1. NAME OF THE MEDICINAL PRODUCT

DECAPEPTYL® CR FOR INJECTION 3.75mg/syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 3.75 mg triptorelin (as acetate) to be suspended in one ml sodium containing suspension agent.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection. Prolonged release in pre-filled syringes.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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, or assisted reproduction techniques, e.g. IVF.

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

4.2 Posology and method of administration

Men

Once every four weeks an injection with one syringe, equivalent to 3.75 mg triptorelin.
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

Once every four weeks an injection with one syringe, equivalent to 3.75 mg triptorelin.
In view of the possible effect on bone density, therapy should not exceed a 6-month period.

Women - Assisted reproduction techniques (ART)

Single administration on cycle days 2 or 3 (follicular phase) or cycle day 22 (luteal phase).

Children – Precocious Puberty

Treatment starts with the injection of one syringe each, equivalent to 3.75 mg triptorelin, on days 0, 14, and 28. Thereafter one injection follows 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 receive 1.875 mg (half dose), children between 20 and 30 kg receive 2.5 mg (2/3 dose), and children with more than 30 kg body weight are given 3.75 mg 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.

General

In view of the possible effect on bone density, DECAPEPTYL® CR therapy without add-back therapy should not exceed a duration of 6 months (see section 4.4 Warnings and Precautions for use).

Special populations

Elderly

There is no need to adjust the dose for the elderly.

Patients with renal or hepatic impairment
According to current data, dose reduction or prolongation of the dosage interval in patients with impaired renal or hepatic function is not necessary (see section 5.2 Pharmacokinetic data).

Method of administration
The product should only be used under the supervision of an appropriate specialist having requisite facilities for regular monitoring of response.

It is important that the injection of the sustained release form be performed strictly in accordance with the instructions given in section 6.7 Instructions for Use}.

The dosage of one syringe, equivalent to 3.75 mg triptorelin, is injected either subcutaneously (e.g. into the skin of the abdomen, the buttock or thigh) or deep intramuscularly. The injection site should be changed each time.

4.3 Contraindications
General
- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to gonadotrophin-releasing hormone (GnRH) or any other GnRH analogue.

Women – ART, Uterine Myoma and Endometriosis
- Pregnancy or Lactation

4.4 Warnings and Precautions for use

General
The use of GnRH agonists may cause reduction in bone mineral density. In men, preliminary data suggest that the use of a bisphosphonates may effectively counteract GnRH agonist induced bone mineral loss. Particular caution is necessary in patients with additional major risk factors for osteoporosis (e.g. chronic alcohol abuse, smoking, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis or malnutrition).

Rarely, treatment with GnRH agonists may reveal the presence of a previously unknown gonadotroph cell pituitary adenoma. These patients may present with a pituitary apoplexy characterized by sudden headache, vomiting, visual impairment and ophthalmoplegia.

There is an increased risk of depression in patients undergoing treatment with GnRH agonists, such as triptorelin. Patients should be informed accordingly and treated as appropriate if symptoms occur.

Patients with known depression should be monitored closely during therapy.

Men – Prostate Cancer
Initially, triptorelin – like any other GnRH agonists – elicits a rapid and transient increase in serum testosterone levels. As a consequence, isolated cases of transient worsening of signs and symptoms of prostate cancer may occasionally develop during the first weeks of treatment. During the initial phase of therapy, consideration should be given to the additional administration of a suitable antiandrogen to counteract the initial rise in serum testosterone and the worsening of clinical symptoms.

A small percentage of patients may experience a temporary worsening of the signs and symptoms of their prostate cancer (tumour flare) and temporary increase in cancer related pain (metastatic pain), which can be managed symptomatically.

As with other GnRH agonists, isolated cases of spinal cord compression or urethral obstruction have been observed. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted, and in extreme cases an immediate orchiectomy (surgical castration) should be considered. Careful monitoring is indicated during the first weeks of treatment, particularly in patients suffering from vertebral metastasis, at the risk of spinal cord compression, and in patients with urinary tract obstruction.

