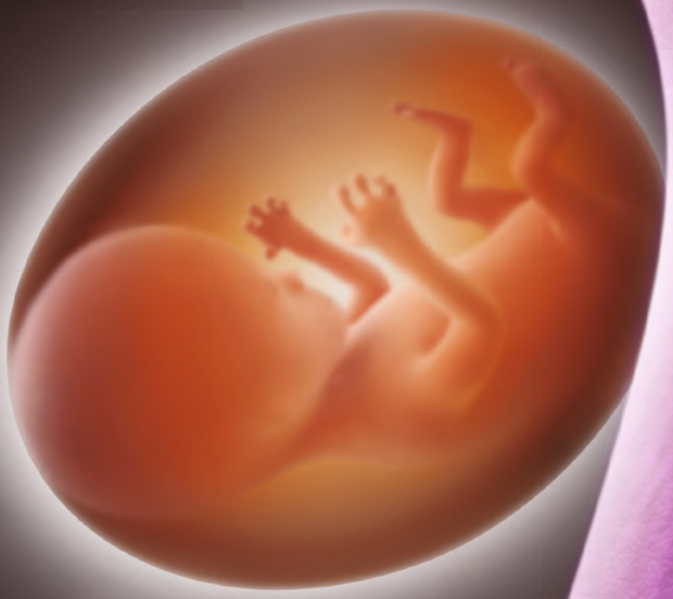
Prolutex® / Lubion™*

Aqueous solution of progesterone
for subcutaneous administration

The new choice for effective luteal support



IBSA

Evidence of life

Prolutex®

a new reliable tool for luteal phase support in ART, a novel choice for patients

Aqueous solution

for subcutaneous injection of natural progesterone (25 mg/day)

for effective luteal phase support

Innovation

IBSA's **aqueous solution** of natural progesterone and cyclodextrins avoids the potentially severe irritation and allergic response that may occur at the injection site associated with other parenteral progesterone injections [1,2].

Predictability & compliance

Self-administration, by convenient **subcutaneous injection**.
This promotes precise dosing and full absorption of the product, compared with vaginal presentations.

Natural model

25 mg/day corresponds to the physiological daily production of progesterone by the corpus luteum during the mid-luteal phase of the ovarian cycle.

Efficacy

The proven alternative to vaginal and intramuscular products for **luteal phase support**. Equally effective as vaginal progesterone[3,4] for priming the endometrium for implantation, even in the total absence of endogenous progesterone.

Innovation:

the first available aqueous solution of progesterone

Progesterone (P) is a steroid that is not water-soluble. Therefore, all injectable preparations to date have been prepared in oil-based solvents (usually peanut or sesame oil or ethyl oleate).
Because progesterone is an hydrophobic molecule, until now it has not been suitable for subcutaneous or even intravenous administration.

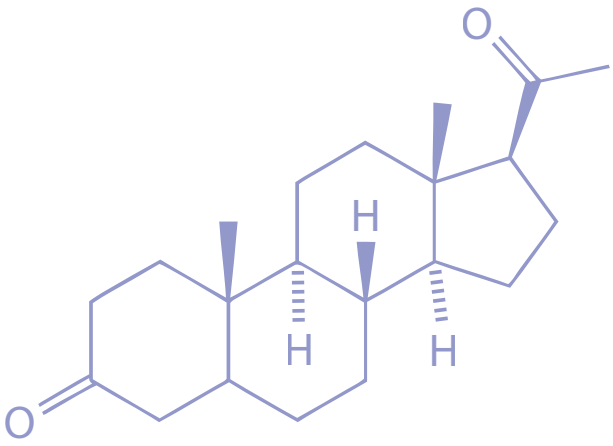


Figure 1:
the molecule of the natural progesterone

Thanks to IBSA's innovative, state-of-the-art technology, progesterone can now be delivered via an aqueous, subcutaneous injection, with the goal of improving local tolerability while maintaining consistent, predictable blood concentration and release/absorption capability.

The solubility of the new IBSA's progesterone is enhanced using cyclodextrins[5,6,7]. Cyclodextrins are starch residues with no therapeutic activity and with a particular molecular structure that closely resembles a 'cap'.

