Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Lubion 25 mg Powder for Solution for Injection
Lubion 25 mg Solution for Injection

Progesterone

UK/H/4170/001-02/DC

PL 21039/0025-26

Applicant: IBSA Farmaceutici Italia Srl

Lubion 25 mg Powder for Solution for Injection
Lubion 25 mg Solution for Injection

PL 21039/0025-26

LAY SUMMARY

On 22nd February 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations to IBSA Farmaceutici Italia Srl for the medicinal products Lubion 25 mg Powder for Solution for Injection and Lubion 25 mg Solution for Injection (PL 21039/0025-26; UK/H/4170/001-02/DC). These medicines are only available on prescription from your doctor.

Lubion contains the active ingredient progesterone. Progestrone is a naturally occurring female sex hormone. The medicine works on the lining of the womb and helps you to become pregnant and stay pregnant.

Lubion is for women who need extra progesterone while undergoing treatment in an Assisted Reproductive Technology (ART) programme who are unable to use or tolerate vaginal preparations.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of treatment with Lubion 25 mg Powder for Solution for Injection and Lubion 25 mg Solution for Injection outweigh the risks, hence Marketing Authorisations were granted.

TABLE OF CONTENTS

Module 1

Product Name	Lubion 25 mg Powder for Solution for Injection Lubion 25 mg Solution for Injection
Type of Application	Article 8.3, Known active
Active Substance	Progesterone
Form	Powder for solution for injection Solution for injection
Strength	25 mg
MA Holder	IBSA Farmaceutici Italia Srl Via Martiri di Cefalonia 2, 26900 Lodi, Italy
RMS	UK
CMSs	Austria, Belgium, Cyprus, Czech Republic, France, Germany, Greece, Hungary, Italy, Luxemburg, Poland, Portugal, Slovak Republic and Spain
Procedure Number	UK/H/4170/001-02/DC
Timetable	Day 210: 20th January 2013

Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Module 4

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

(Cardboard outer packaging)

(The product name will appear on three non-opposing sides of the carton)

1. NAME OF THE MEDICINAL PRODUCT

Lubion 25 mg powder for solution for injection

Progesterone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 25 mg Progesterone
After reconstitution with 1 ml water for injection, the reconstituted solution (1.119 ml) contains 25 mg progesterone.

3. LIST OF EXCIPIENTS

Hydroxypropylbetadex

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for Solution for injection.
Pack contains 1vial
7 vials
14 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intramuscular or subcutaneous use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use as directed by physician.

The medicinal product must be used immediately after first opening and reconstitution. Any remaining solution must be discarded.

Patient self-administration: Subcutaneous injection only
Healthcare administration: By s.c and i.m injection

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 25°C. Keep the vial in the outer carton, in order to protect from light. Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

IBSA Farmaceutici Italia Srl
Via Martiri di Cefalonia 2
26900 Lodi (Italy)

12. MARKETING AUTHORISATION NUMBER(S)

PL 21039/0025

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

N/A - only applies to non-prescription medicines

16. INFORMATION IN BRAILLE

Lubion 25 mg powder for solution for injection

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

(Type I glass vial)

1. NAME OF THE MEDICINAL PRODUCT A

Lubion 25 mg powder for solution for injection

Progesterone

For i.m. or s.c. use.

2. METHOD OF ADMINISTRATION

For i.m. or s.c. use.

Read the package leaflet before use

2. NAME OF THE MARKETING AUTHORISATION HOLDER

IBSA Farmaceutici Italia Srl
Via Martiri di Cefalonia 2
26900 Lodi (Italy)

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. OTHER

Store below 25^{0}C. Use immediately after reconstitution.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING>

(Cardboard outer packaging)

(The full product name will be stated on three non-opposing sides of the carton)

1. NAME OF THE MEDICINAL PRODUCT

Lubion 25 mg solution for injection

Progesterone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial (1.119 ml) contains 25 mg of progesterone (theoretical concentration 22.35 mg/ml).

3. LIST OF EXCIPIENTS

Hydroxypropylbetadex
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
Pack contains 1vial
7 vials
14 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intramuscular or subcutaneous use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use as directed by physician.

The medicinal product must be used immediately after first opening. Any remaining solution must be discarded.

