HEALTH PROFESSIONALS' USER LEAFLET

PROSTAP PD DCS leuprorelin acetate depot injection 1.88 mg

1. NAME OF THE MEDICINAL PRODUCT

PROSTAP PD DCS 1.88 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROSTAP Powder: Each pre-filled syringe 1.88 mg leuprorelin acetate (equivalent to 1.79 mg base).

After reconstitution each ml of suspension contains 1.88 mg leuprorelin acetate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection in pre-filled syringe.

Powder: A lyophilised, white powder in front chamber of the pre-filled syringe.
Solvent: A slightly viscous, odourless solvent in rear chamber of the pre-filled syringe.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of central precocious puberty (girls under 9 years of age, boys under 10 years of age with a body weight of less than 20 kg) (see section 5.1).

4.2 Posology and method of administration

Posology

The treatment of children with leuprorelin acetate should be under the overall supervision of the paediatric endocrinologist.

The dosing scheme needs to be adapted individually.

The recommended starting dose is dependent on the body weight.

Children with a body weight < 20 kg
In these rare cases, the following dosage should be administered according to the clinical activity of the central precocious puberty:

1 ml (1.88 mg leuprorelin acetate) is administered once a month as a single subcutaneous injection.

Children with a body weight ≥ 20 kg
Use a higher strength preparation (e.g. 3.75 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe administered once a month).

The child's weight gain should be monitored.

Depending on the activity of the central precocious puberty, it may be necessary to increase the dosage in the presence of inadequate suppression (clinical evidence e.g. spotting or inadequate gonadotropin suppression in the GnRH test). The minimal effective monthly dose to be administered should then be determined by means of the GnRH test.

Sterile abscesses at the injection site often occurred when leuprorelin acetate was administered intramuscularly at higher than the recommended dosages. Therefore, in such cases, the medicinal product should be administered subcutaneously (see section 4.4).

The duration of treatment depends on the clinical parameters at the start of treatment or during the course of treatment (final height prognosis, growth velocity, bone age and/or bone age acceleration) and is decided by the treating paediatrician together with the legal guardian and, if appropriate, the treated child. The bone age should be monitored during treatment at 6-12 month intervals.

In girls with bone maturation of older than 12 years and boys with bone maturation of older than 13 years discontinuation of treatment should be considered taking into account the clinical parameters.

In girls, pregnancy should be excluded before the start of treatment. The occurrence of pregnancy during treatment cannot be generally excluded. In such cases, medical advice should be sought.

Note:
The administration interval should be 30 ± 2 days in order to prevent the recurrence of precocious puberty symptoms.

Method of administration

Read this Instructions For Use before injecting.

This product should be prepared, reconstituted and administered only by healthcare professionals who are familiar with these procedures.

Warnings

Wash hands before opening the syringe package.

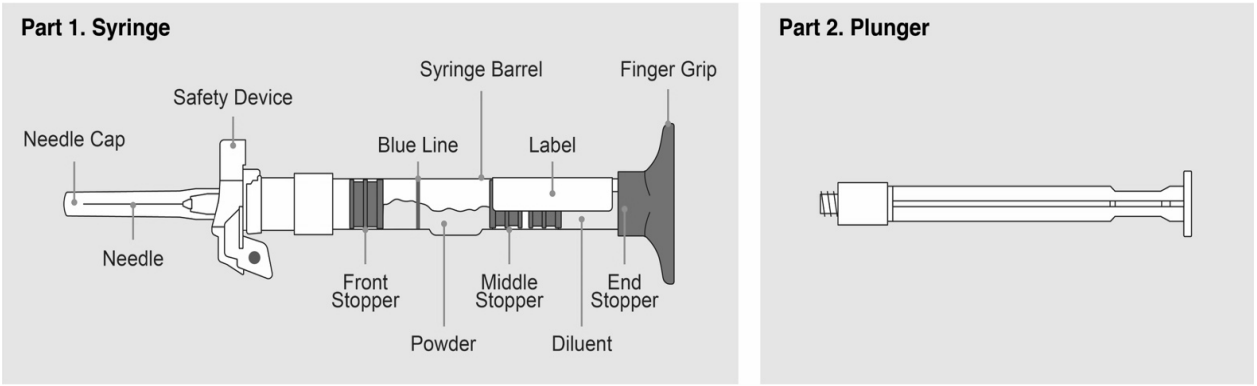
Hold syringe upright (with needle side up) throughout entire preparation to prevent leakage.

