Triptorelin acetate

Decapeptyl® CR

3.75 mg Controlled Release microcapsules
for reconstitution for S.C./I.M. injection

Formulation
One syringe contains injectable amount 3.75 mg triptorelin (D-Trp^6-LHRH) encapsulated in a biodegradable polymer, poly(DL-lactide-co-glycolide). One syringe suspension medium contains polysorbate 80, dextran 70, sodium chloride, sodium dihydrogen phosphate dihydrate, sodium hydroxide solution to adjust the pH, and water for injection 1 ml.

Indications
Triptorelin acetate (Decapeptyl® CR) is indicated in situations where lowering of sex steroid serum levels to castrate level is desired, such as prostate cancer, endometriosis or uterine myoma.

Treatment of confirmed central precocious puberty (preterm sexual development) (girls under 9 years, boys under 10 years of age).

Pharmacokinetics
After i.m. administration of Triptorelin acetate (Decapeptyl® CR), the plasma concentrations of triptorelin are determined by the (slow) degradation of the poly-(glycolic acid, lactic acid) polymer. The mechanism inherent to this administration form enables this slow release of triptorelin from the polymer.

After i.m. or s.c. application of Triptorelin acetate (Decapeptyl® CR) sustained-release microcapsules, a rapid increase in the concentration of triptorelin in plasma is recorded, with a maximum in the first hours. Then the triptorelin concentration declines notably within 24 hours. On day 4 the value reaches a second maximum, falling below detection limit in a biexponential course after 44 days. After s.c. injections the triptorelin increase is more gradual and in a somewhat lower concentration than after IM injections. After s.c. injection, the decline in the triptorelin concentration takes longer, with values falling below the detection limit after 65 days.

During treatment over a period of 6 months and an administration every 28 days, there was no evidence of triptorelin accumulation in both modes of administration. Plasma triptorelin values decreased to approx. 100 pg/ml before the next application after i.m. or s.c. application (median values). It is to be assumed that the non-systemically available proportion of triptorelin is metabolized at the injection site, e.g. by macrophages.

In the pituitary, the systemically available triptorelin is inactivated by N-terminal cleavage via pyroglutamyl-peptidase and a neutral endopeptidase. In the liver and the kidneys, triptorelin is degraded to biologically inactive peptides and amino acids. 40 minutes after the end of an infusion of 100 µg triptorelin (over 1 hour) 3-14% of the administered dose has already been eliminated by the kidney. For patients with an impaired renal function, adaptation and individualization of therapy with the triptorelin depot-formulation seems to be unnecessary, on account of the subordinate significance of the renal elimination route and the broad therapeutic range of triptorelin as an active component.

Bioavailability:
Men:
The systemic bioavailability of the active component triptorelin from the intramuscular depot is 38.3% in the first 13 days. Further release is linear at 0.92% of the dose per day on average. Bioavailability after S.C. application is 69% of i.m. availability.

Women:
After 27 test days, 35.7% of the applied dose can be detected on average, with 25.5% being released in the first 13 days and further release being linear at 0.73% of the dose per day on average.

General:
Calculation of the model-depending kinetic parameters (t½, Kel, etc.) is inapplicable in presentations with a strongly protracted release of the active component.

Pharmacology
Triptorelin, the active ingredient in Triptorelin acetate (Decapeptyl® CR) is a synthetic analogue of gonadorelin (GnRH). As a result of the substitution of the 6th amino acid residue in the native molecule, the agonistic effect is more pronounced and the plasma half-life prolonged.

Injection of Triptorelin acetate (Decapeptyl® CR) initially results in a stimulation of the pituitary release of LH and FSH. After prolonged stimulation the pituitary becomes refractory, the gonadotrophin release declines, resulting in a decrease of sex steroids to castrate levels. These effects are reversible.
After a single injection of Triptorelin acetate (Decapeptyl® CR) plasma levels remain at a therapeutic level for 30 days.

Dosage and Administration
One syringe of Triptorelin acetate (Decapeptyl® CR) is injected once every 28 days either subcutaneously (e.g. in the skin of the abdomen, the buttock or thigh) or intramuscularly. The injection site should be changed.

Men
Therapy of prostate carcinoma: It is important that the 4-week cycle be observed. As a diagnostic: It can be generally clarified after 3 months treatment whether the prostate cancer is androgen dependent or not. If so, administration can be continued.

Women
Uterine myoma and endometriosis:
In view of the possible effect on bone density, therapy should not exceed a 6-month period.

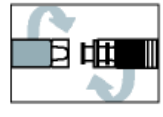
Children:
The dosage regime is based on body weight. Treatment is commenced with the appropriate dose administrated on days 0, 14, and 28. Thereafter, the same dose should be repeated every 4 weeks. Should the effect be insufficient, the dose may be repeated every 3 weeks. The doses are as follows:
Body weight less than 20 kg: 1.875mg triptorelin (1/2 dose)
Body weight from 20kg and 30 kg: 2.5mg triptorelin (2/3 dose)
Body weight greater than 30 kg: 3.75mg triptorelin (full dose).
Treatment should be stopped if a bone maturation of older than 12 years in girls and older than 13 years in boys has been achieved.

Directions for Reconstitution/Dilution
Instructions to the doctor on how to prepare Triptorelin acetate (Decapeptyl® CR) slow release microcapsules suspension
As successful treatment depends upon correct preparation of the suspension, the following instructions must be followed closely.

1. **Preparation**
   - Remove the Triptorelin acetate (Decapeptyl® CR) pack from the refrigerator.
   - Remove the cap from the disposable syringe containing the slow release microcapsules.
   - Open the package containing the connector but do not remove the connector.
   - Screw the syringe containing the slow release microcapsules into the connector in the package and then remove.
   - Screw the syringe with the suspension medium tightly into the free end of the connector and ensure that it is secure (1).

