LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Utrogestan
(progesterone)

SE/H/2242/01/E/01

This module reflects the scientific discussion for the approval of Utrogestan. The procedure was finalised on 2023-03-28. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Utrogestan, 300 mg, vaginal capsule, soft.

The active substance is progesterone. A comprehensive description of the indication and posology is given in the summary of product characteristics (SmPC).

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application is an extension, new strength, of the previously authorised product Utrogestan, 200 mg, vaginal capsule, soft, marketed by Besins Healthcare Ireland Limited since 2019-03-25.

The application for Utrogestan, 300 mg, vaginal capsule, soft, is submitted according to Article 8(3) of Directive 2001/83/EC. The applicant, Besins Healthcare Ireland Limited, applied through the National Procedure in Finland and later on underwent a Mutual Recognition Procedure (MRP) with Finland acting as reference member state (RMS) and BE, BG, EE, HR, HU, IE, LU, LV, NL, NO, SE, SI and SK as concerned member states (CMS). The MRP application was withdrawn in CZ, DE, LT, PL and UK. A RMS transfer from Finland to Sweden was completed in March 2022. The applicant applied through the Repeat Use Procedure with Sweden acting as reference member state (RMS) and CY, CZ, DK, ES, FR, IS, IT, LT, PL, RO, PT and MT as concerned member states (CMS).

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of progesterone are well known. As progesterone is a widely used, well-known active substance, the applicant has not provided additional studies along with this application and further studies are not required.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

Environmental Risk Assessment (ERA)
Progesterone is a natural hormone that is derived from cholesterol steroids. Much greater quantities of progesterone are synthesised endogenously by humans, animals and plants compared to the amount synthesised for Utrogestan, 300 mg, vaginal capsule, soft. In view of this and since progesterone will be degraded in the environment as a natural hormone, it may be inferred by reference to the CHMP guideline that an environmental risk assessment is not necessary. However, a comprehensive assessment has been performed.

Based on this ERA assessment, a very small increase in the environmental exposure to progesterone is expected. It is concluded that the environmental risk is negligible as a result of the use of Utrogestan, 300 mg, vaginal capsule, soft.

IV. CLINICAL ASPECTS

The applicant's Clinical overview of Utrogestan 300 mg vaginal capsule, soft presents information on the pharmacokinetics, efficacy, and safety of vaginally administered progesterone, primarily derived from studies using 100 mg and 200 mg vaginal capsule, soft. The Clinical overview is considered adequate.

Pharmacokinetics (PK)

Pharmacokinetic data is based on literature search, no new clinical studies have been carried out. Non-linear pharmacokinetics seems to occur in dose ranges between 300 mg to 600 mg progesterone given vaginally. This suggests that the absorption mechanism is saturated in the larger recommended clinical doses, and this information on non-linear pharmacokinetics has been adequately addressed in the SmPC. The pharmacokinetic properties of vaginally administered progesterone are well-characterised. In the Clinical overview, the applicant presents data on the absorption, distribution and elimination of progesterone administered either by oral route or vaginally. Available studies show that within the recommended daily doses, plasma progesterone concentrations are relatively low and close to normal physiological levels during the luteal phase of menstrual cycle. Progesterone levels in uterus may exceed those in plasma after vaginal administration. When given vaginally, the first-pass metabolism is avoided, and the metabolite profile is somewhat different than after oral administration. Kidneys are the main elimination route.

The absorption, distribution, elimination and biotransformation are adequately addressed in the SmPC. See SmPC for details.

During the MRP process, major objections (MOs) were raised due to lack of PK data and several rounds of assessments of responses were performed. At the end of the MRP procedure, it could be concluded

that even though there is no direct clinical evidence from PK studies between e.g., 2 x 300 mg and 3 x 200 mg Utrogestan doses, the total daily systemic exposure to progesterone from the 2x300 mg is not expected to be clinically significantly different with that of 3x200 mg regimen. The maximum daily dose remains the same (600 mg), and the dissolution profiles of the new 300 mg vaginal capsule, soft are rather identical to the approved formulations. The approval of the new strength of 300 mg was based on clinical efficacy and safety data, supported by dissolution data, and not on direct PK comparison.

