Prolutex® | Pleyris®

Aqueous solution of progesterone for subcutaneous administration

Harbour of life

Prepare. Nurture. Perform.

IBSA

Caring Innovation

Prescribing information on page 12.

Prolutex® | Pleyris®

Aqueous solution of progesterone for subcutaneous administration

The first water-based solution for luteal phase support. A precious ally for ART patients[1].

WATER-BASED INNOVATION

Thanks to its newly-conceived hydrophilic aqueous solution[2], **Prolutex® enables the convenient self-administration of progesterone by systemic subcutaneous injection[1], thus ensuring precise dosing and full product absorption**[3].

NATURAL COMPLIANCE

Prolutex®'s original preservative and solvent-free formulation successfully side-steps the potentially severe irritation and allergic responses that may occur with oil-based progesterone injections[4,5] as well as the the sometimes uncomfortable local side-effects associated with the vaginal route[6,7].

EFFECTIVE PERFORMANCE

Prolutex® provides a reliable choice in manifold ART protocols requiring luteal phase support[1]. It can also be effective as vaginal progesterone[8,9] priming the endometrium for implantation even when there is no endogenous progesterone present[10].

IBSA

Natural progesterone

The progesterone (P) steroid is not water-soluble (Figure 1). Therefore, all injectable preparations made to date have been produced with oil-based solvents (usually peanut or sesame oil or ethyl oleate).
Due to its hydrophobic characteristics, progesterone has not been available until now for subcutaneous or even intravenous administration.
As its name suggests, progesterone is the principal 'progestational' hormone that primes endometrial receptivity[11] necessary for embryo implantation and enables the state of utero quiescence[12] indispensable for the development of pregnancy to term.

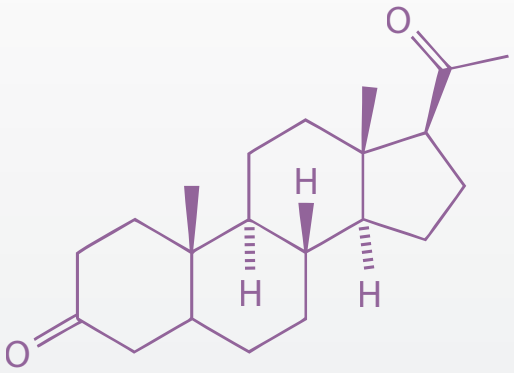

Figure 1. The molecule of the natural progesterone (P) (Adapted from Zoppetti)[2]

The primary contributor of high serum P levels encountered in the luteal phase (LP) is the corpus luteum (CL) formed after ovulation in the ovary. During pregnancy, the ovarian production of progesterone is rapidly taken over by the placenta, which becomes the sole producer of progesterone by the 7-11th week of pregnancy[13]. The daily production of progesterone in the menstrual cycle ranges from a minimum of 2 mg/day during the follicular phase, as a result of adrenal production[14], to an acme of approximately 25 mg/day in the mid-luteal phase as a result of active production by the corpus luteum[15].

CYCLODEXTRINS, SOLUBILITY ENHANCERS

Cyclodextrins (CD), described for the first time in 1891, are cyclic oligosaccharides characterised by an outer hydrophilic portion and a central lipophilic cavity (Figure 2). CD are widely used in the pharmaceutical industry for their ability to form inclusion complexes with hydrophobic drugs, thus increasing their water solubility. The complexes are then easily absorbed[16].

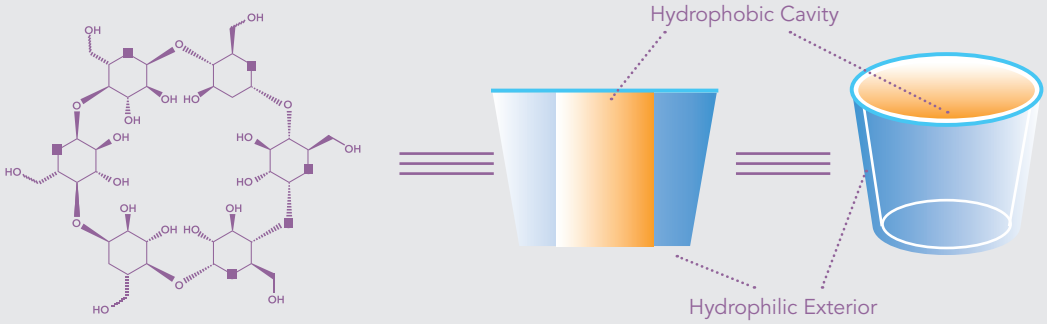

Figure 2. Schematic representation of cyclodextrin (CD) molecule (Adapted from Zoppetti)[2]

