Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lubion 25 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe (1.112 ml) contains 25 mg of progesterone (22.48 mg/ml).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.
Clear colourless solution, essentially free from visible particles.
The solution has an osmolality around 250 mOsmol/Kg and a pH between 5 and 8.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lubion is 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.

4.2 Posology and method of administration

Posology
Adults
Once daily injection of 25 mg from day of oocyte retrieval, usually until 12 weeks of confirmed pregnancy.

As the indications for Lubion are restricted to women of child-bearing age, dosage recommendations for children and the elderly are not appropriate.

Lubion is given subcutaneously (25 mg) by the patient herself after instruction or by a healthcare professional or a doctor.
Special populations
Elderly
No clinical data have been collected in patients over age 65.
Renal and hepatic impairment
There is no experience with use of Lubion in patients with impaired liver or renal function.
Paediatric population
The safety and efficacy of Lubion in children (0 to 18 years) has not been established.
There is no relevant use of Lubion in the paediatric population or elderly in the indication for luteal support as part of an Assisted Reproductive Technology (ART) treatment program in infertile women.

Method of administration
Treatment with Lubion should be initiated under the supervision of a physician experienced in the treatment of fertility problems.
Lubion is intended for subcutaneous administration.

Choose an appropriate area (front of thigh, lower abdomen), swab proposed area, pinch the skin together firmly and insert the needle at an angle of 45° to 90°. The product should be injected slowly to minimise local tissue damage.

Each pre-filled syringe is intended for single-use injection only.

4.3 Contraindications

Lubion should not be used in individuals with any of the following conditions:

- Hypersensitivity to progesterone or to any of the excipients listed in section 6.1
- Undiagnosed vaginal bleeding
- Known missed abortion or ectopic pregnancy

- Severe hepatic dysfunction or disease

- Known or suspected breast or genital tract cancer
- Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events
- Porphyria
- A history of idiopathic jaundice, severe pruritus or pemphigoid gestationis during pregnancy.

4.4 Special warnings and precautions for use

Lubion should be discontinued if any of the following conditions are suspected: myocardial infarction, cerebrovascular disorders, arterial or venous thromboembolism, thrombophlebitis, or retinal thrombosis.
Caution is indicated in patients with mild to moderate hepatic dysfunction.
Caution is indicated in patients with moderate to severe renal dysfunction, because accumulation of cyclodextrins may occur.
Patients with a history of depression need to be closely observed. Consider discontinuation if symptoms worsen.
Because progesterone may cause some degree of fluid retention, conditions that might be influenced by this factor (e.g. epilepsy, migraine, asthma, cardiac or renal dysfunction) require careful observation.
A decrease in insulin sensitivity and thereby in glucose tolerance has been observed in a small number of patients on oestrogen-progestogen combination drugs. The mechanism of this decrease is not known. For this reason, diabetic patients should be carefully observed while receiving progesterone therapy (see section 4.5).
Sex steroid use may also increase the risk of retinal vascular lesions. To prevent these latter complications, caution is to be taken in users >35 years, in smokers, and in those with risk factors for atherosclerosis. Use should be terminated in case of transient ischemic events, appearance of sudden severe headaches, or vision impairments related to papillary oedema or retinal haemorrhage.
Abrupt discontinuation of progesterone dosing may cause increased anxiety, moodiness, and increased sensibility to seizures.
Before starting treatment with Lubion, the patient and her partner should be assessed by a doctor for causes of infertility or pregnancy complications.
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs known to induce the hepatic cytochrome-P450-3A4 system (e.g. rifampicin, carbamazepine, griseofulvin, phenobarbital, phenytoin or St. John's Wort (Hypericum perforatum-containing herbal products)) may increase the elimination rate and thereby decrease the bioavailability of progesterone.
In contrast ketoconazole and other inhibitors of cytochrome P450-3A4 may decrease elimination rate and thereby increase the bioavailability of progesterone.
Since progesterone can influence diabetic control an adjustment in antidiabetic dosage could be required (see section 4.4).

Progestogens may inhibit ciclosporin metabolism leading to increased plasma-ciclosporin concentrations and a risk of toxicity
The effect of concomitant injectable products on the exposure of progesterone from Lubion has not been assessed.
Concomitant use with other drugs is not recommended.

4.6 Fertility, pregnancy and lactation

Fertility
Lubion is used in the treatment of some forms of infertility (see section 4.1 for full details).

Pregnancy
Lubion is indicated for luteal support as part of an Assisted Reproductive Technology (ART) treatment program in infertile women.
There is limited and inconclusive data on the risk of congenital anomalies, including genital abnormalities in male or female infants, following intrauterine exposure during pregnancy. The rates of congenital anomalies, spontaneous abortion and ectopic pregnancies observed during the clinical trial were comparable with the event rate described in the general population although the total exposure is too low to allow conclusions to be drawn.

Breast-feeding

Progesterone is excreted in human milk and Lubion should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Lubion has minor or moderate influence on the ability to drive and use machines. Progesterone may cause drowsiness and/or dizziness; therefore caution is advised in drivers and those operating machinery.