Patient self-administration: Subcutaneous injection only
Healthcare administration: By s.c and i.m injection

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 25oC. Keep the vial in the outer carton in order to protect from light. Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

IBSA Farmaceutici Italia Srl
Via Martiri di Cefalonia 2
26900 Lodi (Italy)

12. MARKETING AUTHORISATION NUMBER(S)

PL 21039/0026

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

N/A - only applies to non-prescription medicines

16. INFORMATION IN BRAILLE

Lubion 25 mg solution for injection

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

(Type I glass vial)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lubion 25 mg solution for injection

Progesterone

For i.m. or s.c. use.

2. METHOD OF ADMINISTRATION

For i.m. or s.c. use.

Read the package leaflet before use

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each vial (1.119 ml) contains 25 mg progesterone (theoretical concentration 22.35 mg/ml).

6. OTHER

Store below 25°C. Use immediately after opening

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

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 applications for Lubion 25 mg Powder for Solution for Injection and Lubion 25 mg Solution for Injection indicated in adults for luteal support as part of an Assisted Reproductive Technology (ART) treatment program in infertile women who are unable to use or tolerate vaginal preparations, could be approved.

These applications were submitted under Article 8(3) of Directive 2001/83/EC, as amended. These Marketing Authorisation Applications concern Lubion 25 mg Powder for Solution for Injection and Lubion 25 mg Solution for Injection which contain the active ingredient progesterone. Progesterone-IBSA is presented in two pharmaceutical forms: a sterile solution for injection and a lyophilised powder for solution for injection that can be constituted with sterile water for injection for intramuscular (i.m.) and subcutaneous (s.c.) use.

With UK as the RMS in these Decentralised Procedures (UK/H/4170/001-02/DC), IBSA Farmaceutici Italia Srl applied for Marketing Authorisations for Lubion 25 mg Powder for Solution for Injection and Lubion 25 mg Solution for Injection in Austria, Belgium, Cyprus, Czech Republic, France, Germany, Greece, Hungary, Italy, Luxemburg, Poland, Portugal, Slovak Republic and Spain.

Progesterone is a naturally occurring steroid that is secreted by the ovaries, placenta, and adrenal glands. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

Since a literature review has been presented for a large proportion of the non-clinical aspects, it cannot be verified whether the studies cited were in compliance with the GLP regulations. However, it is assumed that the studies conducted by the originator would have been conducted in compliance with the standards prevailing at the time. Pharmacokinetic data and two local tolerance studies have been submitted.

Satisfactory clinical studies were provided with these applications. Four pharmacokinetic studies were performed to characterise the pharmacokinetic characteristics of progesterone-IBSA. A Pharmacodynamic study was conducted to demonstrate the endometrial effects of daily subcutaneous administration of progesterone 25 and 50 mg aqueous formulation.

Two efficacy studies (07EU/prg06 and 07US/prg05) were carried out to demonstrate that progesterone-IBSA administered subcutaneously is non-inferior to Crinone gel administered when used as luteal support in patients undergoing IVF.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. Satisfactory Risk Management Plan (RMP) has been provided with these applications.

All member states agreed to grant a licence for each of the above products at the end of the procedure (Day 210 – 20th January 2013). After a subsequent national phase, the UK granted licences for these products on 22nd February 2013 (PL 21039/0025-26).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Lubion 25 mg Powder for Solution for Injection Lubion 25 mg Solution for Injection
Name(s) of the active substance(s) (USAN)	Progesterone
Pharmacotherapeutic classification (ATC code)	G03DA04, Sex hormones and modulators of the genital system; Progestogens; Pregnen-(4) derivatives,
Pharmaceutical form and strength(s)	Powder for solution for injection Solution for injection 25 mg
Reference numbers for the Decentralised Procedure	UK/H/4170/001-02/DC
Reference Member State	United Kingdom
Concerned Member States	Austria, Belgium, Cyprus, Czech Republic, France, Germany, Greece, Hungary, Italy, Luxemburg, Poland, Portugal, Slovak Republic and Spain
Marketing Authorisation Number(s)	PL 21039/0025-26
Name and address of the authorisation holder	IBSA Farmaceutici Italia Srl Via Martiri di Cefalonia 2, 26900 Lodi, Italy

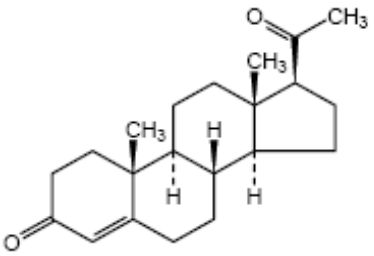
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Progesterone
Chemical Names: Pregn-4-ene-3,20-dioneΔ^4-pregnone-3,20-dione

Structure:



Molecular formula: $C_{21}H_{30}O_2$

Molecular weight: 314.5

Physical form: A white or almost white, crystalline powder or colourless crystals.
.
Solubility: practically insoluble in water, freely soluble in ethanol, 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 are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients
Other ingredients consist of the pharmaceutical excipient hydroxypropylbetadex.