HIGHLIGHTS

- **First ingenious system to deliver progesterone by the subcutaneous route[2]**
- **Progesterone complexed with cyclodextrins in aqueous solution[2]**
- **No solvents and preservatives that may cause severe reaction or abscesses at the injection site[1,4,5]**

WATER-BASED INNOVATION

The first aqueous progesterone solution to allow self-administered subcutaneous injections

The solubility of IBSA's new progesterone solution is enhanced with hydroxypropyl-ß-cyclodextrin (HPBCD)[2,17,18] (Figure 3).

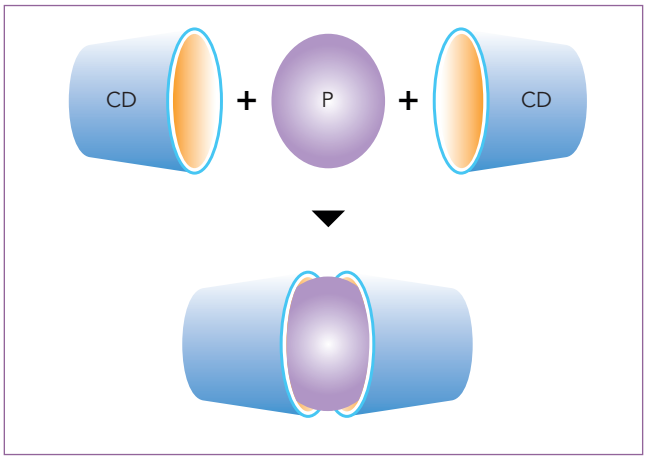

Figure 3. Schematic representation of complex molecular association (Adapted from Zoppetti)[2]

IBSA's new aqueous progesterone solution is excipient-free[1]. Each vial of **Prolutex®** is formulated as follows[1]:

- 25 mg of progesterone
- hydroxypropyl-ß-cyclodextrin (HPBCD)
- water for injection

Manufactured in single-use preparations, it does not contain the preservatives normally added in multiple-use oil-based injectable progesterone preparations. Side-effects such as sterile abscesses, marked inflammation at injection sites or severe hypersensitivity reactions are therefore eliminated[4,5].

None of the above-listed severe side-effects were reported in the two currently available pivotal phase III clinical trials of **Prolutex®** [8,9], even after 10 weeks of daily subcutaneous treatment.

Once the complex is injected and absorbed, the progesterone molecule is immediately dissociated from its cyclodextrins coating, **remaining free in the circulation as if produced endogenously by the ovaries** (Figure 4). Cyclodextrins are easily metabolised by the liver, as any starch product, with no further activity in the body.

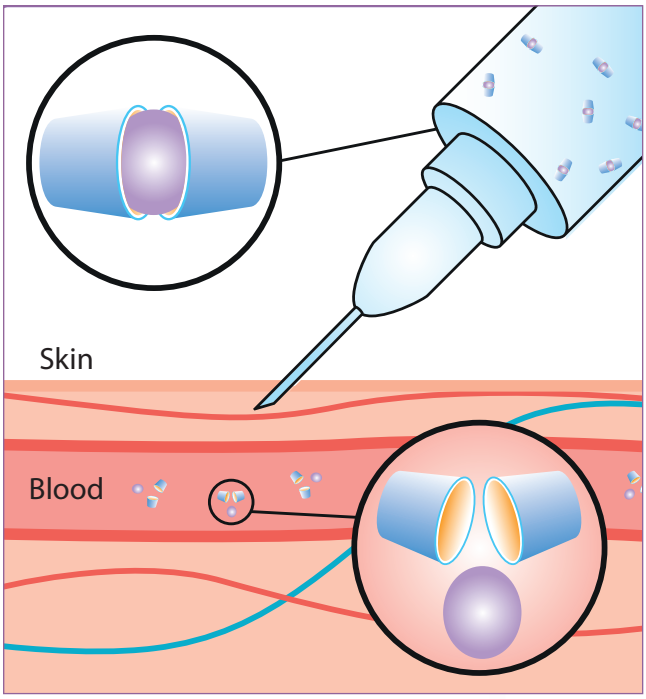

Figure 4. Schematic representation of the separation of the molecules in the blood stream