After surgical castration, triptorelin does not induce any further decrease in serum testosterone levels.

Long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with accelerated bone loss, which may lead to osteoporosis and increased risk of bone fracture.

Androgen deprivation therapy may prolong the QT interval.
In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5 Interaction with Other Medicinal Products) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating DECAPEPTYL® CR.

In addition, from epidemiological data, it has been observed that patients may experience metabolic changes (e.g. glucose intolerance, fatty liver), or an increased risk of cardiovascular disease during androgen deprivation therapy. However, prospective data did not confirm the link between treatment with GnRH analogues and an increase in cardiovascular mortality. Patients at high risk for metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.

Administration of triptorelin in therapeutic doses results in suppression of the pituitary gonadal system. Normal function is usually restored after treatment is discontinued. Diagnostic tests of pituitary gonadal function conducted during treatment and after discontinuation of therapy with GnRH analogues may therefore be misleading.

<u>Women – ART, Uterine Myoma and Endometriosis</u>
It should be confirmed that the patient is not pregnant before prescription of triptorelin.

Loss of bone mineral density
The use of GnRH agonists is likely to cause reduction in bone mineral density averaging 1% per month during a six-month treatment period. Every 10% reduction in bone mineral density is linked with about a two to three times increased fracture risk. For this reason, treatment without add-back therapy should not exceed duration of 6 months. In the majority of women, currently available data suggest that recovery of bone loss occurs within 6 - 9 months after cessation of therapy.

No specific data is available for patients with established osteoporosis or with risk factors for osteoporosis (e.g. chronic alcohol abuse, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis, malnutrition, e.g. anorexia nervosa). Since reduction in bone mineral density is likely to be more detrimental in these patients, treatment with triptorelin should be considered on an individual basis and only be initiated if the benefits of treatment outweigh the risk following a very careful appraisal. Consideration should be given to additional measures in order to counteract loss of bone mineral density.

Women – Uterine Myoma and Endometriosis

Menstruation does not occur during treatment. A supervening metrorrhagia in the course of treatment is abnormal (apart from the first month) and should lead to verification of plasma estrogen level. Should this level be less than 50 pg/ml, possible associated organic lesions should be sought. After withdrawal of treatment, ovarian function resumes, e.g. menstrual bleeding will resume after 7-12 weeks after the final injection.

Non-hormonal contraception should be used during the initial month of treatment as ovulation may be triggered by the initial release of gonadotrophins. It should also be used from 4 weeks after the last injection until resumption of menstruation or until another contraceptive method has been established.

It is recommended that during treatment of uterine myomas, the size of the myoma is determined regularly. There have been a few reports of bleeding in patients with submucous myomas following GnRH analogue therapy. Typically the bleeding has occurred 6 - 10 weeks after the initiation of therapy.

Since menses should stop during DECAPEPTYL® CR treatment, the patient should be instructed to notify her physician if regular menstruation persists.

Women – ART

Assisted reproduction techniques are associated with an increased risk of multiple pregnancies, pregnancy loss, ectopic pregnancies and congenital malformations. These risks are also valid with usage of DECAPEPTYL® CR as adjunct therapy in controlled ovarian stimulation. The use of DECAPEPTYL® CR in controlled ovarian stimulation may increase the risk of ovarian hyperstimulation syndrome (OHSS) and ovarian cysts.

Follicular recruitment, induced by gonadotrophins following treatment with GnRH analogues, may be markedly increased in a minority of predisposed patients, particularly in case of Polycystic Ovarian Syndrome.

As with other GnRH analogues there have been reports of OHSS associated with the use of triptorelin in combination with gonadotrophins.

Ovarian Hyperstimulation Syndrome (OHSS)

OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS is a syndrome that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities. The following symptoms may be observed in severe cases of OHSS: abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Clinical evaluation may reveal hypovolaemia, haemoconcentration, electrolyte imbalances, ascites, haemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events. Excessive ovarian response to gonadotrophin treatment seldom gives rise to OHSS unless hCG is administered to trigger ovulation. Therefore, in cases of OHSS it is prudent to withhold hCG and advise the patient to refrain from coitus or to use barrier methods for at least 4 days. OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event, therefore patients should be followed for at least two weeks after the hCG administration.