Use immediately after mixing as the suspension settles out very quickly following reconstitution.

Check the expiration date printed on the syringe label, and check the powder and diluent in the syringe barrel. The powder should be white and dry, and the diluent should be clear. Inspect the syringe for any damage.

- **Do not** use the syringe if the expiration date has passed.
- **Do not** use the syringe if the powder appears clumped or caked.
- **Do not** use the syringe if powder or diluent appear discoloured.
- **Do not** use the syringe if any part of it is damaged.

Parts Overview



Step 1. Attach plunger and tighten needle

- Remove the plunger (part 2) from the package.
- Screw the plunger rod into the bottom of the syringe until the end stopper begins to rotate. **(Figure A)**
  - **Do not** twist or pull the plunger rod back once it has been attached.

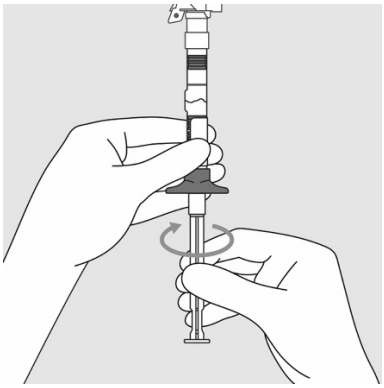


Figure A: Screw in plunger rod

- Without removing the needle cap, twist the needle to the right (clockwise) to ensure it is secured tightly. **(Figure B)**
  - **Do not** remove needle cap until you are ready to inject.

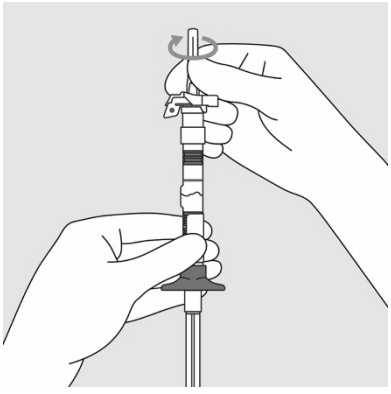


Figure B: Twist needle to tighten

Step 2. Release diluent

- Holding the syringe upright, release the diluents by **slowly** pushing the plunger until the middle stopper reaches the blue line in the middle of the syringe. You should see the diluent flowing into the interior chamber above the blue line. **(Figure C)**
  - **Do not** push the plunger too quickly or push past the blue line as these actions may cause leaking.
  - **Do not** withdraw plunger again.

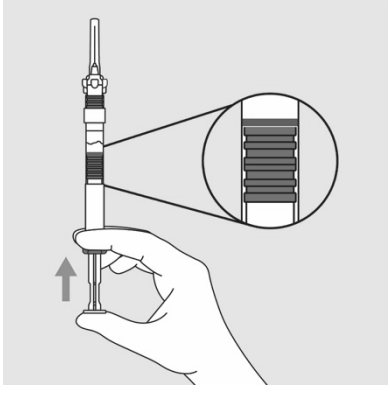


Figure C: Release diluent

Step 3. Mix suspension

- Gently tap the syringe against the palm of your hand to mix the powder and diluent until it forms a uniform suspension. When properly mixed, the suspension should appear milky with no visible lumps. **(Figure D)**
    - Note: If particles stick to the stopper during mixing, dislodge them by gently tapping the syringe with your finger.
- Avoid hard tapping or shaking to prevent the generation of bubbles.
- Use immediately after mixing as the suspension settles out very quickly following reconstitution.