Pharmacodynamics

Mechanism of action

Progesterone is a natural endogenous hormone of the corpus luteum, and it is the most important hormone of the corpus luteum and the placenta. It acts on the endometrium by converting the proliferating phase to the secretory phase. Utrogestan 300 mg vaginal capsule, soft have all the properties of endogenous progesterone with induction of a full secretory endometrium and in particular has a gestagenic, antiestrogenic, slightly anti-androgenic and antialdosterone effects.

Progesterone given vaginally in doses recommended by the applicant is effective and can be considered to provide adequate Luteal Phase Support (LPS) during Assisted Reproductive Technology (ART) cycles. The mechanism of action of progesterone in this indication is well-known and based on its physiological effects of progesterone on the endometrium. The mechanism of action and pharmacodynamic properties of progesterone are adequately reviewed by the applicant.

Clinical efficacy

The clinical efficacy data is based on data presented from two company-sponsored efficacy studies (**Table 1**) and review of the literature. Concerning details on clinical study results and summary of the literature review, please refer to Clinical AR.

The company-sponsored multicentre, open-label, parallel-group, non-inferiority study in 430 women, performed by Kleinstein and colleagues showed that LPS with UTROGESTAN vaginal capsules (200 mg) resulted in similar rates of implantation, ongoing pregnancy, and abortion as CRINONE 8% vaginal gel. Fifty-five (55) patients in the UTROGESTAN Group and 47 patients in the CRINONE group completed the study, all with ongoing pregnancies at or beyond the 12th week of gestation. According to the pre-specified criteria, the pregnancy rate in the UTROGESTAN group was demonstrated to be non-inferior to that in the CRINONE group.

Salat-Baroux conducted a company sponsored study which was an unmonitored, one-arm, prospective study that evaluated endometrial morphology and pregnancy outcomes following the administration of UTROGESTAN and estradiol in women without ovarian function participating in an oocyte donation program. UTROGESTAN was administered vaginally in the following regimen: 100 mg in the evenings of Days 13, 14, and 15 then 100 mg twice daily on Days 16 to 25. Transfer of frozen-thawed embryos (following in-vitro fertilization (IVF) using donated oocytes) was undertaken on Day 14 and was successful in 4 of 12 transfers (31%). At the time the publication was written pregnancy was progressing well in three patients, whilst one patient aborted at six weeks.

Table 1. Tabular summary of company-sponsored efficacy studies (performed in collaboration with the applicant) (Source 2.7.3. Summary of clinical efficacy studies, Table 2).

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy / Safety	Kleinstein 2001 (protocol) (study report number, Kleinstein 2002)	5.3.5.1 and 5.4 Published as Kleinstein 2005	Comparison of the efficacy and safety of vaginal Utrogestan 200 mg three times daily and vaginal 1.125 g Crinone 8% gel twice daily, for up to 12 weeks, in providing luteal phase support to women undergoing in vitro fertilisation	Open, multicentre, comparative-controlled, randomised, parallel-group Phase III trial	Utrogestan 200 mg capsules [a]: 3 times/day; vaginal 1.125 g Crinone 8% gel; 2 times/day; vaginal	430 (Utrogestan: n = 218 Crinone: n = 212)	Women who had successful transfer of 2 or 3 embryos during their first treatment cycle of IVF / ICSI.	From the evening of transfer until the 12th week of pregnancy	Completed. Clinical Study Report and Published Reference
Efficacy / Safety	Salat-Baroux 1988	5.4 Published as Salat-Baroux 1988	To evaluate endometrial morphology and pregnancy outcomes following the administration of Utrogestan and oestradiol in women without ovarian function participating in an oocyte donation program.	Single-centre, open-label study	Utrogestan 100 mg [a]: One capsule/day on D13 / 14, and one capsule bid on D15 to 25. The dose was increased to 300 mg/day on D26, 400 mg/day on D29, 500 mg/day on D36 and 600 mg/day on D44-60; vaginal. Oestradiol gel 1.5 mg/day on D1 to 5 of the substitution cycle, bid on D6 to 25, and once on D26 to 28. 3 mg once daily from D29 to 35 and 4.5 mg once daily from D36 to 43 and 6 mg once daily from D44 to 60; topical Oestradiol valerate: 2 mg on D11 to 13.; oral.	22 patients	7 women with primary ovarian failure and 15 with secondary ovarian failure.	Oestradiol was administered up to D60 of the substituted cycle while progesterone was administered from D13 to 60	Completed. Clinical Study Report and Published Reference

