DECAPEPTYL CR 3.75 MG

SUMMARY OF PRODUCT CHARACTERISTICS

TRADE NAME AND PHARMACEUTICAL FORM

Decapeptyl CR 3.75 mg
Active Ingredient: Triptorelin Acetate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Indication group

D-Trp^{6}-GnRH, synthetic analogue of gonadorelin (GnRH) cytostatic agent and metastasis inhibitor.

Medically active components:

1 disposable syringe with 172 mg controlled-release microcapsules contains:
4.12 mg triptorelin acetate, corresponding to 3.75 mg triptorelin.

Other componenets:

1 disposable syringe with 172 mg controlled-release microcapsules contains:
156 mg poly (glycolic acid, lactic acid)1:1, propylene glycoloctanoat decanoat.
1 disposable syringe with 1 ml suspension contains:
polysorbate 80, dextran 70, sodium chloride solution, sodium dihydrogen phosphate-dihydrate, sodium hydroxide solution for pH stabilization, water for injection purposes.

CLINICAL PARTICULARS

Therapeutic Indications

Lowering sexual hormones, prostate cancer, endometriosis, uterus myomatosus, fertility treatment IVF, central precocious puberty.

Posology and Method of Administration

Doses with single and daily doses:
Decapeptyl CR 3.75 mg is injected once every 28 days.
For sustained suppression of testosterone levels, it is essential to keep administration to the four-weekly rhythm. After one single application, testosterone cannot be expected to rise beyond the castration level before the 40th day in cases of testosterone suppression.
As far as is known, it is not necessary to reduce the dose or to lengthen the dosing interval for patients with an impaired renal function.

Childeren:

At the beginning of treatment, one injection with one syringe, equivalent to 3.75 mg triptorelin, on days 0,14, 28. Thereafter one injection every 4 weeks. Should the effect be insufficient, the injections may be given every 3 weeks. Dosing should be based on body weight. Children weighing less than 20 kg are injected with 1.875 mg (half dose), children between 20 and 30 kg receive 2.5 mg (2/3dose), and children weighing more than 30 kg are injected with 3.75 mg (full dose).

Form and duration of application

Decapeptyl CR 3.75 mg is injected either subcutaneously e.g. into the abdominal skin, the buttocks or the thigh or deep into the muscle. The injection site must be constantly changed.
As an alternative to starting therapy with Decapeptyl CR 3.75 mg, therapy can also be started with Decapeptyl 0.5 mg injection solution for subcutaneous application once a day (non-depot triptorelin) for 7 days.
Decapeptyl CR 3.75 mg is then applied on the eighth day of therapy.
As a rule, treatment of the hormone-dependent prostate carcinoma with Decapeptyl CR 3.75 mg is a long-term therapy. The therapeutic success (remission, stabilization of symptoms) should be verified by regular clinical examination (sonography, radiology, skeletal scintiscanning) and by controlling the prostate-specific antigen (PSA) and serum testosterone. Treatment with Decapeptyl CR 3.75 mg should be continued as long as there is any evidence of hormone-dependence of the illness.
When the preparation is used for diagnostic purposes, it normally takes about 3 months to clarify whether the advance prostate carcinoma is sensitive to androgen. The primary diagnostic parameter is the serum concentration of the prostate-specific antigen (PSA), which is normally above 10 ng/ml when a tumor is at an advanced stage. Testing is done to examine the response of the PSA value after androgen withdrawal induced by Decapeptyl CR 3.75 mg. For this reason, both the PSA and the total testosterone content in the serum must be determined at the start and after 3 months of Decapeptyl application. The test result is deemed to be positive if the testosterone level is at castration level (< ng/ml) after 3 months and the PSA value has fallen. Hormone-ablative therapy (e.g. Decapeptyl CR 3.75 mg) is then indicated. The test result is deemed to be negative if the PSA value remains unchanged or has risen with suppressed testosterone. In this case, continuation of the hormone-ablative therapy is unsuitable. If, however, the patient has responded clinically (e.g. improvement in pain symptoms and in dysuric complaints, reduction in size of the prostate) the possibility of a false-negative result must be considered. In these rare cases, Decapeptyl CR 3.75 mg administration should be continued for another 3 months and the PSA value should then be checked once again. The patient should moreover be closely monitored with respect to the clinical symptoms.