OHSS may be more severe and more protracted if pregnancy occurs. Most often, OHSS occurs after hormonal treatment has been discontinued and reaches its maximum severity at about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. If severe OHSS

occurs, gonadotrophin treatment should be stopped if still ongoing, the patient hospitalised and specific therapy for OHSS started. This syndrome occurs with higher incidence in patients with polycystic ovarian disease. The risk of OHSS might be higher with use of GnRH agonists in combination with gonadotrophins than with use of gonadotrophins alone.

Ovarian cysts
Ovarian cysts may occur during the initial phase of treatment with GnRH agonist. They are usually asymptomatic and non-functional.

Special populations
Despite this prolonged exposure in patients with renal and hepatic impairment, triptorelin is not expected to be present in circulation at the time of embryo transfer (see section 5.2 Pharmacokinetic data).

Children – Precocious Puberty
The chronological age at the beginning of therapy should be under 9 years in girls and under 10 years in boys.

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

In girls initial ovarian stimulation at treatment initiation, followed by the treatment-induced oestrogen withdrawal, may lead, in the first month, to vaginal bleeding of mild or moderate intensity.

After finalizing the 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.

Bone mineral density 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 capital femoral epiphysis can be seen after withdrawal of GnRH agonist treatment. The suggested theory is that the low concentrations of estrogen during treatment with GnRH agonists weaken 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.

Pseudo-precocious puberty (gonadal or adrenal tumour or hyperplasia) and gonadotropin-independent precocious puberty (testicular toxicosis, familial Leydig cell hyperplasia) should be precluded.

Idiopathic intracranial hypertension
Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in paediatric patients receiving triptorelin. 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 triptorelin should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Men – Prostate Cancer
Since androgen deprivation treatment may prolong the QT interval, the concomitant use of DECAPEPTYL® CR with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade

de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4 Warnings and Precautions for use).

General
When triptorelin is co-administered with drugs affecting pituitary secretion of gonadotrophins caution should be given and it is recommended that the patient's hormonal status should be monitored.

No formal drug-drug interaction studies have been performed. The possibility of interactions with commonly used medicinal products, including histamine liberating products, cannot be excluded.

4.6 Fertility, Pregnancy and Lactation

Pregnancy
Prior to treatment, potentially fertile women should be examined carefully to exclude pregnancy. Triptorelin should not be used during pregnancy since concurrent use of GnRH agonists is associated with a theoretical risk of abortion or foetal abnormality. Very limited data on the use of triptorelin during pregnancy do not indicate an increased risk of congenital malformations. (5, 29) However, long-term follow-up studies on development are too limited. Animal data do not indicate direct or indirect harmful effects with respect to pregnancies or postnatal developments, but there are indications for delayed fetal development and parturition (see section 5.3 Preclinical Safety Information). Based on the pharmacological effects disadvantageous influence on the pregnancy and the offspring cannot be excluded and DECAPEPTYL® CR should not be used during pregnancy. Non-hormonal methods of contraception should be employed during therapy until menses resume. If a patient becomes pregnant while receiving triptorelin, therapy should be discontinued.

When triptorelin is used for infertility treatment, there is no clinical evidence to suggest a causal connection between triptorelin and any subsequent abnormalities of oocyte development or pregnancy outcome.

Lactation
It is not known whether triptorelin is excreted in human milk. Because of the potential for adverse reactions from triptorelin in nursing infants, breastfeeding should be discontinued prior to and throughout administration.

4.7 Effect on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, the ability to drive and use machines may be impaired if the patient experiences dizziness, somnolence and visual disturbances which could be possible undesirable effects of treatment or resulting from the underlying disease.

4.8 Undesirable Effects

General
Adverse experiences reported among patients treated with triptorelin during clinical trials and from post-marketing surveillance are shown below.