All excipients comply with the relevant European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for this excipient.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the pharmaceutical development programme was to obtain a stable product containing progesterone that can reduce discomfort, thereby increasing patient compliance and allow auto-medication.

Suitable pharmaceutical development data have been provided for these applications.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated and have shown satisfactory results. Process validation data on

commercial batches have been provided. The results are satisfactory.

Finished Product Specifications
The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The finished product is supplied in Colourless Type I glass vial fitted with a bromobutyl rubber stopper, aluminium seal and 'flip-off' cap. The pack sizes are 1, 7 or 14 vials.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with relevant guidelines.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Lubion 25 mg Powder for Solution for Injjection
Based on the results, a shelf life of 48 months for unopened vials with storage conditions 'Store below 25°C', 'Do not refrigerate or freeze' and 'Store in the original package in order to protect from light' are set.

After first opening and reconstitution, the reconstituted solution must be used immediately. Any remaining solution should be discarded.

Lubion 25 mg for Solution for Injection
A shelf-life of 2 years with a storage conditions 'Store below 25°C', 'Do not refrigerate or freeze' and 'Store in the original package in order to protect from light' are set.

This medicinal product must be used immediately after first opening: any remaining solution must be discarded.

The shelf-lives and storage conditions are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PILs and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.

The Marketing Authorisation holder has stated that not all pack sizes may be marketed. They have committed to obtain approval of the mock-ups for unmarketed pack sizes before those packs are commercially marketed.

Marketing Authorisation Application (MAA) Form
The MAA forms are pharmaceutically satisfactory.

Expert Report
A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of progesterone are well known.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Data was provided to demonstrate the pharmacokinetic properties of progesterone following intramuscular and intravenous injection and have confirmed that the pharmacokinetic profile of the progesterone HP-β-CD formulation following intravenous and intramuscular administration is generally comparable to that observed following administration of the currently marketed injectable products containing progesterone.

The majority of the toxicity data for the active substance, progesterone and the excipient, hydroxypropylbetadex (HP-β-CD) was obtained from the literature. The applicant has confirmed that the potential for the proposed product to cause genotoxicity and carcinogenicity is low.

Two local tolerance studies have been conducted with injectable progesterone in the rabbit and these studies were conducted in accordance with Good Laboratory Practice (GLP). Overall, the non-clinical data demonstrated that the administration of injectable progesterone is associated with some degree of irritancy at the injection site, which is in line with the adverse events as reported during the clinical studies. The nature of the findings from the local tolerance studies (following both subcutaneous and intramuscular administration) have now been accurately reflected in the SmPC.

Based on the maximum dose of 100 mg per day, the proposed limit for any individual impurity within the drug substance exceeds the limit of 0.15% as specified by ICH Q3A(R2). However, since the active substance is compendial, the impurities in the drug substance are considered to be qualified. The proposed impurity levels within the drug product comply with the limit of 0.5% as specified by ICH Q3B(R2) Impurity in New Drug Products. The proposed limits for the residual solvents, hexane and methanol are in accordance with ICHQ3C(R5) Impurities: Guideline for residual solvents and are acceptable.

The applicant has conducted a Phase I environmental risk assessment. A commitment has been provided to submit a full environmental risk assessment (ERA) within 36 months of approval.

There are no objections to the approval of these products from a non-clinical point of view.

III.3 CLINICAL ASPECTS
Pharmacokinetics (PK)
Four pharmacokinetic studies have been conducted to characterise the PK profile of Lubion

(aqueous Progesterone IBSA) after single dose administration and at steady state concentrations.

Study CRO-PK-03-55
This was a single centre, randomised, single-dose, three way crossover comparative bioavailability study of three progesterone oily or aqueous formulations, administered as intramuscular (i.m.) or subcutaneous (s.c.) injections at a dose of 100 mg conducted in 24 post menopausal healthy Caucasian female volunteers.