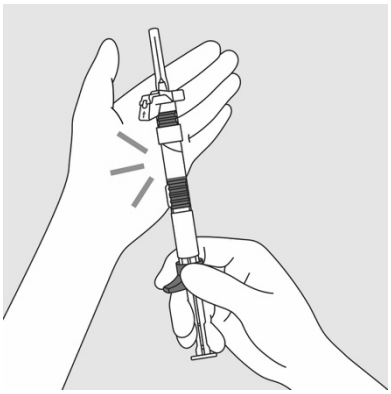


Figure D: Tap syringe against palm to mix

Step 4. Remove needle cap and prime syringe

- Remove the needle cap by pulling it straight upwards. **(Figure E)**
    - **Do not** twist the needle cap.
- Prime the syringe by pushing the plunger upward until all air has been expelled from the syringe.

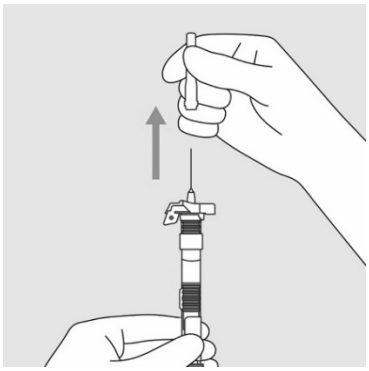


Figure E: Pull upwards to remove needle cap

Step 5. Inject

- The syringe is now ready for injection. Use immediately as the suspension settles out very quickly following reconstitution.
- At the time of injection, check the direction of the safety device (with round mark pointing towards you) and inject the entire contents of the syringe subcutaneously **(Figure F)** or intramuscularly **(Figure G)** as you would for a normal injection**.**

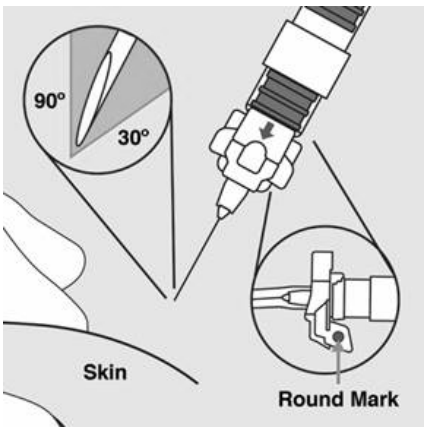


Figure F: Subcutaneous Injection. Ensure correct needle orientation

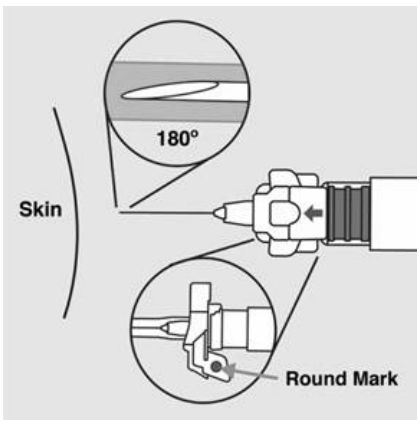


Figure G: Intramuscular Injection. Ensure correct needle orientation

Step 6. Activate safety device

- When injection is complete, withdraw the needle from the patient. Immediately activate the safety device by pressing upward from just below the arrow until a "CLICK" is heard or felt and the needle is fully covered. **(Figure H)**

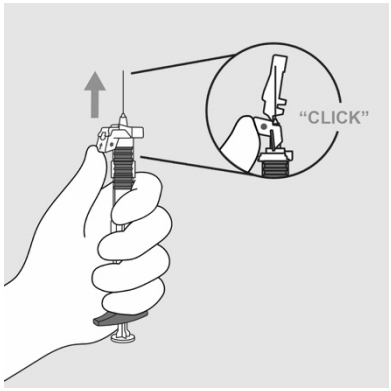


Figure H: Activate safety device

Step 7. Dispose of syringe

- Dispose of the used device in the appropriate sharps container in accordance with your local standard procedure.

4.3 Contraindications

Hypersensitivity to the active substance, any of the excipients listed in section 6.1 or to other synthetic gonadotrophin releasing hormone (GnRH) analogues or GnRH derivatives.

In girls:
Pregnancy and breastfeeding.
Undiagnosed vaginal bleeding.