Central precocious puberty (CPP):

Tretment should be stopped if a bone maturation of older than 12 years in girls and older than 13 years in boys has been achieved.

Instructions for production of the Decapeptyl CR 3.75 mg controlled-release microcapsule suspension

As production of the suspension as per instructions is an indispensable precondition for therapeutic success, the following instructions should be strictly observed.

1. <u>Preparation</u>:

- Take the pack of Decapeptyl CR 3.75 mg from the refrigerator.
- Remove the cap from the disposable syringe containing the controlled-release microcapsules.
- Open the pack with the connector without removing the connector.
- Screw the syringe containing the controlled-release microcapsules onto the connector provided in the pack and remove it.
- Screw the syringe containing the suspension agent firmly to the free end of the connector and check that it fits tightly.

Connector
Controlled-Release microcapsules
Suspension agent

2.<u>Forming a suspension with the Decapeptyl CR 3.75 mg controlled-release microcapsules:</u>

- Force the suspension from the one syringe into the syringe with the controlled-release microcapsules and then force the compound back again. Do not execute the first two or three movements as far as the limit stop.
- The compound must be moved carefully to and fro between the two syringes until a homogenous, milky suspension has been produced.

Mixing process

Mix 10 times.

3. <u>Injection:</u>

- Remove the connector together with the empty syringe.
- Mount the injection needle on the syringe with the ready-to-use suspension.
- Inject subcutaneously or deep into the muscle immediately (within 3 minutes of mixing).

Contra-indications

Treatment with Decapeptyl CR 3.75 mg is not indicated with proven hormone-independence of the carcinoma. Following surgical castration, Decapeptyl CR induces no further fall in the testosterone level.
Known hypersensitivity to triptorelin, poly(glycolic acid, lactic acid), dextran or any other component.
In children: Progressive brain tumors.

Special Warnings and Special Precautions for Use

Prostatic carcinoma patients with impending spinal cord compression or severe urinary tract disorders.
Premenstrual syndrome (exacerbation of symptoms)
Renal insufficiency (data for triptorelin are lacking; however, a significant prolongation of the half-life of another luteinizing hormone, goserelin, has been reported. The clinical significance of this finding is unclear).
Bone loss has been reported in some studies during long-term triptorelin therapy in women with endometriosis or uterine leiomyoma.
Paralysis arising from a transient activation of the tumour and its metastases.
In hypertensive patients, blood pressure must be monitored regularly (risk of increase in blood pressure).
In diabetic patients, blood sugar levels must be checked regularly (risk of deterioration of metabolic control)
Patients with a history of depression must be monitored carefully and if necessary, treated (risk of recurrence or worsening of depression).
Certain adverse effects (e.g. dizziness) may impair the ability to concentrate and react, and therefore, constitute a risk in situations where these abilities are of particular importance (e.g. operating a vehicle or machinery).

Children :

The chronological age at the beginning of therapy should be under 9 years in girls and under 10 years in boys.
After finalising the therapy, development of puberty characteristics will occur. Information with regard to future fertility is still limited. In most girls menses will start on average 1 year after ending the therapy, which in most cases is regular.
Pseudo-precocious puberty (gonadal or adrenal tumour or hyperplasia)
And gonadotropin-independent precocious puberty (testicular toxicosis, familial Leydig cell hyperplasia) 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.

Interactions

There are no known interactions with other drugs. Interference of calcium antagonists with the mechanism of action underlying GnRH and GnRH analogues is theoretically conceivable. Initial test results with Decapeptyl CR 3.75 mg on the long-term suppresibility of serum testosterone during simultaneous therapy with calcium antagonists have, however, provided no evidence of such an interaction.

Pregnancy and Lactation

Situations where maintenance of endogenous sex hormone activity is essential.