Investigator-initiated study: patients evaluate subcutaneous treatment with Prolutex® compared to vaginal progesterone administration for frozen-thawed blastocyst transfer

DESIGN AND SETTING

The aim of the study[19] was to evaluate patients' perspectives on a progesterone subcutaneous (SC P) formulation for the endometrial preparation of frozen-thawed blastocyst transfer. In this prospective study, all women participants had been previously treated with vaginal progesterone (VG P). At enrolment, they completed a first questionnaire (Q1) aimed at gathering information on their experience with VG P treatment and their expectations for SC P treatment. The patients were then asked to evaluate their experience with SC P in a second questionnaire (Q2) after 5 days of treatment, followed by a third questionnaire (Q3) after 13 days of treatment. Main outcome measures were patients' opinions on comfort, ease of use, convenience, overall satisfaction, level of anxiety and pain associated with the administration of SC P in comparison with their previous VG P experience. Sixty-nine women (mean age 36 ± 4.5 y) completed the questionnaires.

CONCLUSIONS

In general, most patients' previous experience with vaginal administration of progesterone was not very favourable. It was evaluated as "sometimes uncomfortable" by nearly 50% of the patients and as "very uncomfortable" by 15.9% of them; only 2.9% of patients reported it as "very comfortable". In terms of ease of use, only 12.3% evaluated the vaginal administration of P as "very easy"; the overall satisfaction of this route was termed "rather high" by 44.9% and "a little" by 43.4% (Table 1).

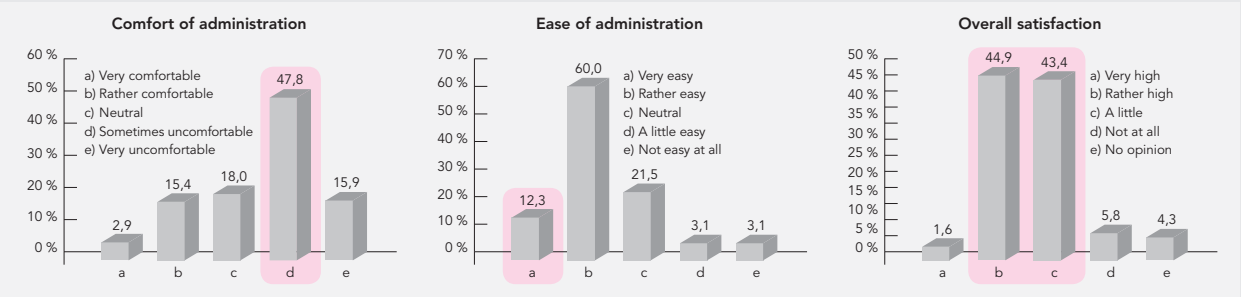

Table 1. Overall patients experience with vaginal preparation (Adapted from Venturella)[19]

When comparing patients' expectations with study outcomes, all evaluations for ease of use and convenience demonstrated that the patients' positive expectations for the subcutaneous route were thoroughly confirmed throughout, reaching a 92.4% of "very or rather convenient" after 13 days of SC treatment (Table 2).

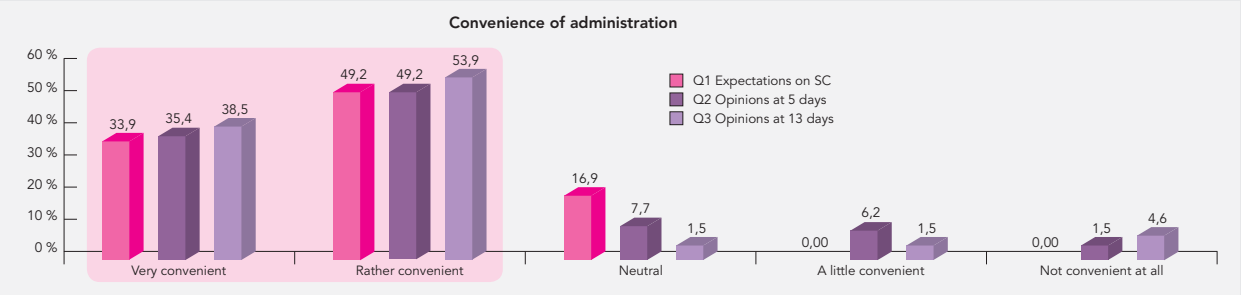

Table 2. Patients' expectations and experience on convenience of subcutaneous route (Adapted from Venturella)[19]