4.4 Special warnings and precautions for use

PROSTAP PD DCSsuspension must be prepared at the time of use and, after reconstitution, used immediately (see section 4.2).

Depression
There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as leuprorelin acetate. Patients should be informed accordingly and treated as appropriate if symptoms occur.

Seizure
Postmarketing reports of seizures have been observed in patients treated with leuprorelin acetate. These events have been reported in those with or without a history of epilepsy, seizure disorders or risk disorders for seizures.

Idiopathic intracranial hypertension
Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in patients receiving leuprorelin. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, vision disturbances and tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of leuprorelin should be considered.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), and Toxic epidermal necrolysis (TEN) which can be life-threatening or fatal, have been reported in association with leuprorelin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. If signs and symptoms suggestive of these

reactions appear, leuprorelin should be withdrawn immediately and an alternative treatment considered (as appropriate).

Metabolic changes associated with GnRH agonist may also include fatty liver disease.

Before starting the therapy, a precise diagnosis of idiopathic and/or neurogenic central precocious puberty is nscessary and, in girls, pregnancy must be excluded (see section 4.3).

The therapy is a long-term treatment, adjusted individually. PROSTAP PD DCS should be administered as precisely as possible in regular monthly periods. An exceptional delay of the injection date for a few days (30 ± 2 days) does not influence the results of the therapy.

In the event of a sterile abscess at the injection site (mostly reported after i.m. injection of higher than the recommended dosage) the absorption of leuprorelin acetate from the depot can be decreased. In this case the hormonal parameters (testosterone, estradiol) should be monitored at 2-week intervals (see section 4.2).

The treatment of children with progressive brain tumours should follow a careful individual appraisal of the risks and benefits.

The occurrence of vaginal bleeding, spotting and discharge after the first injection may occur as a sign of hormone withdrawal in girls. Vaginal bleeding beyond the first/second month of treatment needs to be investigated.

Bone mineral density (BMD) may decrease during GnRHa therapy for central precocious puberty. However, after cessation of treatment subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected by treatment.

Slipped femoral epiphysis can be seen after withdrawal of GnRHa treatment. The suggested theory is that the low concentrations of estrogen during treatment with GnRH agonists weakens the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.

PROSTAP PD DCS contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per injection, that is to say it is essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
Safe use of leuprorelin acetate in pregnancy has not been established clinically.

Studies in animals have shown reproductive toxicity (see section 5.3). Before starting treatment with PROSTAP PD DCS, pregnancy must be excluded. There have been reports of foetal malformation when PROSTAP PD DCS has been given during pregnancy.

PROSTAP PD DCS must not be used in girls who are pregnant (see section 4.3).

When used monthly at the recommended dose, PROSTAP PD DCS usually inhibits ovulation and stops menstruation. Contraception is not ensured, however, by taking PROSTAP PD DCS and therefore patients should use non-hormonal methods of contraception during treatment and after cessation of treatment until the return of menses.

Patients should be advised that if they miss successive doses of PROSTAP PD DCS, breakthrough bleeding or ovulation may occur with the potential for conception. Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, the drug must be discontinued. The patient must be apprised of this evidence and the potential for an unknown risk to the foetus.

Breastfeeding
PROSTAP PD DCS must not be used in girls who are breastfeeding (see section 4.3).

4.7 Effects on ability to drive and use machines

Leuprorelin acetate can influence the ability to drive and use machines due to visual disturbances and dizziness.

4.8 Undesirable effects

Adverse reactions seen with leuprorelin acetate are due mainly to the specific pharmacological action, namely increases and decreases in certain hormone levels.

The following table lists adverse reactions with leuprorelin based on experience from clinical trials as well as from post-marketing experience. Adverse reactions are grouped by MedDRA System Organ Classes and frequency classification. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

In the initial phase of therapy, a short-term increase as flare-up of the sex hormone level occurs, followed by a decrease to values within the pre-pubertal range. Due to this pharmacological effect, adverse events may occur particularly at the beginning of treatment.