The three formulations were:

- **Formulation A: Prontogest®** as reference marketed formulation, 1 x 100 mg vial i.m.
- **Formulation B: Progesterone-IBSA** 2 x 50 mg vials i.m. (Lubion)
- **Formulation C: Progesterone-IBSA** 2 x 50 mg vials s.c. (Lubion)

Each woman received a single 100 mg dose of progesterone, administered during 3 consecutive study periods, separated by 14-day wash-out intervals. The serum progesterone concentrations were collected at pre-dose (0), 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours post-dose, for Prontogest and pre-dose (0), 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72 and 96 hours post-dose, for Progesterone-IBSA i.m. and s.c.

Table 11: Prontogest 100 mg I.M. (Formulation A) vs Progesterone-IBSA 100 mg I.M. (Formulation B)

Formulation A vs. B	Cmax	AUC0-t	AUC0-∞
Sequence effect	0.3159	0.3776	0.1828
Treatment effect	0.0000	0.0164	0.0058
Period effect	0.8263	0.1144	0.1925
PE (ratio of the geometric means)	26.93%	108.05%	109.59%
90% CI (of the ratio of the geometric means)	21.93 - 33.06%	102.67 - 113.71%	104.10 - 115.36%
Conclusions	*Non equivalent*	*Equivalent*	*Equivalent*

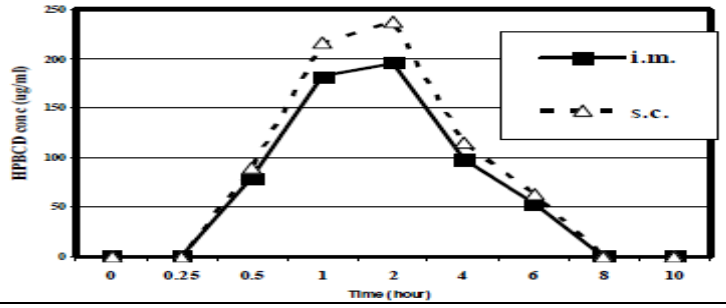
Table 12: Prontogest 100 mg I.M. (Formulation A) vs Progesterone-IBSA 100 mg SC (Formulation C)

Formulation A vs. C	Cmax	AUC0-t	AUC0-∞
Sequence effect	0.0108	0.0272	0.0247
Treatment effect	0.0000	0.0006	0.0005
Period effect	0.2563	0.3204	0.4651
PE (ratio of the geometric means)	34.71%	110.78%	111.61%
90% CI (of the ratio of the geometric means)	29.60 - 40.71%	106.01 - 115.78%	106.64 - 116.81%
Conclusions	*Non equivalent*	*Equivalent*	*Equivalent*

The baseline corrected PK parameters have been presented along with the 90% CI. Progesterone-IBSA 100 mg i.m. and s.c. are bioequivalent to Prontogest i.m. with regards to AUC $_{0\text{-}t}$ and $AUC_{0\text{-}inf}$.

Addendum to Study CRO-PK-03-55
This study was carried out to verify the hypothesis that progesterone and β-cyclodextrin 2-hydroxylpropyl ether have a different pharmacokinetic pattern. β-cyclodextrin 2-hydroxylpropyl ether was measured in the serum samples obtained from 6 out of 24 volunteers enrolled in Study CRO-PK-03-55 as they were the ones with sufficient plasma samples.

Figure 2: Mean plasma concentrations of HPB after i.m. and s.c. administration of Progesterone-IBSA.



The results showed that The PK parameters for β-cyclodextrin 2-hydroxylpropyl ether were different from those for progesterone IBSA in the 6 subjects studied.

Study CRO-PK-05-143

This single centre, open-label, randomised, 3 way, cross-over pharmacokinetic study was performed to find out if pharmacokinetic parameters for Progesterone-IBSA are linear within the dose ranges commonly used in clinical practice.

In order to minimise the possible influence of endogenous steroid on the PK of exogenous progesterone, 12 post-menopausal healthy volunteers (naturally amenorrhoeic for at least 1 year, or patients that had undergone surgical menopause) were selected. Patients were randomly assigned to receive a single injectable dose of 25, 50 or 100 mg of Progesterone-IBSA in a 1 ml volume by s.c. injection. There was a 14-day washout period between medications. Venous blood samples were collected at pre-dose (0), 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72 and 96h post-dose.

The primary and secondary PK endpoints were:

- Primary end point –AUC 0-t and F_{rel}
- Secondary endpoints – C-max, T-max, AUC 0-∞ t1/2 and MRT

The results of study CRO-PK-05-143 performed to find out if the pharmacokinetic parameters for Progesterone-IBSA are linear suggests that there is a dose proportional increase in C_{max} and AUC_{0-t} over the dose range 25-100 mg.