Undesirable Effects

Initially, there is a regular short-term rise in serum testosterone, resulting in temporary intensification of certain symptoms (occurrence of or increase in bone pain, obstruction of the urinary tract and its sequelae, contusion of the spinal cord, muscular weakness in the legs, lymphatic oedema). In these cases, patients must be closely monitored in the first month of therapy and given symptomatic treatment if necessary.
For the initial phase of therapy, supplementary administration of an appropriate antiandrogenic agent, should be considered as a means of diminishing the initial rise in testosterone and the deterioration in clinical symptoms.
Androgen withdrawal frequently results in hot flushes with profuse sweating and with loss of libido and potency. In less frequent cases, gynaecomastia, testicular atrophy and sleeplessness have been reported.
Sporadic reports have been received of Decapeptyl CR 3.75 mg leading to changes in weight (increase and decrease), loss of appetite, headaches, depressive moods, elevated enzyme levels (LDH, GT, SGOT, SGPT) and thrombophlebitis. One patient suffered a pulmonary embolism.
As with other peptides, hypersensitivity reactions (e.g. itching, skin rash, high temperature, anaphylaxis) may occur in individual cases. Hypersensitivity reactions have also been observed after the administration of dextran.
In rare cases, temporary pain may occur at the injection site.

Endocrine effects

Hot flushes, breakthrough bleeding, vaginal dryness and reduced libido.

Central Nervous System Effects

Headache, sleep disturbances, tiredness, emotional lability, tremors, dizziness and nausea.

Genitourinary

Ovarian Cysts
Ovarian cysts have been reported as a result of triptorelin administration during in vitro fertilization protocols. However, they do not interfere with induction of ovulation or achievement of pregnancy, and programs should not be cancelled because of their occurence.

Sepsis

Anaerobic and gram-negative sepsis related to expulsion of necrotic myomas into the cervical canal has been reported during triptorelin therapy of uterine lelomyomas. It is speculated that shrinkage of normal uterine tissue may exceed that of necrotic myomatous tissue in some patients, resulting in myoma nascence and subsequent sepsis. Examination and localization of uterine fibroids via hysteroscopy and/or ultrasonography is suggested, with dose patient monitoring, to minimize the risk of necrotic myoma expulsion in patients treated with triptorelin.

Children:

Uncommon Adverse Reactions (1/100-1/1000) seen are -
Endocrine: Vaginal bleeding and discharge.
Gastrointestinal: Vomiting, nausea.
General: Anaphylaxis.

Overdose

Due to the broad therapeutic scope of the active ingredient triptorelin, overdosage and intoxication are not to be expected.
A specific antidote against Decapeptyl CR 3.75 mg is not known.

PHARMACOLOGICAL PROPERTIES

Pharmacological characteristics

Decapeptyl CR 3.75 mg blocks the hypothalamic-pituitary-gonadal axis.
Following initial short-term stimulation of the gonadotrophins, Decapeptyl CR induces desensitisation of the gonadotrophic partial function of the pituitary gland and thus suppression of LH and FSH, with consequent inhibition of testicular androgen secretion. Suppression of serum testosterone to castration level inhibits growth of the hormone-dependent prostate carcinoma.

Toxicological characteristics

Acute toxicity

The acute toxicity of triptorelin can be classified as very low. With intraperitoneal application, the LDso of triptorelin in the rat is between 90 and 100 mg/kg body weight and in the mouse is between 160 and 200 mg/kg body weight. In comparison, the mean therapeutic dose of 0.00125 mg/kg body weight per day can be regarded as non-toxic.