Tabulated list of adverse reactions in children

SOC	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders					Hypersensitivity (rash, pruritus, urticaria, wheezing, fever, chills and anaphylactic reactions)	
Psychiatric disorders		Depression (see Section 4.4), emotional lability				
Nervous system disorders		Headache			Pituitary apoplexy has been reported following initial administration in patients with pituitary adenoma, pituitary haemorrhage	Seizure, idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4)
Gastrointestinal disorders		Abdominal pain / abdominal cramps, nausea/vomiting				
Skin and subcutaneous tissue disorders		Acne				Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN) (see section 4.4), Toxic Skin Eruption, Erythema Multiforme

Musculoskeletal and connective tissue disorders			Myalgia			
Respiratory, thoracic and mediastinal disorders						Interstitial lung disease
Reproductive system and breast disorders		Vaginal haemorrhage, spotting**, vaginal discharge				
General disorders and administration site conditions		Injection site reactions (e.g. induration, erythema, pain, abscess, swelling, nodules and necrosis)				

** In general, the occurrence of vaginal spotting with continued treatment (subsequent to possible withdrawal bleeding in the first month of treatment), should be assessed as a sign of potential underdosage. Pituitary suppression should then be determined by gonadotropin releasing hormone (GnRH) stimulation test.

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 Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No case of overdose has been reported.

In animal studies, doses of up to 500 times the recommended human dose resulted in dyspnoea, decreased activity and local irritation at the injection site. In cases of overdose, the patients should be monitored closely and management should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophin Releasing Hormone Analogues, ATC code: L02AE 02.

PROSTAP PD DCS contains leuprorelin acetate, a synthetic nonapeptide analogue of naturally occurring GnRH which possesses greater potency than the natural hormone. Leuprorelin acetate is a peptide and therefore unrelated to the steroids. Chronic administration results in an inhibition of gonadotrophin production and subsequent suppression of ovarian and testicular steroid secretion. This effect is reversible on discontinuation of therapy.

Administration of leuprorelin acetate results in an initial increase in circulating levels of gonadotrophins which leads to a transient increase in gonadal steroid levels. Continued administration of leuprorelin acetate results in a decrease of gonadotrophin and sex steroid levels.

The drug is well absorbed from the subcutaneous or intramuscular route, binds to gonadotropin releasing hormone (GnRH) receptors and is rapidly degraded. In this dose form, an initial high level of leuprorelin acetate in the plasma is achieved within 3 hours followed by a drop over 24-48 hours to maintenance levels.

Leuprorelin acetate is inactive when given orally.

In children, reversible suppression of pituitary gonadotropin release occurs, with a subsequent decrease in estradiol (E2) or testosterone levels to values in the pre-pubertal range.

Initial gonadal stimulation (flare-up) may cause vaginal bleeding in girls who are already post-menarchal at start of treatment. Withdrawal bleeding may occur at the start of treatment. The bleeding normally stops as treatment continues.

The following therapeutic effects can be demonstrated:
- Suppression of basal and stimulated gonadotropin levels to pre-pubertal levels;
- Suppression of prematurely increased sexual hormone levels to pre-pubertal levels and arrest of premature menstruation;
- Arrest/involution of somatic pubertal development (Tanner stages);
- Improvement/normalisation of the ratio of chronological age to bone age;
- Prevention of progressive bone age acceleration;
- Decrease of growth velocity and its normalization;
- Increase in final height.

Treatment result is the suppression of the pathologically, prematurely activated hypothalamic-pituitary-gonadal axis according to pre-pubertal age.

In a long-term clinical trial in children treated with leuprorelin at doses up to 15 mg monthly for > 4 years resumption of pubertal progression were observed after cessation of treatment. Follow up of 20 female subjects to adulthood showed normal menstrual cycles in 80% and 12 pregnancies in 7 of the 20 subjects including multiple pregnancies for 4 subjects.

5.2 Pharmacokinetic properties

In a study with the 1.88 mg leuprorelin formulation administered subcutaneously (s.c.) in children with central precocious puberty, leuprorelin serum levels rose rapidly following the first injection declining gradually over the next 3 days, remaining in the range 0.02 to 0.03 ng/mL for 3 weeks and declining to 0.01 ng/mL at 4 weeks after administration.