Table 3: PK parameters calculated in the dose linearity study after s.c. administration of a Progesteron IBSA single dose of 25 mg, 50 mg and 100 mg (Study CRO-PK-05-143).

PK parameter	25 mg	50 mg	100 mg
C_{max} (ng/ml)	54.7 ± 13.1	115.3 ± 26.6	249.9 ± 67.0
T_{max} (h)	0.9 ± 0.4	0.9 ± 0.4	0.9 ± 0.4
AUC_{0-t} (ng/ml/h)	441.5 ± 92.9	978.8 ± 341.4	1683.2 ± 240.1
$AUC_{0-\infty}$ (ng/ml/h)	521.2 ± 113.0	1103.8 ± 438.4	1771.1 ± 247.4
$\%AUC_{extra}$	14.9 ± 6.7	10.6 ± 5.3	5.0 ± 2.3
t½ (hour)	41.3 ± 17.9	39.2 ± 17.8	27.3 ± 9.4
MRT (hour)	43.4 ± 15.0	35.8 ± 11.9	23.2 ± 4.9

The results suggest that there is a dose proportional increase in C_{max} and AUC_{0-t} and $AUC_{0-\infty}$ over the dose range 25-100 mg.

Study CRO-05-66

This study was conducted to demonstrate the endometrial effects of daily subcutaneous

administration of progesterone 25 and 50 mg aqueous formulation to healthy female volunteers. The primary end-point was ≥ 90% partial predecidual changes and ≥ 80% full predecidual changes in endometrial samples obtained on the 11th day of exposure to the investigational product and the secondary end-point was the pharmacokinetic profile of steady-state progesterone following two treatments (25 and 50 mg/day) of the new subcutaneous aqueous formulation (IBSA). The PK results suggested a dose proportional increase in C_{max} and AUC_{0-t} and the PD results showed that there were histological changes within the endometrium.

Table 4: Main progesterone PK parameters (mean ± SD) at the steady-state after administration of Progesterone-IBSA 25 or 50 mg s.c. (n = 12 for each group) (Study CRO-05-66).

PK Parameter	T1: Progesterone-IBSA 25 mg	T2: Progesterone-IBSA 50 mg
C_{ssmax} (ng/ml)	54.5 ± 13.6	109.6 ± 20.7
C_{ssmin} (ng/ml)	4.8 ± 1.1	7.8 ± 2.3
T_{ssmax} (h)	1.0 ± 0.4	0.9 ± 0.4
$C_{ssaverage}$ (ng/ml)	14.5 ± 1.7	26.6 ± 4.2
AUC_{ss} (ng/ml×h)	346.9 ± 41.9	638.2 ± 101.6
Vd_{ss} (mL)	769682.6 ± 196106.0	848089.6 ± 265376.9
Cl_{ss} (ml/h)	60177.7 ± 9649.8	66708.3 ± 13351.9
MRT (h)	13.2 ± 4.6	13.4 ± 6.0
%PTF (%)	344.2 ± 84.0	386.5 ± 74.3
%Swing (%)	1116.2 ± 506.6	1422.2 ± 531.5

There appears to be a dose proportional increase in Cmax and AUC 0-t. Pre-dose concentrations were detected in all subjects suggesting an endogenous production of progesterone.

Overall, progesterone-IBSA appears to have linear pharmacokinetics and appear to be similar to oily progesterone preparations in terms of AUC but with a higher C-max.

Pharmacodynamics (PD)
The pharmacodynamic characteristics of progesterone are known. The PD results of Study CRO-05-66 are considered to be relevant to the PD characteristics of progesterone IBSA and a summary of the results is given below.

Study CRO-05-66
This study was conducted to test the efficacy of progesterone 25 and 50 mg aqueous formulations (IBSA) in inducing endometrial pre-decidual changes. Primary end-point: To find ≥ 90% partial pre-decidual changes and ≥ 80% full pre-decidual changes in endometrial samples obtained on the 11th day of exposure to progesterone IBSA.
Twenty-five (25) subjects were randomized and included in the study. 24 subjects completed the study according to the protocol (i.e. 24 biopsies were obtained). One subject discontinued the study for safety reasons after the occurrence of a mild AE (exanthema on both thighs).