In conclusion, this prospective observational study **demonstrated that Prolutex® is comfortable, easy to use and leads to a high level of satisfaction among patients who had previously used vaginal progesterone.**

NATURAL COMPLIANCE

An original excipient-free formulation to reduce uncomfortable side-effects[1,4,5,6,7]

Prolutex®'s first sign of optimal compliance was registered in a pivotal European clinical study during which, **despite its 10-week length**, the two different regimens (injections vs. per vaginum insertion) were not statistically significant different in terms of comfort of the preparation or overall satisfaction (p=0.77 and p=0.75, respectively)[8].

Numerous real-life cases consistently validate the compliance of **Prolutex®**.
Indeed a recent study[20] confirmed that subcutaneous injections of **Prolutex®** are clearly preferred to the vaginal route, taking into account both the overall comfort and the treatment's impact on daily activities.
In this study, 45 patients under estrogen treatment for frozen ETs were asked to use **Prolutex®** (25 mg/day SC) for 7 days followed by 7 more days of vaginal progesterone (400 mg/12h VG). After completing both treatments, patients were asked to fill out a questionnaire with 9 items related to their feelings and preferences about subcutaneous and vaginal routes. Results are reported in Table 3.
In a pilot prospective controlled trial[21] comparing a 7 weeks LPS performed with **Prolutex®** 25 mg/day vs. vaginal P gel 90 mg/day in 246 women undergoing IUI cycles, comparative tolerability and satisfaction scores of the patients were also collected beside the clinical efficacy. Patients reported in their questionnaires several advantages from the SC injections: the possibility of self-administration, no need for special "confidence" with lower genital tract, no vaginal side-effects and no interference with sexual activities.

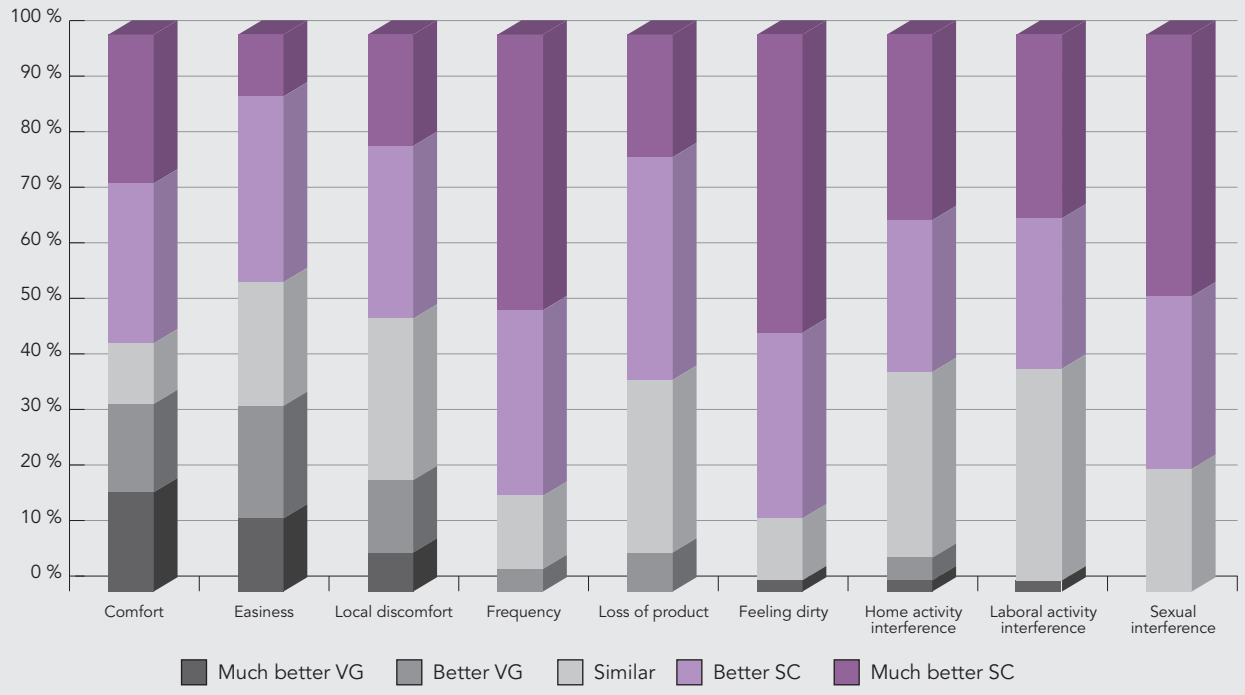

Table 3. Results of the questionnaire.
Subcutaneous progesterone was preferred in all items selected in the questionnaire (p<0,05). Graphic elaboration from textual data[20]