In the Clinical Overview, the applicant reviewed current literature describing the use of progesterone in various doses to support the luteal phase during the ART cycles. Based on studies presented, the efficacy of Utrogestan is well-documented and the knowledge how progesterone dosing should be started and how long the treatment should last is based on long clinical experience.

However, the applicant did not report data on any studies in which the new strength 300 mg of Utrogestan vaginal soft capsules are used. During the review process of the National MAA (marketing authorisation application) Procedure in the RMS, the applicant was requested to give explanation for the lack of a more recent study in which Utrogestan 300 mg vaginal soft capsules have been used, and additionally to provide evidence based on which the pharmacokinetics, efficacy and safety could be considered to be identical between different preparations delivering the same dose (e.g., one 300 mg capsule compared to three 100 mg capsules).

In the response, the applicant did not provide direct in vivo data comparing the bioequivalence of the new strength formulation (300 mg soft vaginal capsules; 300 mg x 2 doses) to the approved strength formulation (200 mg vaginal soft capsules; given as 200 mg x 3 doses). Instead, the applicant developed a new dissolution method and performed acceptable dissolution studies with Utrogestan 300 mg soft vaginal capsules. The results showed rather identical dissolution curves for the new strength compared to the currently approved strength. These data demonstrate that the new strength formulation is dose-proportional formulation of 200 mg vaginal soft capsules, and that the new formulation is supposed to release corresponding amounts of progesterone into the vagina.

During the MRP process which originally involved the review of a combined dossier comprising of two Utrogestan vaginal capsule strengths (300 mg capsule and 400 mg capsule) CMSs raised major objections (MOs) concerning the proposed posology (300 - 600 mg once or twice daily) for the combined two-strength dossier. The need for the higher 400 mg strength in the market for the proposed posology was questioned (as an MO). As a consequence, the applicant proposed to change and clarify the posology of Utrogestan 300 mg vaginal capsules from 300-600 mg/day to 600 mg/day divided in two doses and proposed to withdraw the 400 mg strength. Within Day 75 responses, the applicant confirmed that the 400 mg strength is withdrawn from the procedure and formal withdrawal letters were provided in the 400 mg eCTD sequence. During the MRP process, information concerning the start of treatment and continuation of treatment were harmonised with Utrogestan 200 mg vaginal soft capsules, also taking new available data into consideration. Also, other clarifications and changes were made in

the SmPC and package leaflet (PL) to harmonise the information with Utrogestan 200 mg vaginal soft capsules.

The current posology reads as follows: "*The recommended dose is 600 mg/day, given in two divided doses, one in the morning and the other at bedtime. The treatment is started not later than the third day after oocyte retrieval day and is continued until at least the 7th week of pregnancy and not later than the 12th week of pregnancy or until menstruation begins*." The final posology of Utrogestan 300 mg, i.e., 600 mg/day divided in two doses, is considered acceptable.

Conclusions on clinical efficacy

The applicant has reviewed the company-sponsored studies and current literature describing the use of progesterone in various doses to support the luteal phase during the ART cycles. The efficacy is well-documented and the knowledge how progesterone dosing should be started and how long the treatment should last is based on long-term clinical experience.

Even though there are no direct clinical evidence from PK studies between e.g., 2 x 300 mg and 3 x 200 mg doses, the total daily systemic exposure to progesterone from the 2 x 300 mg is not expected to be clinically significantly different with that of 3 x 200 mg regimen. The maximum daily dose remains the same (600 mg), the dissolution profiles of the new 300 mg vaginal soft capsules are rather identical to the approved formulation, and available clinical evidence support that no significant differences are expected in the PK profiles or clinical efficacy with either twice or three times daily dosing. Based on the totality of the evidence provided by the applicant in the responses and in the original submission, the new strength formulation of 300 mg is considered acceptable from efficacy point of view.