Progesterone-IBSA, administered once daily by s.c. injection at the doses of 25 mg (T1) or 50 mg (T2) for 11 consecutive days. Before treatment with the test product, the subjects were administered GnRH-a (Enantone® gyn 3.75mg) to ensure a safe and temporary suppression of ovarian function. Administration of GnRH-a was followed by the administration of exogenous E2 (Estradot® 50µg/24h patch or estrofem® 2mg) for proper estrogen priming. The endometrial biopsies were obtained on the 11th day of progesterone treatment using a Pipelle uterine sampler (Pipelle de Cornier).

Results
Twenty-four biopsies were obtained for the evaluation of endometrial predecidual changes. Of these, 22 were evaluated and included in the efficacy analysis. Two did not contain any tissue and one contained insufficient tissue for complete endometrial dating, but enough for

assessment of cycle phase and stroma decidualisation. Both pathologists found partial pre-decidual changes (at the periphery of spiral artery) or full pre-decidual changes (full thickness) in all the samples. The partial and full predecidual changes in endometrial samples were considered for analysis by both observers according to: a) the days of luteal phase; b) the cycle phase; c) the presence of cellular decidualisation in the stroma.

Days of luteal phase: The frequency of partial predecidual changes was 100%, irrespective of dose or observer. Full pre-decidual changes were observed in at least in 80% of the subjects irrespective of dose. In all cases, there was no statistical difference between the 2 dose groups. Thus, it can be concluded that the primary end-point has been achieved.

Cycle phase: Both pathologists observed a mid- or late-secretory transformation in 100% of the biopsies. Therefore, partial predecidual changes were observed in 100% of the evaluated biopsies, independently of the treatment group.

Decidualisation of the stroma: Both observers always gave a score of at least 1 (i.e. at least 1% of cells showed decidualisation); leading to the conclusion that stromal decidualisation was always observed (i.e. in 100% of the evaluated biopsies). Again, the primary end-point has been confirmed, since more than 90% of the biopsies displayed at least partial pre-decidual changes. All results are summarised in table 2.

Table 2: The number of patient biopsies showing decidualisation in the 25 mg and 50 mg Progesterone-IBSA treatment groups. The degree of decidualisation was independently assessed by two pathologists.

	In 25 mg treatment group	50 mg
Between 1-25 % of cells show decidualisation	10%	8.33 - 25%
Between 26-50 % of cells show decidualisation	50 - 60%	8.33 - 33.33%
Over 50 % of cells show decidualisation	58.33 - 66.67%	58.33 - 66.67%

Endometrial changes were observed in all the samples examined.

Endogenous progesterone exerts function on the cervix, uterus, endometrium, tubes, the central nervous system, pituitary and the breast. Yet, the primary target organ of progestogens in infertility treatments is the endometrium, where it is necessary for nidation (implantation) of the embryo and for maintenance of pregnancy.
At the uterine level, progesterone exerts 3 primary actions:

(i) Anti proliferative effects on endometrial glandular and stromal components that antagonize the endometrial proliferation induced by E2 (Ferenczy 1979) during the follicular phase (Clarke 1990). This is primarily mediated by inhibiting the expression of estrogen receptors (ER) (Tseng 1975a;Hsueh 1976) and transforming E2 in less active E1 (Tseng 1975b).

(ii) Differentiation or predecidual transformation of the endometrium occurs through sets of cell type-specific expression and regulation of growth factor receptors and their peptide ligands (Clarke 1990; Christian 2002;Aghajanova 2010). Predecidual transformation of the endometrium aims at fostering endometrial receptivity to embryo implantation or 'window of implantation' (WOI).

(iii) Finally, progesterone also exerts utero-relaxing effects characterized by the prompt disappearance of contractility encountered in the follicular phase (Perusquia 1994;Zervou 1999;Ayoubi 2001) and establishment of a state of uterine quiescence during the luteal phase.

In women with adequate endogenous estrogen, progesterone transforms the endometrium from a proliferative to a secretory tissue (Nunobiki 2003; Rosario 2003). The abrupt decline in the secretion of progesterone at the end of the menstrual cycle is principally responsible for the onset of menstruation (Casper 1996). Accordingly, if the duration of the luteal phase is artificially lengthened, either by sustaining luteal function or by treatment with progesterone, decidual changes in the endometrial stroma similar to those observed in early pregnancy can be induced (Goodman 1996). Progesterone suppresses menstruation and uterine contractility (Perusquia 1994;Zervou 1999).