4.8 Undesirable effects

The most frequently reported adverse drug reactions during treatment with Lubion during clinical trial are administration site reactions, breast and vulvo-vaginal disorders.
The table below displays the main adverse drug reactions in women treated with Lubion in the pivotal clinical trial. Data is expressed by system organ class (SOC) and frequency.

System Organ Class (SOC)	***Very common (≥ 1/10)***	***Common (≥ 1/100 to< 1/10)***	***Uncommon (≥ 1/1000 to < 1/100)***
Psychiatric disorders			Mood altered
Nervous system disorders		Headache	Dizziness, Somnolence
Gastrointestinal disorders		Abdominal distension Abdominal pain Nausea Vomiting Constipation	Gastrointestinal disturbances
Skin and subcutaneous tissue disorders			Pruritus Rash
Reproductive system and breast disorders	Uterine spasm Vaginal haemorrhage	Breast tenderness Breast pain Vaginal discharge Vulvo vaginal pruritus Vulvo vaginal discomfort Vulvo vaginal inflammation OHSS	Breast disorders
General disorders and administration site conditions	Administration site reactions*	Injection site haematoma Injection site induration Fatigue	Feeling hot, Malaise Pain

*Administration site reactions, such as irritation, pain, pruritus and swelling.

Class effects
The following disorders although not reported by patients in clinical studies using Lubion have been described with other drugs in this class of medicines.

System Organ Class (SOC)	
Psychiatric disorders	Depression
Nervous system disorders	Insomnia
Hepatobiliary disorders	Jaundice
Reproductive system and breast disorders	Menstrual disturbances Premenstrual like syndrome
Skin and subcutaneous tissue disorders	Urticaria, Acne, Hirsutism, Alopecia
General disorders and administration site conditions	Weight gain Anaphylactoid reactions

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance www.hpra.ie.

4.9 Overdose

High doses of progesterone may cause drowsiness.
Treatment of overdose consists of discontinuation of Lubion together with initiation of appropriate symptomatic and supportive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system; Progestogens; Pregnen-(4) derivatives, ATC code: G03DA04.
Progesterone is a naturally occurring steroid that is secreted by the ovary, 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.

Clinical efficacy and safety
Ongoing pregnancy rates following 10-week luteal support with Lubion 25 mg/day (N= 318) in patients who had an embryo transfer in the Phase III clinical trial were 29.25% (95% CI: 24.25 - 34.25).

Paediatric population
The European Medicine Agency has waived the obligation to submit the results of studies with Lubion in all subsets of the paediatric population in the granted indications.

5.2 Pharmacokinetic properties

Absorption
Progesterone serum concentrations increased following the subcutaneous (s.c.) administration of 25 mg of Lubion to 12 healthy post-menopausal females. By one hour post-administration of a single s.c. dose the mean Cmax was 50.7±16.3 ng/ml. The progesterone serum concentration decreased following a mono-exponential decay, and by twelve hours post-administration the average concentration was 6.6±1.6 ng/ml. The minimum serum concentration, 1.4±0.5 ng/ml, was reached at the 96-hour time-point. Pharmacokinetic analysis demonstrated linearity of the three s.c. doses tested (25 mg, 50 mg and 100 mg).
Following multiple dosing of 25 mg/daily via subcutaneous administration, steady state concentrations were attained within approximately 2 days of treatment with Lubion. Trough values of 4.8 ± 1.1 ng/ml were observed with AUCs of 346.9 ± 41.9 ng*hr/ml on Day 11.

Distribution
In humans, 96-99% of progesterone is bound to serum proteins like albumin (50-54%) or transcortin (43-48%), and the remainder is free in the plasma. Owing to its lipid solubility, progesterone travels from the bloodstream to its target cells through passive diffusion.

Biotransformation
Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites that are excreted in the bile may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation, and epimerization.

Excretion
Progesterone undergoes renal and biliary elimination.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on available studies of genotoxicity and carcinogenic potential. Local tolerance and repeated dose toxicity studies performed with Lubion confirmed the safety profile of the product.

Environmental risk assessment (ERA)
Environmental risk assessment studies have shown that progesterone may pose a risk for the aquatic compartment (see section 6.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylbetadex,
Disodium phosphate,
Sodium dihydrogen phosphate dihydrate,
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not refrigerate or freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Siliconized colorless glass syringe with a staked stainless steel needle, closed at one end by a needle shield and at the other end by a siliconized bromobutyl plunger stopper. Each carton box contains 7 or 14 pre-filled syringes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution is for single-use only.
The solution should not be administered if it contains particles or is discoloured.
This medicinal product may pose a risk to the environment (see section 5.3).
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

IBSA Farmaceutici Italia S.r.l
Via Martiri di Cefalonia 2,
26900 Lodi (LO)
Italy

8 MARKETING AUTHORISATION NUMBER

PA1104/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd November 2024

10 DATE OF REVISION OF THE TEXT

May 2025