   Diagram 1 – Preparation

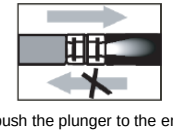
   Suspension medium

   Connector Controlled-release microcapsules

2. **Mix the Triptorelin acetate (Decapeptyl® CR) slow release microcapsules with the suspension medium**
   - Empty the syringe containing the suspension medium into the syringe containing the slow release microcapsules (2) and

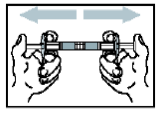
   Diagram 2 – Mixing

   then empty it back again. Do not push the plunger to the end the first two or three times.

- Direct the mixture carefully back and forth between the two syringes until a homogenous, milky suspension is obtained (3).

Diagram 3 - Mix approximately 10 times.



3. Injection
- Remove the connector together with the empty syringe.
- Mount the injection needle on the syringe with the ready to use suspension.
- Inject **immediately** either subcutaneously or intramuscularly.

Precautions and Special Warnings
Monitoring of the therapy should be performed by determining the sex steroid serum levels.

Men: The initial transient increase of serum testosterone has, in a few patients, been associated with a temporary aggravation of secondary symptoms of the disease, e.g. urinary obstruction, skeletal pain due to metastases, compression of the spinal cord, muscular fatigue and lymphatic oedema of the legs. The patient should be advised to consult the physician, if any of these symptoms aggravates. In the initial phase of therapy, supplementary administration of an appropriate antiandrogen agent should be considered as a means of diminishing the initial rise in testosterone and the deterioration in clinical symptoms.

Women: Potentially fertile women should be examined carefully before treatment to exclude pregnancy. Non hormonal methods of contraception should be employed during therapy and in case of endometriosis or myoma should be continued until menses are resumed. Women should not use preparations containing estrogens during the period of Triptorelin acetate (Decapeptyl® CR) therapy. During treatment of uterine myoma, uterus and myoma size should be measured regularly by means of, for example, ultrasonography. Unproportionally rapid reduction of uterus volume in comparison with that of myoma has, in a few cases, caused bleeding and sepsis. Since menses should stop during Triptorelin acetate (Decapeptyl® CR) treatment the patient should be instructed to notify her physician if regular menstruation persists.

Children: The chronological age at the beginning of therapy should be under 9 years in girls and under 10 years in boys. After completion of therapy, development of puberty characteristics will occur. Information with regards to future fertility is still limited. In most girls menses will start on average one year after ending the therapy, which in most cases is regular. Special forms of precocious puberty (Pseudo-precocious puberty and gonadotrophin-independent precocious puberty) should be precluded.

Allergic and anaphylactic reactions have been reported in adults and children. These include both local site reactions and systemic symptoms. The pathogenesis could not be elucidated. A higher reporting rate was seen in children.

Pregnancy and Lactation
In animal tests no teratogenic effects have been detected. In humans, there is insufficient experience. Therefore, pregnancy should be excluded prior to initiation of therapy. There are insufficient data relating to the use of Triptorelin acetate (Decapeptyl® CR) during lactation.

Contraindications
Men
- Hormone independent prostate carcinoma.
- Following surgical castration. Triptorelin acetate (Decapeptyl® CR) induces no further decrease in the testosterone level.

Women
- Clinically manifest osteoporosis or risk of osteoporosis (e.g. reduced bone density).
- Pregnancy.
- Lactation period.

Men and Women
- Known hypersensitivity reaction to triptorelin, poly (DL-lactide-co-glycolide), dextran or any other ingredients.

Children
- Progressive brain tumors.

Adverse Effects
The pharmacological side effects owing to the suppression of hormone production include *in men*: Hot flushes, impotence, loss of libido, and in rare cases gynaecomastia and testicular atrophy; *in women*: Hot flushes, bleeding or spotting, vaginal dryness and/or dyspareunia. As a consequence of the lowered estrogen levels, slight trabecular bone loss may occur. However, this is generally reversible within 6-9 months after treatment has been discontinued.

Other possible side effects include *in men*: Depressive mood, increased enzyme activity (LDH, γGT, SGOT, SGPT) and thrombophlebitis. One patient suffered a pulmonary embolism. *In women*: Depressive mood, loss of libido, sporadically elevated enzyme levels (LDH, γGT, SGOT, SGPT), slight rise in serum cholesterol, paraesthesia, and visual disturbances.

In men and women:
Hypersensitivity reactions (e.g. itching, skin rash, fever, anaphylaxis) may occur in individual cases. Hypersensitivity reactions have also been observed after the administration of dextran. In rare cases there may be temporary pain at the injection site.
In general, the side effects are mild and disappear after treatment has been stopped.

Children:
In children, occasionally bleedings and discharge, vomiting, nausea and anaphylaxis may occur.

Drug Interactions
No interactions with other drugs have been reported.

Shelf-Life
36 months.
Reconstituted solution must be applied immediately after preparation as per instructions.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription

Reg. No.: DR-XY26657

Availability
1 disposable syringe containing 172 mg slow release microcapsules +
1 disposable syringe containing 1 ml of suspension medium
3 disposable syringes containing 172 mg slow release microcapsules +
3 disposable syringes containing 1 ml of suspension medium

Storage
Triptorelin acetate (Decapeptyl® CR) has to be stored between 2-8 °C and transported only in a refrigeration chain.

Manufactured by:
Ferring GmbH
Wittland 11
D-24109 Kiel, Germany

Packed by:
Ferring International Center SA
Chemin de la Vergognausaz
1162 St-Prex, Switzerland

Imported and Distributed by:
Metro Drug, Inc.
Mañalac Avenue, Bagumbayan
Taguig City, Philippines