Clinical Efficacy
Two studies are provided to demonstrate efficacy:

Study 07EU/Prg06
This is a phase III, open-label, randomised, parallel-group, multicentre, two-arm study comparing the safety and effectiveness of Progesterone-IBSA to Crinone for luteal support in patients undergoing IVF. Patients were enrolled in the study and randomised in a 1:1 ratio to receive either subcutaneous Progesterone-IBSA at a daily dose of 25 mg or treatment with Crinone gel at a daily dose of 90 mg. The total duration of treatment for each patient was a maximum of 10 weeks, over two study phases.

The primary efficacy variable was the proportion of patients pregnant 10 weeks after start of treatment. The secondary efficacy variables were; implantation rate, positive β-HCG test rate, biochemical pregnancy, clinical pregnancy rate and early spontaneous abortions, delivery rate including live rate and newborn status. These efficacy variables are considered acceptable.

Non-inferiority was assessed by calculating the 95% confidence interval (CI) of the difference between the two proportions. If the lower bound of the 95% CI of the difference (p_e- p_c) was greater than −0.10, then Progesterone-IBSA was to be considered non-inferior to Crinone treatment.

It is claimed that intent-to-treat (ITT) population consisted of all patients who received at least one dose of Progesterone-IBSA or Crinone, with the exclusion of major violator patients and that analyses were performed on the ET population, as well as the population who became pregnant. Ideally, in a non-inferiority study analysis should be done on the mITT and the PP population.

Results

Table 6 Ongoing Pregnancy Rate at 10 Weeks

Ongoing Pregnancy Rate	Progesterone-IBSA	Crinone	Difference versus Crinone
	n (%)		(95% CI)
ITT Population[1]	93 (27.4)	105 (30.5)	-3.09 (-9.91%, 3.73%)
mITT Population[2]	93 (27.9)	100 (29.9)	-2.10 (-8.98%, 4.79%)
PP Population[3]	93 (29.2)	100 (31.2)	-2.00 (-9.12%, 5.13%)

[1] N=339 in the Progesterone-IBSA and 344 in the Crinone group.
[2] N=334 in both the Progesterone-IBSA and the Crinone group.
[3] N=319 in the Progesterone-IBSA and 321 in the Crinone group.

Table 7 Secondary Efficacy Analysis results (ITT Population)

		Progesterone-BSA N=339	Crinone N=344	P value[1]
Implantation rate[2]	Mean (SD)	22.6 (35.0)	23.1 (33.1)	0.85
Positive β-hCG Test rate	N (%)	134 (39.5)	148 (43.0)	0.35
Clinical pregnancy rate	N (%)	103 (30.4)	113 (32.9)	0.49
Biochemical pregnancy rate	N (%)	7 (2.1)	11 (3.2)	0.36
Early Spontaneous Abortion	N (%)	15 (4.4)	15 (4.4)	0.97
Pregnancy Loss Rate	N (%)	22 (6.5)	18 (5.2)	0.48
Delivery rate	N (%)	91 (26.8)	98 (29.9)	0.37
Live births rate	N (%)	91 (26.8)	98 (29.9)	0.37

[1]Student t-test for continuous variables, χ^2 test for categorical variables.
[2]Implantation rate: N=322 in the Progesterone-IBSA and in N=331 the Crinone group.

The results showed similar ongoing pregnancy rates between progesterone-IBSA and crinone at 10 weeks of gestation as seen in the table above. Progesterone was demonstrated to be non-inferior to Crinone but the lower limit of the 95% CI is quite close to the chosen 10% margin.

Study 07US/prg05

This study was conducted to support the efficacy of progesterone-IBSA when used for luteal phase support. This study carried out in the US; the comparator was Endometrin at a dose of 100 mg bid (this dose is not approved in the EU). The study protocol of this study is superimposable on the protocol of study 07EU/Prg06 (i.e. procedures and inclusion/exclusion criteria are the same,

Table 20: Ongoing Pregnancy Rate at 10 Weeks (ITT and PP Populations)

Ongoing Pregnancy Rate	Progesterone-IBSA	Endometrin	Difference versus Endometrin (95% CI)
	n (%)		
ITT Population[1]	163 (40.8)	173 (43.3)	−2.5 (−9.4%, 4.4%)
PP Population[2]	163 (41.6)	173 (44.4)	−2.8 (−9.7%, 4.2%)

[1] N=400 in both the Progesterone-IBSA and in the Endometrin group.
[2] N=392 in the Progesterone-IBSA group; N=390 in the Endometrin group.