A representation of the IBSA's water-soluble complex made of progesterone and hydroxypropyl-ß-cyclodextrin (HPBCD) at a 1:2 molar ratio, is shown in figure 2:

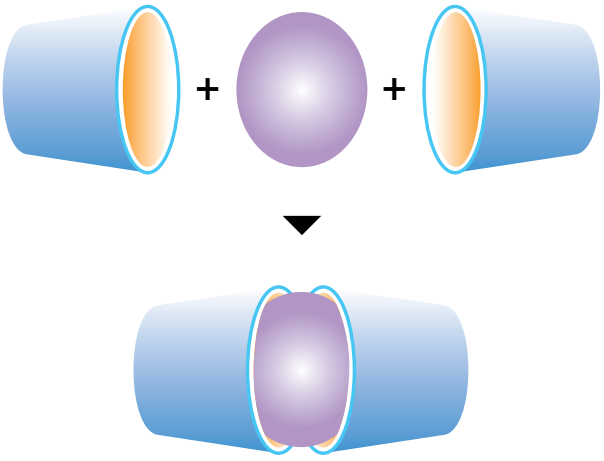


Figure 2:
mechanism of molecular association of the complex

Figure 3:
icon representing the new IBSA's water-soluble complex of progesterone and HPBCD.

Once absorbed after injection, the progesterone molecule is immediately dissociated from its cyclodextrin 'cap', remaining free in the circulation as if produced endogenously by the ovaries.

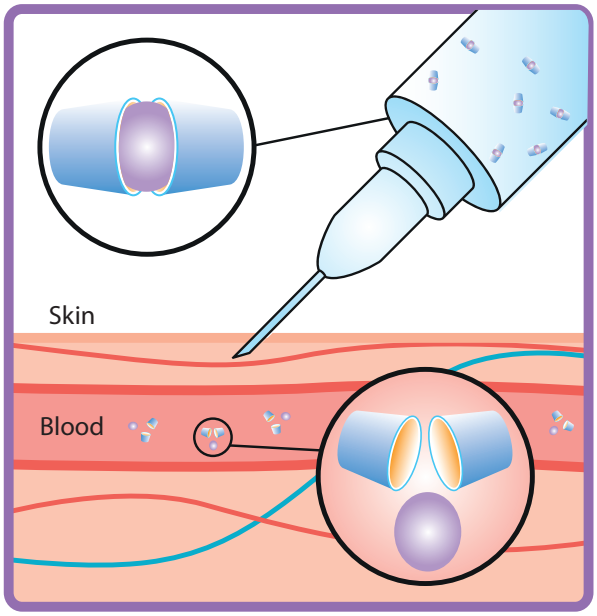


Figure 4:
separation of the molecules in the blood

Each vial of **Prolutex®** is formulated as follow:
- 25 mg of natural progesterone
- hydroxypropyl-ß-cyclodextrin (HPBCD)
- water for injection

IBSA's new aqueous solution of progesterone is free of other excipients. Specifically, it does not contain solvents and preservatives that are typically added to the progesterone-in-oil injectable preparations.

Consequently, side effects such as sterile abscesses and marked inflammation[1] at the injection site or severe hypersensitivity reactions[2] are avoided.

None of the severe side effects listed above were reported in the two currently available pivotal phase III clinical trials of Prolutex® [3,4] even after 10 weeks of daily subcutaneous treatment.

Highlight

- **novel ingenious system to deliver progesterone by the subcutaneous route**
- **natural progesterone complexed with cyclodextrins in aqueous solution**
- **no solvents and preservatives that may cause severe reactions or abscesses at the injection site**

Predictability & patient compliance: the benefits of s.c. injection

IBSA's aqueous progesterone preparation for s.c. injection is the first systemic progesterone of its kind for the provision of luteal phase support (LPS).

New therapeutic option for patients	To date, neither the vaginal nor the intramuscular route of administration of P 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[8,9,10] and, in the case of the progesterone gel, the tendency to form clumps[11] 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[1,2].
Convenient 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 appropriately 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.
Precise dosing	The total dose of P 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)[8,12,13,14] and on the possibility of unquantifiable losses due to discharge.
Single, daily, systemic administration	Despite the high doses usually administered (range from 90 mg/day up to 800 mg/day divided over two/three administrations), the vaginal route results in relatively low serum concentrations of P, but shows a preferential distribution to the uterus[15]. In comparison with systemic administration, higher doses of vaginal P would be necessary for duplicating the serum concentrations of progesterone typically encountered in the luteal phase of the menstrual cycle[16]. Moreover, certain effects of progesterone are mediated primarily outside of the pelvic cavity, for example the immomodulatory effect of progesterone on peripheral cell-mediated immunity[17]. No study exists to date to determine whether such effects – desired in pregnancy – are serum level-dependent and therefore may be dependent on the route of administration.

Highlight

- **First systemic P in aqueous solution**
- **Novel alternative treatment choice**
- **Full and predictable dose of P absorbed**
- **Patient-friendly daily self-administration**

Clinical data: pharmacokinetic comparison of a single-dose of Prolutex® s.c. vs. an oily solution i.m.

DESIGN AND SETTING:
In a comparative bioavailability study performed in 24 healthy post-menopausal female volunteers[18], a single dose of **Prolutex®** was administered either i.m. and s.c. and compared to a same dose of an oil-based progesterone preparation administered intramuscularly.

CONCLUSIONS:
As expected, the oil-based preparation caused more complaints of discomfort at the injection site.

In comparison to progesterone-in-oil preparation, IBSA's new aqueous solution administered by s.c. route resulted in a 3 fold higher and more rapid P peak serum concentrations, as shown in the below figure adapted from Zoppetti et al.[7]:

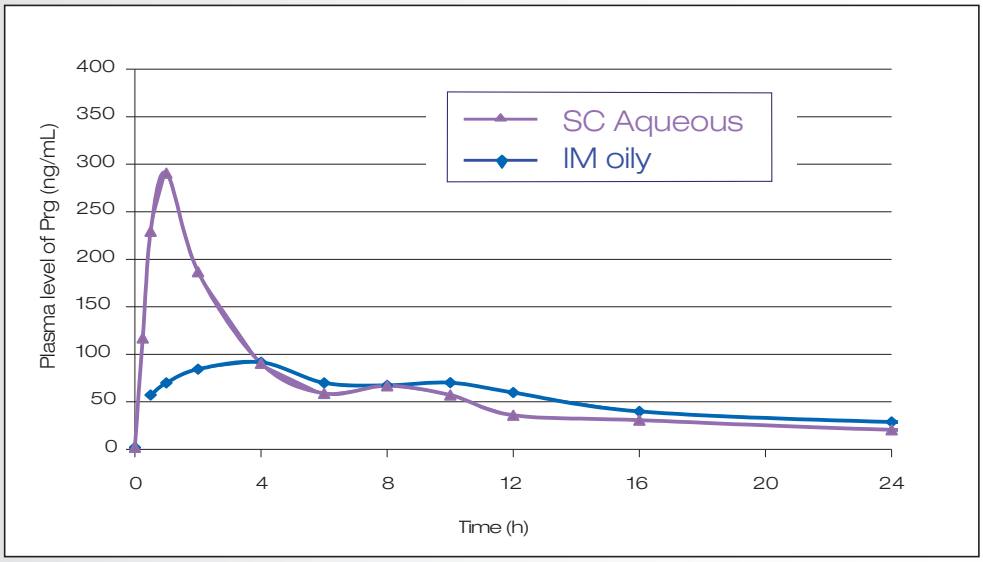


Figure 5: Plasma levels of progesterone after oily intramuscular and aqueous subcutaneous administration

In contrast, progesterone bioavailability (in terms of AUC_{0-t}) did not differ statistically between the two formulations.

Highlight

- **Improved local tolerability**
- **Easy self-administration**

The natural model:

25 mg/day

The natural progesterone

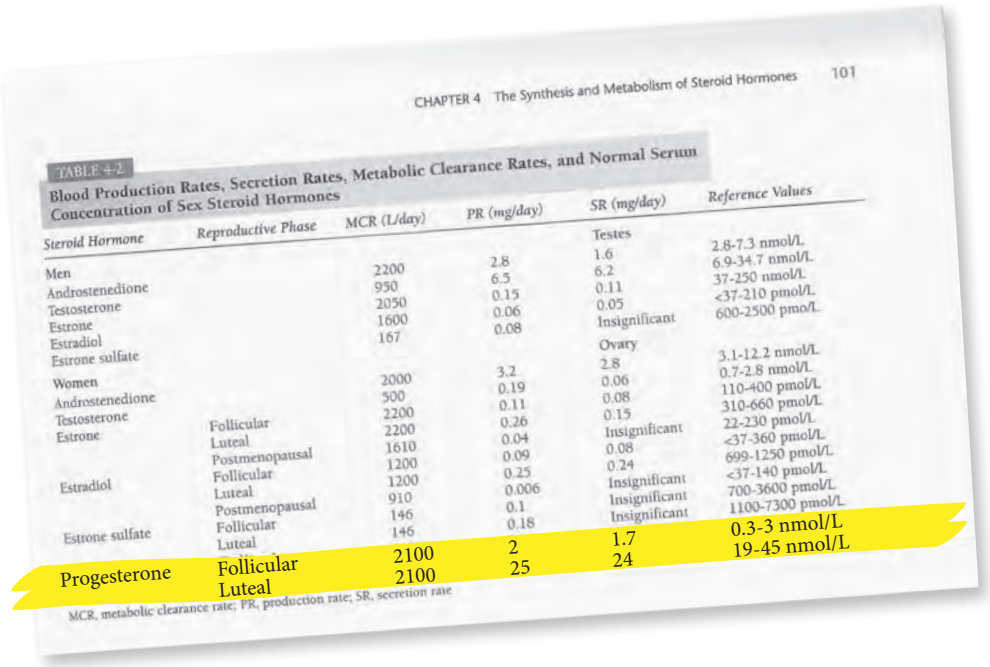
Progesterone is the primary 'pro-gestational' hormone in the human body. Progesterone primes endometrial receptivity[19] necessary for embryo implantation and is responsible for the state of utero quiescence[20] indispensable for allowing the development of pregnancy to term.

In the body, progesterone is formed from cholesterol primarily in the ovary (or testis), adrenals and placenta, but also in the central and peripheral nervous system of women and men[21]. In women, the primary contributor of the high serum progesterone levels encountered in the luteal phase is the evolving corpus luteum in the ovary. During pregnancy, the ovarian production of progesterone is rapidly replaced by the placental production of human placental lactogen, which takes over the role of progesterone in maintaining the pregnancy by the 7-11th week of pregnancy[22].

Other pro-gestational roles of progesterone are the contribution to suppressing the maternal immunological response to the fetal antigens allowing implantation and serving as substrate pool for fetal adrenal production of gluco- and mineral-corticoids[23].

Secretion profile of progesterone in ovulatory cycles

The daily production of progesterone in a physiological menstrual cycle ranges from a minimum of 2 mg/day during the follicular phase, as a result of the adrenal production[24], and culminates at approximately 25 mg/day in the mid-luteal phase due to active production by the corpus luteum (CL)[25].



CHAPTER 4 The Synthesis and Metabolism of Steroid Hormones 101

TABLE 4-2
Blood Production Rates, Secretion Rates, Metabolic Clearance Rates, and Normal Serum Concentration of Sex Steroid Hormones

Steroid Hormone	Reproductive Phase	MCR (L/day)	PR (mg/day)	SR (mg/day)	Reference Values
				Testes	
Men					
Androstenedione		2200	2.8	1.6	2.8-7.3 nmol/L
Testosterone		950	6.5	6.2	6.9-34.7 nmol/L
Estrone		2050	0.15	0.11	37-250 nmol/L
Estradiol		1600	0.06	0.05	<37-210 pmol/L
Estrone sulfate		167	0.08	Insignificant	600-2500 pmol/L
				Ovary	
Women					
Androstenedione		2000	3.2	2.8	3.1-12.2 nmol/L
Testosterone		500	0.19	0.06	0.7-2.8 nmol/L
Estrone	Follicular	2200	0.11	0.08	110-400 pmol/L
	Luteal	2200	0.26	0.15	310-660 pmol/L
	Postmenopausal	1610	0.04	Insignificant	22-230 pmol/L
Estradiol	Follicular	1200	0.09	0.08	<37-360 pmol/L
	Luteal	1200	0.25	0.24	699-1250 pmol/L
	Postmenopausal	910	0.006	Insignificant	<37-140 pmol/L
Estrone sulfate	Follicular	146	0.1	Insignificant	700-3600 pmol/L
	Luteal	146	0.18	Insignificant	1100-7300 pmol/L
Progesterone	Follicular	2100	2	1.7	0.3-3 nmol/L
	Luteal	2100	25	24	19-45 nmol/L

MCR, metabolic clearance rate; PR, production rate; SR, secretion rate

Figure 6 (adapted from Strauss[25]):
average daily production of progesterone by the CL during the mid-luteal phase of the menstrual cycle (25 mg/day)

Highlight

- **25 mg/day is the physiological peak of production of P by the CL during the mid-luteal phase of the cycle**

Following the natural model, the dose of 25 mg/day for the treatment of the luteal phase deficiency in ART and for donor eggs cycles with Prolutex® fits perfectly with the daily physiological production of the CL during the first stages of pregnancy.

Thereafter the progesterone production is taken over entirely by the placenta until delivery, when the production of progesterone approximates 250 mg/day[20].
Moreover, in a previous experiment[16], the authors confirmed that the intramuscular administration of 25 mg of natural progesterone was sufficient to obtain plasma levels corresponding to those encountered during a physiological luteal phase.

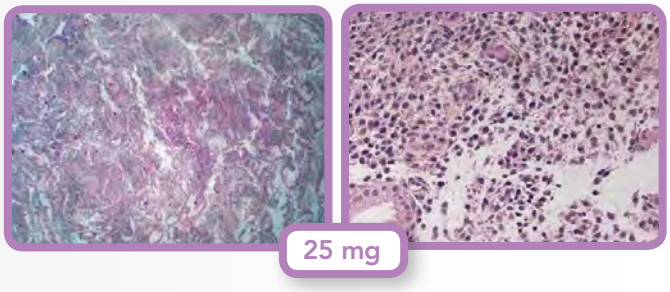
Clinical data: endometrial effects of Prolutex® 25 mg/day s.c. for 11 consecutive days

DESIGN AND SETTING:
In a recent clinical trial[18], the daily subcutaneously 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-a.

The achievement of the steady state (constant level) was already achieved after 4 days of both treatments (25 mg/day and 50 mg/day).
In these women, the administration of **Prolutex®** at the dose of 25 mg/day raised the daily circulating levels (range from 3.37±1.03 ng/ml to 53.08± 13.70 ng/ml as minimum and maximum concentration after daily dose) of progesterone within an adequate range to prime the endometrium (i.e. >5 ng/ml)[26].
These levels do not differ from the fluctuating levels of progesterone encountered in the mid-luteal phase of the menstrual cycle (range from 4.1 ng/ml to 40.1 ng/ml)[27] due to the pulsatile nature of the secretion by the corpus luteum in response to the pulsatility of LH[28].
In the same study, endometrial biopsies were taken at the end of the treatment period (11 days) in order to assess the presence of appropriate pre-decidual changes.

CONCLUSIONS:
Both the 25 mg/day and 50 mg/day treatments with the new aqueous progesterone preparation were equally effective at triggering the secretory transformation and pre-decidual changes of the endometrium on 100% of the assessable biopsies, in the total absence of endogenous progesterone[29].

Figure 7: Endometrial changes observed on the 11th day of exposure to progesterone at the dose of 25 mg/day administered s.c.



Highlight

- **The treatment with 25 mg/day of Prolutex® results in appropriate circulating P levels to achieve adequate priming of the endometrium and pre-decidual transformations**

Efficacy:

the alternative choice for luteal support in ART

Clinical data: safety and efficacy comparison of Prolutex® s.c. vs. Crinone® vaginal gel

DESIGN AND SETTING:
A randomised, open, multicentre, controlled phase III clinical trial[3] 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 randomized to receive either **Prolutex®**, IBSA 25 mg/day or Crinone® gel, Merck Serono 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 on-going 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.

In addition, none of the secondary efficacy endpoints (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 statistically different between the groups.

Although the route of administration of the two regimens was different (injections vs per vaginum insertion) there was no statistically significant difference between the two treatment groups regarding comfort of the preparation or overall satisfaction (p=0.859 and p=0.794, respectively).

The safety and tolerability of **Prolutex®** were generally comparable to Crinone® treatment.

Highlight

- **After 10 weeks of treatment, IBSA's subcutaneous progesterone and the vaginal gel Crinone® were statistically comparable in terms of on-going pregnancy rate, in spite of the considerable difference in the total dose administered**
- **Comparable implantation rate**
- **No difference in patient comfort despite the difference in the method of administration;**
- **Comparable safety and tolerability**

Clinical data: safety and efficacy comparison of Prolutex® s.c. vs. Endometrin® vaginal tablets

DESIGN AND SETTING:
In a second pivotal randomised, multicentre phase III clinical trial[4] conducted in 8 IVF centres across the USA, the safety and efficacy of lutael support sustained by **Prolutex®** s.c. 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 25mg/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 end-point 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.

Highlight

- **Prolutex® administered s.c. at the 'physiological' dose of 25 mg/day and Endometrin® tablets administered per vaginal route at the higher dose of 200 mg/day for 10 weeks were statistically comparable in terms of on-going pregnancy rate**
- **No difference in implantation, delivery, live birth and take-home baby rates**
- **Comparable safety and tolerability, in spite of the parenteral vs. local administration**

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