During 4 weekly repeated treatment for 12 months, plasma leuprorelin concentrations before each dose and at 4 weeks after the 12th dose were 0.01 ± 0.02 ng/mL indicating sustained release of leuprorelin over the dosing interval and no accumulation.

Figure 1 presents leuprorelin serum levels after a single s.c. administration of leuprorelin acetate depot at a dosage of 30 µg/kg body weight. Peak serum levels are reached sixty minutes after administration (7.81 ± 3.59 ng/m)l. The AUC_{0-672} is 105.78 ± 52.40 ng x hr/ml.

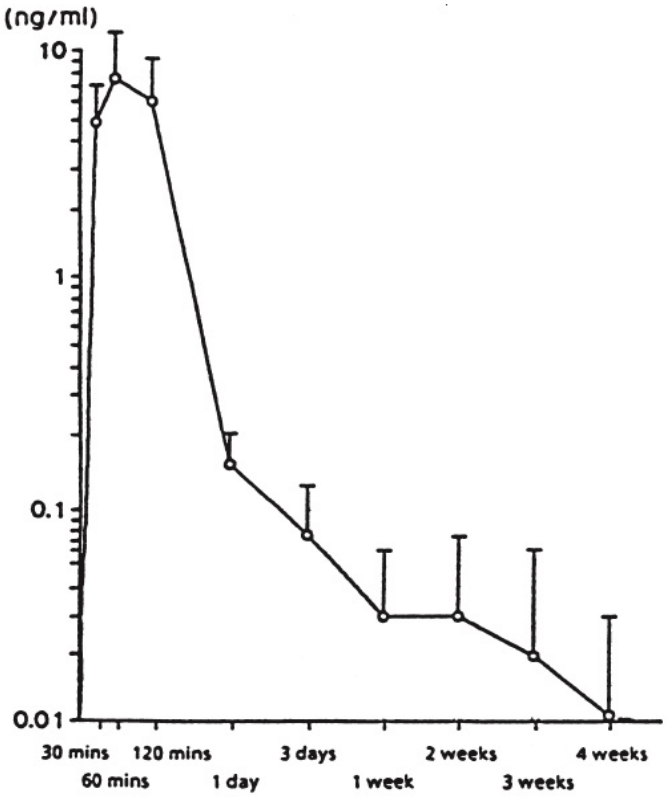


Figure 1: Leuprorelin serum levels after single s.c. administration of 30 µg/kg body weight of leuprorelin acetate as depot formulation (n=6) (Mean ± SD)

5.3 Preclinical safety data

Animal studies have shown that leuprorelin acetate has a high acute safety factor. No major overt toxicological problems have been seen during repeated administration. Whilst the development of pituitary adenomas has been noted in chronic toxicity studies at high doses in some animal species, this has not been observed in long-term clinical studies. No evidence of mutagenicity or teratogenicity has been shown. Animal reproductive studies showed increased foetal mortality and decreased foetal weights reflecting the pharmacological effects of this GnRH agonist.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Copolymer (DL-lactic acid/glycolic acid) (75:25 mol%)
Mannitol (E421)

Sterile solvent
Carmellose sodium
Mannitol (E421)
Polysorbate 80
Acetic acid, glacial
Water for Injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years unopened.

Once reconstituted with sterile solvent, the suspension should be administered immediately.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

One dual chamber pre-filled syringe containing 1.88 mg leuprorelin acetate powder in the front chamber and 1 ml of sterile solvent in the rear chamber.

1 x 25 gauge syringe needle fitted with safety device
1 x syringe plunger

6.6 Special precautions for disposal and other handling

Prepare the injectable suspension at the time of use and, after reconstituting, use immediately. Always ensure the safety device to prevent needle-stick injury is deployed after injection.

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

7. MARKETING AUTHORISATION HOLDER

Takeda UK Limited,
1 Kingdom Street
London
W2 6BD
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8. MARKETING AUTHORISATION NUMBER(S)

PL 16189/0038

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/2021

10. DATE OF REVISION OF THE TEXT

June 2024