The benefits of the subcutaneous injection

A NEW THERAPEUTIC OPTION FOR ART PATIENTS

To date, neither the vaginal nor the intramuscular progesterone administration routes have been considered optimal in terms of patient compliance despite their proven efficacy in LPS.

As reported in the literature, vaginal preparations may cause various degrees of uncomfortable local side effects, including vaginal discharge, irritation, local inflammation[6,7] and, in the case of the progesterone gel, the tendency to form clumps[22] that may require manual removal.

The practical issues encountered with repeated i.m. injections using oil-based products preclude self-administration; pain occurs at the site of injection because the oil vehicle tends to dissect the muscle. Furthermore the oil-based products are known to cause local inflammatory reaction sometimes developing into sterile abscesses[4,15].

EASIER PREPARATION AND SELF-ADMINISTRATION

Vaginal administration is usually carried out in a sitting or lying position. Clearly, vaginal application should be performed at home or in an appropriate private place where the patient feels comfortable. This necessitates time and planning for the patients.

Moreover, certain patients are reluctant to undertake vaginal administration before or after pregnancy is confirmed or for cultural reason[23].

PRECISE DOSING

The total dose of progesterone absorbed and the number of daily doses necessary to achieve sustained serum progesterone concentrations using transvaginal administration largely depends on the formulation used (whether tablets, capsules, suppositories or gel)[6,24,25,26] and on the possibility of unquantifiable losses due to discharge.

CLEANER AND MORE CONVENIENT TRANSFER PROCEDURE

By eliminating locally placed progesterone, the use of systemic injections of P provides physicians performing the Embryo Transfer (ET) procedure with a more pristine vaginal environment in which to place the catheter, thus optimising the process.

DAILY, SYSTEMIC ADMINISTRATION

Despite the normally high doses administered (range from 90 mg/day up to 800 mg/day divided over two/three administrations), the vaginal route yields relatively low serum concentrations of progesterone, but shows a preferential distribution to the uterus[27]. In comparison with systemic administration, higher doses of vaginal progesterone would be necessary for duplicating the serum concentrations of progesterone typically encountered in the luteal phase of the menstrual cycle[28].

Moreover, certain effects of progesterone are mediated primarily outside of the pelvic cavity, for example the immunomodulatory effect of progesterone on peripheral cell-mediated immunity[29]. No study exists to date to determine whether such effects – desired in pregnancy – are serum level-dependent and may therefore be dependent on the route of administration.

HIGHLIGHTS

- **First systemic P for LPS in aqueous solution**[1]
- **Full and predictable dose of P absorbed**[3]
- **Novel alternative treatment choice**
- **Patient-friendly daily self-administration**

EFFECTIVE PERFORMANCE

A reliable natural choice for luteal phase support in ART programs

Efficacy of Prolutex® for inducing the predecidual transformation of the endometrium[10]

To determine the efficacy of **Prolutex®** at inducing the predecidual transformation of the endometrium, a prospective single-blind, randomised, parallel pilot trial was conducted during the development of this product[10].
In particular, donor-egg ART (DE-ART) cycles were used as a study model for challenging the new progesterone preparation and determining its ability at priming endometrial receptivity. Indeed, when LPS is tested in regular ART, it is difficult to single out the respective effects of endogenously produced or exogenously administered progesterone. On the contrary, in mock DE-ART cycles, the effects observed – assessed on endometrial biopsies – solely result from the tested product.
A daily subcutaneous administration of either 25 mg or 50 mg for 11 consecutive days of **Prolutex®** was tested in 25 healthy female volunteers of childbearing age whose endogenous ovarian production of progesterone was blocked by a long acting preparation of GnRH-agonist protocol.
None of the subjects were exposed to endogenous progesterone prior to starting progesterone SC administration, as evidenced by serum levels <1.5 ng/mL.

The SC administration of **Prolutex®** in estrogen-primed ovarian-suppressed women induced the predecidual transformation of the endometrium in 100% of the 22/24 evaluable endometrium specimens. This was evidenced on endometrial biopsies performed on the 11th day of exposure to this water-soluble progesterone. There were no differences between the 2 doses tested, 25 and 50 mg/day despite different nadir plasma progesterone levels, as reported elsewhere.
These findings indicate that this water-soluble progesterone preparation available for SC administration is a valid therapeutic option for luteal-phase support in ART (Figure 5).

More recently, a spontaneous study[30] was conducted in 24 egg donors to compare the efficacy of **Prolutex®** 25 mg/day vs Intramuscular P 50 mg/day to induce an appropriate endometrial transformations after COS antagonists protocol, with GnRH agonists triggering. Using histological and deeper transcriptomic endometrial evaluation in 23 specimens, the authors proved the effectiveness of 25 mg/day of **Prolutex®** SC in LPS and suggest the use of the product in regular IVF cycles to improve the wellness of patients.

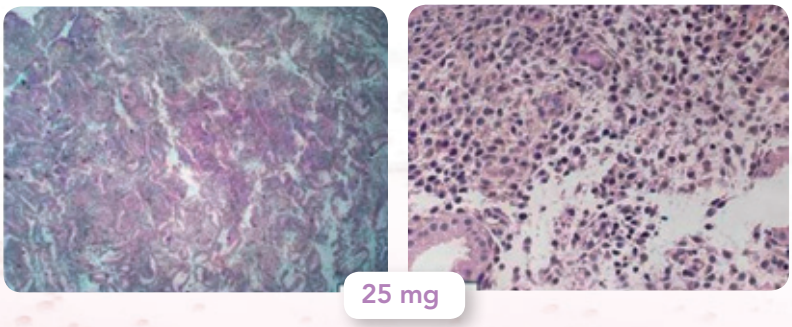

Figure 5. (Adapted from De Ziegler)[10] Endometrial changes observed on the 11th day of exposure to progesterone at the dose of 25 mg/day administered SC

EU phase III trial: Prolutex® SC vs. Crinone® vaginal gel

DESIGN AND SETTING

A randomised, open, multicentre, controlled phase III clinical trial[8] tested the safety and efficacy of **Prolutex®** in 13 European IVF centres in comparison to the progesterone vaginal gel Crinone®, used as reference preparation:

Product	Dosage	Method	Duration
Prolutex®	25 mg/day	SC	10 weeks
Crinone® 8% gel	90 mg/day	vaginal	10 weeks

Eligible patients receiving controlled ovarian stimulation (COS) protocols in both agonist and antagonist protocols as determined by each institution (n=683) were randomised to receive either **Prolutex®**, 25 mg/day or Crinone® gel, 90 mg/day, for 10 weeks commencing the day of oocyte retrieval, provided that at least three oocytes had been obtained.

CONCLUSIONS

In spite of the significant difference in the dose administered (total dose over 10 weeks was 1750 mg. for Prolutex® vs. 6300 mg. for Crinone® gel, i.e. more than three times higher), the two regimens used for the LPS were statistically comparable in terms of ongoing pregnancy rate at 10 weeks (27.4% and 30.5% in the Prolutex® and Crinone® groups respectively, p-value=0.399).

Moreover, no statistically significant differences between the groups were reported for implantation rate (22.6±35.01 and 23.1±33.1 for Prolutex® and Crinone® gel respectively) thus proving the efficacy of the endometrial changes induced by the IBSA treatment.

Further, none of the secondary efficacy end-points (positive ß-hCG test rate; clinical pregnancy rate at 4-5 weeks of treatment; early spontaneous abortion) and pregnancy follow-up information such as delivery rate and live birth rate were found to be statistically different between the two groups. The safety and tolerability of **Prolutex®** were generally comparable to the Crinone® treatment.