The results showed that In the ITT population, ongoing pregnancy rates at 10 weeks were comparable between the two treatment groups (40.8% and 43.3% in the Progesterone-IBSA and Endometrin groups, respectively). The difference between the groups was −2.5% (95% CI, −9.4, 4.4) and in the PP population (41.6% and 44.4% in the Progesterone-IBSA and Endometrin groups, respectively), with a difference between the groups of −2.8% (95% CI, −9.7, 4.2). In this study, the lower limit of the 95% confidence interval is also very close to the chosen 10% margin.

The results of the two studies (07EU/prg06 and 07US/prg05) suggested that Lubion might be less efficacious when compared to vaginal preparations but the preganancy rate with placebo has been provided and is estimated to be 12.5% which suggest that progesterone-IBSA might be better than placebo.

Tolerability

A tolerability study CRO-06-82 was conducted to compare the local tolerability and safety of Progesterone-IBSA 25 mg with Prontogest (an oily progesterone preparation). The volunteers assessed the pain intensity at injection site by means of a Visual Analogue Scale (VAS) 0-10 cm, where 0 = no pain and 10 cm = severe pain). The duration of pain at injection site was also assessed. The results showed that the differences in daily and average pain intensity between the two treatments were not statistically significant at any of the post-dose assessment times. In terms of duration, pain lasted longer after Prontogest than after

Progesterone-IBSA treatment, although this difference was not statistically significant. In addition, no significant differences were found when comparisons were based on the global scores reported during the study.

Clinical Safety
The evaluation of the safety of Progesterone-IBSA is based on the analysis of Adverse Events (AEs) and tolerability performed during the PK studies (CRO-PK-03-55 and CRO-PK-05-143), tolerability study (CRO-06-82), PK/PD study (CRO-05- 66), the efficacy and safety study (07EU/Prg06) and the information provided by literature on the use of progesterone by i.m. or s.c.

The adverse event profile of the pharmacokinetic study CRO-06-82 suggests that there were injection site events in both the oily progesterone and progesterone-IBSA groups. However, injection site swelling and redness appear to occur more frequently in the oily progesterone group when compared to progesterone-IBSA. 3.87% versus 0% and 30.97% versus 23.87%, respectively.

In the pivotal study 07EU/Prg06 the adverse events profile was similar in the progesterone-IBSA and the Crinone group. Overall, no significant adverse events were identified in the studies conducted with progesterone-IBSA.

Pharmacovigilance system
The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan (RMP)
Satisfactory risk management plan has been provided.

Summary of Product Characteristics (SmPC)
The approved SmPCs are satisfactory for these products.

Patient Information Leaflet (PIL)
The final PIL is in line with approved SmPC and is satisfactory.

Labelling
The labelling is satisfactory.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Form
The MAA forms are satisfactory from a clinical perspective.

CONCLUSION
There are no objections to the approval of these products from a clinical point of view.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Lubion 25 mg Powder for Solution for Injection and Lubion 25 mg Solution for Injection 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

Satisfactory non-clinical data were submitted.

CLINICAL

Four pharmacokinetic studies were performed to characterise the pharmacokinetic characteristics of progesterone-IBSA. Overall, it appears to have linear pharmacokinetics and seem to be similar to oily progesterone preparations in terms of AUC but has a higher C-max.

The results of the Pharmacodynamic study suggested that progesterone-IBSA administered subcutaneously is able to induce histological changes within the endometrium after down-regulation with GnRH and priming with exogenous oestrogen.

The efficacy studies conducted suggested that Lubion might be less efficacious when compared to vaginal preparations but the preganancy rate with placebo has been provided and is estimated to be 12.5% which suggest that progesterone-IBSA might be better than placebo.

In conclusion, although there is a suggestion that Lubion is not as efficacious as vaginal preparations, taking into consideration the proposed indication and the overall uncertainty regarding the optimal dose, timing and duration of use for progesterone for luteal phase support; the benefit risk is considered positive. It could be an option for women who might not be comfortable with using vaginal preparations and therefore might be of benefit to some women.

SAFETY

The adverse event profile in the tolerability study suggests that there were injection site events in both the oily progesterone and progesterone-IBSA groups. However, injection site swelling and redness appear to occur more frequently in the oily progesterone group when compared to progesterone-IBSA. In addition the adverse events profile of the pivotal efficacy study was comparable in the progesterone-IBSA and the Crinone groups. Overall, no significant adverse events were identified in the studies conducted with progesterone-IBSA.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT

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

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome