SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Prolutex solution for injection

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 the active substance 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

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	Injection site	Feeling hot,

administration site conditions	site reactions*	haematoma Injection site induration Fatigue	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.
Any suspected adverse events should be reported to the Ministry of Health according to the national regulation by using an online form https://sideeffects.health.gov.il/.

4.9 Overdose

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/dayof 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

The expiry date of the product is indicated on the packaging materials.

The medicinal product must be used immediately after 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

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

CTS Ltd.
4 Haharash St.
Hod-Hasharon
Israel

8 MARKETING AUTHORISATION NUMBER(S)

175-15-37196-99

Approved in 01/2024 by the MOH.