Clinical safety

Since approval of Utrogestan capsules for oral administration in 1980 in France for the treatment of postmenopausal syndrome, the product has been approved for oral and vaginal administration in more than 80 countries. Based on information provided by the MAH in the original submission, the worldwide cumulative exposure to progesterone in terms of Patient Treatment Years (PTYs) for 200 mg vaginal soft capsules is estimated to be 2,475,805 PTYs by March 2018. During the MRP procedure, the applicant updated safety information and according to the latest Periodic Safety Update Report (PSUR), cumulative patient exposures were by June 2020 estimated to be 3,483,235 and 3,679,916 patient years for the 200 mg vaginal soft capsules. No new or unexpected safety concerns were identified.

As to be expected for a naturally occurring hormone, the safety profile of progesterone as the LPS during the ART cycles in pharmaceutical formulations is well established based on the long experience of clinical use. This is also reflected in the significant pool of published information on the safe use of micronised progesterone. The data presented show that extensive safety monitoring has been conducted, and that the safety profile of progesterone is well understood. The adverse event profile of vaginally administered progesterone is acceptable and well documented.

<u>The following safety finding has been identified and described in the SmPC:</u>
Local intolerance (burning, itching or oily discharge) has been observed in clinical studies and has been reported in publications, but the incidence is reported to be extremely rare, as indicated in the current SmPC.

The MAH has also indicated that although there are no known systemic adverse effects reported from clinical studies, including drowsiness or dizziness (observed with the orally-administered form of the medicine), when used as recommended, transient fatigue or dizziness may occur within 1 – 3 hours of taking the medicine.

<u>Reporting of suspected adverse reactions after authorisation</u>
The information below is based on experience gathered after the authorisation of progesterone administered into the vagina.

The following frequency conventions are used in the rating of undesirable effects: Very common (≥1/10); Common (≥1/100 to < 1/10); Uncommon (≥1/1000 to < 1/100); Rare (≥1/10000 to < 1/1000); Very rare (< 1/10000); Not known (cannot be estimated from the available data).

System Organ Class (SOC)	**Frequency Not known (Cannot be estimated from the available data)**
Skin and subcutaneous tissue disorders	Pruritus
Reproductive system and breast disorders	Vaginal haemorrhage Vaginal discharge

Conclusions on clinical safety
Clinical safety of the use of progesterone as the LPS treatment during the ART cycles is well-documented based on the long experience of clinical use of the drug product. The adverse effect profile of vaginally administered progesterone is acceptable. Minor changes in the SmPC and PL were made during the MRP in the safety-related sections to harmonise information between SmPC and PL, and also to harmonise information with Utrogestan 200 mg vaginal soft capsules, and also to harmonise presentation with the most recent QRD template.

However, during the MRP process, the applicant made changes in the SmPC and PL for Utrogestan 300 mg vaginal soft capsules, which were not all in line with the Utrogestan 200 mg vaginal soft capsules. During the MRP process, the applicant has given commitment to harmonize all SmPCs and PLs (100 mg, 200 mg and 300 mg) in the RMS and CMSs, where applicable, after the current MRP process has been finalised.

Risk Management Plan

Safety specification
The RMP version 5.3 (Finland), January 2020 for vaginal soft capsules lists no important identified risks, no important potential risks and no missing information in the safety specification.

Pharmacovigilance plan
There are no additional pharmacovigilance activities in place for progesterone.

Risk minimisation plan
There are no additional risk minimisation measures in place for progesterone.

The RMP is approved.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Utrogestan 200 mg vaginal soft capsules, SE/H/2023/01 and by referring to a focus test for Utrogestan Vaginal 200 mg Capsules, MHRA: PL 28397/0005. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Main concerns during assessment

During the national MAA review process, other concerns (OCs) on Quality concerning Drug Substance and Drug product were raised. All these OCs have been adequately addressed, and SmPC and PL have been revised accordingly.

Concerning PK, efficacy and safety, a MO was raised during the national MAA review, as the applicant had not provided clinical data showing that the new strength (300 mg vaginal soft capsules) provide bioequivalent plasma progesterone concentrations, have similar clinical effects, better patient compliance and similar adverse event profile than with similar dosage using the 200 mg capsules. The efficacy was considered to be demonstrated by provided clinical efficacy and safety data, supported by new dissolution study data showing dose-proportionality, and the issue was considered clarified by the RMS.