Chronic toxicity

Studies on chronic toxicity have been carried out on rats, dogs and apes over a 6 month administration period.
In rats, the 6 month treatment period (daily s.c. injections of 2-200 µg/kg) was followed by a 2 month reversibility phase, during which time the liver, kidneys, thymus, suprarenal glands and ovaries regained their normal weight, with slight weight deficits being observed in the heart and testicles. Testicular atrophy was dose-dependent and was accompanied by hyperplasia of the interstitial tissue. The changes occuring at the ovaries were almost all renormalised after 2 months.
Beagle hounds (administration in controlled-release form, corresponding to a daily active component release of 0.2, 2.0 or 20 µg/kg body weight) displayed in particular no changes in the main biochemical parameters. Organic elements such as the liver, kidneys, heart, suprarenal glands, pituitary gland and brain remained normal in both sexes.
Pronounced, dose-dependent effects were recorded at the target organs, the gonads, with the weight of the testicles and ovaries declining with higher doses. The sexual hormones were suppressed. Morphological examination revealed testicular atrophy, inhibited spermatogenesis and hyperplasia of the interstitial tissue or ovarian atrophy and inhibited follicular maturity.
Apes were given daily s.c. injections of 2.20 or 200 µg/kg over a 6 month period. Haematological examination revealed no changes, while biochemistry revealed an elevated cholesterol level. The testosterone level underwent a dose-dependent fall in the males.
In the females, the lack of FSH and LH suppressed the development of the follicles and the corpus luteum. After discontinuation of treatment, the follicle formation was rapidly reversible, but regeneration of the corpus leteum was delayed.
None of the tests produced any findings which might make human application inadvisable.

Mutagenicity

In none of the used test systems for gene and chromosome mutations was there any indication of mutagenic effects due to triptorelin.

Local tolerance

Local tolerance was tested in rabbits after one intramuscular, subcutaneous and intravenous administration. Intramuscular application resulted in histological changes, as are known from other parenteral depot formulations with degradable polymers. No local intolerance reactions were recorded after subcutaneous application, whereas intravenous administration (not a scheduled method of application) induced temporary intolerance reactions.

Pharmacokinetics

Pharmacokinetic tests on prostate carcinoma patients and healthy probands have shown that an i.m. injection of Decapeptyl CR 3.75 mg includes a maximum concentration of the active component in the blood after ca. 60 min. followed by a biexponential fall in concentrations until 24 hours. The value then rises on day 4 to a second maximum, declining in a biexponential course to below the detection limit after 44 days. The rise is more gradual and in a somewhat lower concentration after s.c. than after i.m. injection, the decline in concentration takes longer, with values falling below the detection limit after 65 days. Computation of model dependent kinetic parameters ($t_{1/2}$, K_{ei}, etc.) is inapplicable for presentations with a strongly protracted release of the active component. Repeated injections at 28 day intervals led to no significant accumulation in either of the modes of administration. Plasma triptorelin values had fallen to ca. 85 pg/ml before the next application after i.m. and to ca 100 pg/ml after s.c. application. < 4% of the active components is excreted unchanged with the urine.
Among prostate carcinoma patients with age-induced impairment of the renal function, total clearance of Decapeptyl CR 3.75 mg was ca. 27% below that of young probands and was subject to greater scatter. Adaptation and individualisation of therapy with Decapeptyl CR 3.75 mg seems to be unnecessary for patients with an impaired renal function on account of the subordinate significance of the renal elimination route and the broad therapeutic range of triptorelin as an active component.

Bioavailability

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.

PHARMACEUTICAL PARTICULARS

Shelf Life

Controlled release microcapsules: 3 years

Suspension agent: 3 years

Ready for use controlled release microcapsule suspension: 3 minutes - must be applied immediately after preparation as per instructions.

Storage Conditions

Between +2°C and 8°C

Nature and Contents of Container

1 disposable syringe with 172 mg controlled-release microcapsules and
1 dosposable syringe with 1 ml suspension agent N1
3 disposable syringes, each with 172 mg controlled-release microcapsules and
3 disposable syringes, each with 1 ml suspension agent N3.

License No.

105 92 28885 00

Manufacturer

Ferring GmbH, Germany

Importer

A. Lapidot Pharmaceuticals Ltd., 8 Hashita Street, Industrial Park, Caesarea.

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in November 2005.

2009050515

Euker druck

Created: **22.05.2007**

Article:	**Decapeptyl**	
Country:	**IL**	Mat-Nr.: **2009050515**
Size:	**340 x 230 mm**	Type size: **8 pt**
Colours:	**black**	
Customer:	**Ferring**	Order-Nr.: **415448**
1. Correction	☐ **druckreif**	☐ **neuer Abzug**