US phase III trial:
Prolutex® SC vs. Endometrin® vaginal tablets

DESIGN AND SETTING

In a second pivotal randomised, multicentre phase III clinical trial[9] conducted in 8 IVF centres across the USA, the safety and efficacy of luteal support sustained by **Prolutex®** SC was compared to a vaginal tablet treatment as follows:

Product	Dosage	Method	Duration
Prolutex®	25 mg/day	SC	10 weeks
Endometrin® tablets	100 mg/ twice a day	vaginal	10 weeks

Eight hundred patients enrolled in a standard IVF were randomly assigned to take either **Prolutex®**, IBSA 25 mg/day or Endometrin® effervescent tablets, Ferring 200 mg/day (400 patients in each group): the daily treatment was continued through embryo transfer for a total of 15±2 days, at which time a serum pregnancy test was performed. In the event of a positive pregnancy test result and subsequent confirmation of ongoing pregnancy, patients continued their treatment for up to a further 8 weeks.

CONCLUSIONS

The primary endpoint of the study, the ongoing pregnancy rates at 10 weeks, was comparable between the two treatment groups (40.8% and 43.3% in Prolutex® and Endometrin® groups, respectively; p-value=0.42), thus confirming that the exposure of the patients to the 'physiological' dose of 25 mg/day of progesterone in contrast with the higher dose of 200 mg/day is sufficient to effectively support the early stages of pregnancy.

No statistically significant differences between the **Prolutex®** and Endometrin® groups were reported for any of the secondary efficacy end-points, including implantation rate, positive ß-hCG test rate, clinical pregnancy rate at 4-5 weeks of treatment, biochemical pregnancy rate and spontaneous abortions.
Pregnancy follow-up and baby status information showed no differences in terms of delivery rate, live birth rate and take-home baby rate.

The safety and tolerability of Prolutex® were generally comparable to Endometrin® treatment, thus confirming that the systemic administration of the new IBSA aqueous solution does not result in higher systemic adverse effects than the vaginal administration.

HIGHLIGHTS

- **Effective for inducing predecidual transformations in the endometrium even in total absence of endogenous P**[10]
- **As effective as IM P 50 mg daily to prepare endometrium to embryo implantation after COS antagonists cycles with GnRH agonists triggering**[30]
- **No statistically significative difference in PR rate after 10 weeks of LPS compared to vaginal treatments**[8,9]

Investigator-initiated study with Prolutex® combined with vaginal treatment in FET

DESIGN AND SETTING

A retrospective study[31] aimed at evaluating the efficacy of the combined administration of subcutaneous and vaginal progesterone for priming frozen blastocysts transfers, looking at progesterone levels and ART outcome. Three hundred and twenty frozen blastocyst transfer cycles were conducted in 213 women aged up to 42 years, BMI between 18 and 30 kg/m2, with anatomically normal uterus who underwent frozen embryo transfers with a combined luteal-phase support associating subcutaneous and vaginal progesterone. Patients with recurrent pregnancy loss (RPL) were excluded.

RESULTS

When using combined vaginal and subcutaneous LPS, serum progesterone level >10.50 ng/mL in 95% of cases, with a minimum value of 7.02 ng/mL. Clinical pregnancy rate (CPR), on-going pregnancy rate (OPR) and global miscarriage rates were 38.4%, 30.9%, and 19.5%, respectively. Analysing results per quartiles, revealed that miscarriage rates were significantly inferior, and IR were higher in the upper two quartiles of serum progesterone (>21.95 ng/mL) on the day before FET, while there was no difference in CPR and OPR.

CONCLUSIONS

The results indicate that the combined administration of subcutaneous and vaginal progesterone offers sufficient progesterone levels 1–2 days prior to frozen blastocyst transfer in 99% of cases. The present results therefore indicate that the combined subcutaneous (Prolutex® 25 mg/day) and vaginal (800 mg/day) progesterone is a valuable option for priming the transfer of vitrified blastocysts. In this respect, these findings parallel the claim made by Devine et al. (ref) that combined injectable IM and vaginal progesterone is effective for frozen blastocysts transfers. The present data also suggests an inverse correlation between plasma progesterone 1–2 days before FET and miscarriage rates.

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Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

Prolutex® 25 mg solution for injection
(Prolutex® is marketed in Italy under the name Pleyris®)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial (1.112 ml) contains 25 mg of progesterone (theoretical concentration 22.48 mg/ml).
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection.
Clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prolutex® 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 Prolutex® are restricted to women of child-bearing age, dosage recommendations for children and the elderly are not appropriate.
Prolutex® is given subcutaneously (25 mg) by the patient herself after instruction or intramuscularly (25 mg) by 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 Prolutex® in patients with impaired liver or renal function.

Paediatric population

The safety and efficacy of Prolutex® in children (0 to 18 years) has not been established.

