200mg Capsules (PL 16468/0007). The bridging report submitted by the applicant has been found to be acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION QUALITY

The important quality characteristics of Utrogestan Vaginal 200mg Capsules 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

No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of progesterone are well-known, no additional data were required.

EFFICACY

With the exception of the efficacy study, no new data were submitted and none are required for this type of application.

The applicant's Utrogestan Vaginal 200mg Capsules has been demonstrated to be non-inferior to Crinone 8% Gel in the supplementation of luteal phase during assisted reproductive technology (ART).

SAFETY

The safety profile of progesterone is well-known. No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Utrogestan Vaginal 200mg Capsules have been demonstrated to be non-inferior to Crinone 8% Gel in the supplementation of luteal phase during assisted reproductive technology (ART). The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION

The grant of a Marketing Authorisation is recommended.

Utrogestan Vaginal 200mg Capsules

(progesterone)

STEPS TAKEN AFTER AUTHORISATION-SUMMARY

The following table lists a non-safety update to the Marketing Authorisation for this product that has been approved by the MHRA since the product was first licensed. The table includes an update that has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Scope	Outcome
09 July 2015	Type IB	To update the Environmental Risk Assessment.	Approved on 15 September 2015

Annex 1

Our Reference: PL 28397/0005- 0016
Product: Utrogestan Vaginal 200mg Capsules
Marketing Authorisation Holder: Besins Healthcare
Active Ingredient(s): Progesterone.

Type of Procedure: National
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable):

Reason:
 To update the Environmental Risk Assessment.

Linked / Related Variation(s) or Case(s):
 None

Supporting Evidence

- Module 1.6.1 Environmental Risk Assessment.
- Published literature

Evaluation

The applicant has used published literature to assess the environmental risk of the drug substance, in accordance with CHMP guideline EMEA/CHMP/SWP/4447/00 corr 2.

A summary of results is provided below:

PBT screening		Result	Conclusion
Bioaccumulation potential- logK _{ow}		LogK _{ow} 3.87	Potential PBT No
PBT-statement:		The log K _{ow} value for Pregn-4-ene-3, 20-dione (progesterone) is < 4.5, therefore screening for PBT is not required as this does not meet the criteria for classification as a PBT compound.	
Phase I			
Calculation	Value	Unit	Conclusion
PEC _{surfacewater, refined}	0.117	µg/L	>0.01 threshold Yes
Other concerns (e.g. chemical class)	Pregn-4-ene-3, 20-dione (progesterone) is considered to be a potential endocrine disruptor.		Yes
Outcome of Phase I :	Since the PEC _{sw} value is > 0.01 µg/L action limit and pregn-4-ene-3, 20-dione (progesterone) is considered to be potential endocrine disruptor, a Phase II environmental fate and effects analysis is required.		

Phase II Tier A Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	Not reported	Adsorption Coefficient $K_{oc} = 8,248$			Value quoted from Smolenski, 2008.
Phase II Tier A Effect studies					
Study type	Test protocol	Endpoint	Value	Unit	Remarks
<i>Daphnia</i> sp. Reproduction Test	Not reported	NOEC (14d)	0.1	mg/L	<i>Daphnia magna</i>
PNEC _{water} PEC _{surfacewater} / PNEC _{water}			0.001 0.117	mg/L	Unlikely to represent a risk to the aquatic environment
PEC _{groundwater} PNEC _{groundwater} PEC/PNEC _{groundwater}			2.93×10^{-5} 0.001 0.0293	mg/L	Unlikely to represent a risk to the aquatic environment

PBT	Persistent, Bioaccumulative and Toxic
PEC _{surfacewater}	Predicted Environmental Concentration _{surfacewater}
PEC _{groundwater}	Predicted Environmental Concentration _{groundwater}
PNEC _{water}	Predicted No Effect Concentration _{water}
PNEC _{groundwater}	Predicted No Effect Concentration _{groundwater}

Estimation of exposure of the environment to progesterone has shown that: screening for persistence, bioaccumulation and toxicity (PBT) of progesterone is not required since the log n-octanol/water partition coefficient (logK_{ow}) value (3.87) is below the guidance lower limit value of 4.5.

In the Phase I assessment, the PEC_{sw} value for progesterone was above the action limit of 0.01 µg/L and the active compound is also considered to be a potential endocrine disruptor, resulting in Phase II analysis being performed.

PEC/PNEC analysis in the Phase IIA assessment showed that no further refinement of the PEC_{sw} and PEC_{gw} was required for Phase IIB and that further assessment of the terrestrial compartment was not required.

The Applicant has quoted a reference by Yotis and Stanke (1966) which found that progesterone exerted an antimicrobial action only on gram-positive bacteria at concentrations, *in vitro*, of 10 µg/ml or greater. The PEC_{surfacewater} concentration of progesterone arising from the use of Utrogestan Vaginal 200mg Capsules has been calculated to be 0.117 µg/l. Since there is an extensive margin between the quoted progesterone concentration that has antimicrobial action and the PEC_{surfacewater} concentration of progesterone, it is agreed that Utrogestan Vaginal 200mg Capsules are unlikely to represent a risk to environmental microorganisms.

Although the log K_{ow} value of 3.87 is below the threshold of 4.5 for screening of persistence, bioaccumulation and toxicity, the K_{ow} value is 7413 (inverse log of 3.87). According to EMEA/CHMP/SWP/4447/00 corr 2, if the n-octanol/water partition coefficient indicates the transfer of the drug substance from the aquatic environment into organisms and a potential to bioaccumulate (i.e. K_{ow} >1000), then the bioconcentration factor should be considered in Tier B studies. However, an increase in environmental exposure to progesterone is deemed unlikely since this is a generic product and there is already extensive literature data on the environmental impact of this class of compound and therefore further screening is not required.

Proposals for Labelling

The Applicant has concluded that the environmental risk, as a result of the prescribed usage of Utrogestan Vaginal 200mg capsules, is negligible and therefore the following statement can be used in the product literature:

“Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.”

The proposed environmental statement for labelling is acceptable.

Conclusions:

Based on the review of the data on safety, the variation for Utrogestan Vaginal 200mg Capsules, to update the environmental risk assessment, could be approved.

Decision – Approved on 17 September 2015.