During the MRP process, CMSs raised MOs mainly concerning the posology (300 - 600 mg once or twice daily) considering that there is no sufficient data to support lower than 600 mg daily dosing and no adequate data for once daily dosing. In addition, the need for the higher 400 mg strength in the market for LPS with the proposed posology was questioned (issue was raised as an MO). As a consequence, the applicant proposed to change the posology of Utrogestan 300 mg vaginal soft capsules to 600 mg/daily divided in two doses and proposed to withdraw the 400 mg strength. Within Day 75 responses, the applicant confirmed that the 400 mg strength is withdrawn from the procedure and formal withdrawal letters were provided in the 400 mg eCTD sequence. The proposed posology of 600 mg/day divided in two doses is considered acceptable.

There were also several other OCs raised by RMS and CMSs, mainly related to start and duration of treatment, and presentation of safety in SmPC and PL. There were also other specific comments and concerns on SmPC and PL. The need for harmonisation of information provided in Utrogestan 100 mg, 200 mg and 300 mg capsules was also raised. During the MRP process the OCs have been clarified. The applicant has given commitment to harmonise all SmPCs and PLs (100 mg, 200 mg and 300 mg) in the RMS and CMSs, where needed, following approval of the current MRP procedure.

Main conclusions from assessment

The clinical efficacy of Utrogestan 300 mg soft vaginal capsules is well-documented and the knowledge of how progesterone dosing should be started and how long the treatment should last is based on long-term clinical experience. The efficacy is adequately demonstrated.

Clinical safety concerning the use of progesterone as the LPS treatment during the ART cycles is as well well-documented based on the long-term and extensive experience of clinical use of the drug product. The adverse event profile of vaginally administered progesterone is acceptable and adequately described in SmPC and PL.

Considering all clinical data and taking into account that that the maximum daily dose of Utrogestan remains the same (600 mg), and that the dissolution profiles of the new 300 mg vaginal soft capsules are rather identical to the approved formulation, the new strength formulation of 300 mg given twice daily is considered acceptable from the efficacy and safety point of view.

Efficacy and safety in subpopulations are sufficiently discussed in labelling documents. Further, there are adequate warnings concerning renal or hepatic impairment, even though no formal studies in these conditions have been performed. The list of contraindications and information concerning interactions with other medications are considered adequate. During the MRP process some new discrepancies in labelling with Utrogestan 100 mg and 200 mg formulations were generated (at least in the RMS), but

the applicant has given commitment to harmonise all labelling documents in the RMS and in CMSs, where applicable.

In the proposed product information, the use of Utrogestan 300 mg vaginal capsule, soft, is restricted to adults, and there is no relevant use in children and in the elderly.

The evaluation of the benefit-risk-ratio in women, in need for the supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles, can be considered positive.

Summary of main conclusions:

Quality
There is no objection to approval of Utrogestan 300 mg vaginal soft capsules from a Quality point of view.

Non-Clinical
There are no objections to approval of Utrogestan 300 mg vaginal soft capsules from a Non-Clinical point of view.

Clinical
The efficacy and safety of Utrogestan 300 mg vaginal soft capsules are well-documented and the knowledge how progesterone dosing should be started and how long the treatment should last is based on long clinical experience.

There are no objections to approval of Utrogestan 300 mg soft vaginal capsules from a Clinical point of view.

RMP
The submitted RMP is acceptable.

In conclusion, the RMS considers that the line extension application for Utrogestan, 300 mg, vaginal soft capsule, in the supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles, is approvable.

The benefit/risk ratio is considered positive and Utrogestan, 300 mg, vaginal capsule, soft is recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Post-approval commitments
Environmental risk assessment: The applicant Besins Healthcare Ireland Limited commits to submitting a variation within three months from end of procedure to provide an updated literature review regarding potential risks of progesterone to fish.

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The mutual recognition procedure for Utrogestan, 300 mg, vaginal capsule, soft was positively finalised on 2023-03-28.

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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)

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