There is no relevant use of Prolutex® 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 Prolutex® should be initiated under the supervision of a physician experienced in the treatment of fertility problems.
Prolutex® is intended for intramuscular or subcutaneous administration.

Intramuscular administration

Choose an appropriate area (femoral quadriceps of the right or left thigh). Swab proposed area, insert a deep injection (needle at an angle of 90°).The product should be injected slowly to minimise local tissue damage.

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.

4.3 Contraindications

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

- Hypersensitivity to progesterone or to any of the excipients
- 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

Prolutex® 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 Prolutex®, the patient and her partner should be assessed by a doctor for causes of infertility or pregnancy complications.

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 Prolutex® has not been assessed. Concomitant use with other drugs is not recommended.

4.6 Fertility, pregnancy and lactation

Fertility

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

Pregnancy

Prolutex® 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.

Breastfeeding

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

4.7 Effects on ability to drive and use machines

Prolutex® 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 Prolutex® 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 Prolutex® 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 Prolutex® 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 the national reporting system at https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

References

4.9 Overdose
High doses of progesterone may cause drowsiness.
Treatment of overdose consists of discontinuation of Prolutex® 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 Prolutex® 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 Prolutex® 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 Prolutex® 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 Prolutex®.
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

Rabbits were treated with 6.7 mg/kg/day of Prolutex® for up to 7 consecutive days by s.c. and i.m. injection. No relevant effect attributed to the treatment with Prolutex® by the s.c. route was seen at local, macroscopic and histopathological examination.

At local examinations, animals dosed with the vehicle and progesterone by the i.m. route for 7 days had slight local reaction such as haematoma or red induration of the muscle. A higher incidence of oedema was observed in animals dosed with Prolutex®. These signs were correlated with a local tissue necrosis and macrophage response at histopathological examination. Moderate fibrosis was associated with intramuscular administration of Prolutex® after the seven day post-treatment observation period. However, none of the histological changes observed were marked or extensive.

A longer term study was performed with administration of Prolutex® at 1 mg/kg/day s.c. or at 4 mg/kg/day i.m. No toxicologically important clinical signs were recorded and the minor signs observed were generally similar to those receiving vehicle. Histopathological examination of the injection sites after 28 days of treatment identified minor changes these were generally similar to those animals receiving vehicle. After the post-treatment observation period (14 days) there were no changes associated with injection of Prolutex®.

Other preclinical studies have not revealed other effects than those which can be explained based on the known hormone profile of progesterone. However, it should be borne in mind that sex steroids such as progesterone can promote the growth of certain hormone-dependent tissues and tumours.

The active substance progesterone shows an environmental risk for the aquatic environment especially to fish.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylbetadex,
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf-life

2 years
The medicinal product must be used immediately after first opening: any remaining solution must be discarded.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Colourless Type I glass vial fitted with a bromobutyl rubber stopper, and an aluminium seal and 'flip-off' cap. Each pack contains 1, 7 or 14 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and handling

The solution is for single use only.

A medical specialist must perform all i.m. injections.

The solution should not be administered if it contains particles or is discoloured.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

"25 mg solution for injection" 1 glass vial AIC 041348044
"25 mg solution for injection" 7 glass vials AIC 041348057
"25 mg solution for injection" 14 glass vials AIC 041348069

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

22/11/2013

10. DATE OF REVISION OF THE TEXT

11/2021

11. CONDITIONS OF PRESCRIPTION AND DISPENSING

Medicinal product subject to medical prescription to be renewed from time to time (RNR).

12. PACKAGING AND CLASSIFICATION FOR REFUNDABILITY

- "25 mg solution for injection" 7 glass vials - Class C, retail price € 42.90 *
- "25 mg solution for injection" 14 glass vials - Class C, retail price € 69.90 *

* Price effective from 01/01/2021

Code 7500001209

Full list of trade names:

Prolutex®
Progedex®
Inprosub®
Progiron®
Pleyris®
Lubion®

IBSA Institut Biochimique SA
Via del Piano 29, 6915 Lugano, Switzerland
www.ibsagroup.com

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

Prolutex® is marketed in Italy under the name Pleyris®
Pleyris 25 mg solution for injection:
7 glass vials - Retail price € 42.90; 14 glass vials - Retail price € 69.90
Class C, prescription to be renewed from time to time (RNR)