Men – Prostate Cancer

Summary of safety profile

As seen with other GnRH agonist therapies or after surgical castration, the most commonly observed adverse events related to triptorelin treatment were due to its expected pharmacological effects: Initial increase in testosterone levels, followed by almost complete suppression of testosterone. These effects included erectile dysfunction, hot flushes and decreased libido.

Tabulated summary of adverse reactions

The following adverse reactions, considered as at least possibly related to triptorelin treatment, were reported. Most of the adverse drug reactions are known to be related to biochemical or surgical castration.

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Frequency not known*
Infections and infestations				Nasopharyngitis
Immune system disorders		Hypersensitivity	Anaphylactic reaction	
Metabolism and nutrition disorders			Decreased appetite	Diabetes mellitus, gout, increased appetite
Psychiatric disorders	Decreased libido	Mood altered**, depression**, depressed mood, sleep disorder		Insomnia, loss of libido, confusional state, decreased activity, euphoric mood, anxiety
Nervous system disorders		Headache		Dizziness, paraesthesia, dysgeusia, somnolence, dysstasia, memory impairment
Eye disorders				Abnormal sensation in eye, visual impairment, vision blurred
Ear and labyrinth disorders				Tinnitus, vertigo
Vascular disorders	Hot flush		Embolism, Hypertension	Hypotension
Respiratory, thoracic and mediastinal disorders			Asthma aggravated	Dyspnoea, orthopnoea, epistaxis
Gastrointestinal disorders		Nausea	Abdominal pain upper, dry mouth	Abdominal pain, constipation, diarrhoea, vomiting, abdominal distension, flatulence, gastralgia
Skin and subcutaneous tissue disorders		Hyperhidrosis	Hypotrichosis, alopecia	Purpura, acne, pruritus, rash, blister, angioedema, urticaria
Musculoskeletal and connective tissue disorders	Bone pain	Myalgia, arthralgia		Back pain, musculoskeletal pain, pain in extremity, muscle spasms, muscular weakness, joint

				stiffness, joint swelling, musculoskeletal stiffness, osteoarthritis
Renal and urinary disorders	Dysuria			
Reproductive system and breast disorders	Erectile dysfunction	Gynaecomastia	Testicular atrophy	Breast pain, testicular pain, ejaculation failure
General disorders and administration site conditions		Injection site pain, Injection site reaction, fatigue, irritability		Asthenia, injection site reactions (HLT)[I], oedema, pain, chills, chest pain, influenza like illness, pyrexia, malaise
Investigations			Blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, alanine aminotransferase increased, weight increased, weight decreased	Aspartate aminotransferase increased, blood creatinine increased, blood pressure increased, blood urea increased, blood alkaline phosphatase increased, body temperature increased, electrocardiogram QT prolonged[II]

* Frequencies of these adverse events cannot be estimated from the available data.

** This frequency is based on class-effect frequencies common for all GnRH agonists.

[I] The injection site reactions High Level Term (HLT) includes several injection site reaction terms that have been reported in postmarketing experience with triptorelin acetate.

[II] See section 4.4 Warnings and Precautions for use and 4.5 Interaction with other Medicinal Products.

Description of selected ADRs

Triptorelin causes a transient increase in circulating testosterone levels within the first week after the initial injection of the sustained release formulation. With this initial increase in circulating testosterone levels, a small percentage of patients (≤ 5%) may experience a temporary worsening of signs and symptoms of their prostate cancer (tumour flare), usually manifested as an increase in urinary symptoms (< 2%) and/or metastatic pain (5%), which can be managed symptomatically. These symptoms are transient and usually disappear in one to two weeks.

Isolated cases of exacerbation of disease symptoms have occurred; either urethral obstruction, which may decrease the kidney function or spinal cord compression by metastasis, potentially causing paraesthesia and weakness in the legs. Therefore, patients with metastatic vertebral lesions and/or with upper or lower urinary tract obstruction should be closely observed during the first few weeks of therapy (see section 4.4 Warnings and Precautions for use).

The use of GnRH agonists, to treat prostate cancer may be associated with increased bone loss and may lead to osteoporosis and increase the risk of bone fracture. Slight trabecular bone loss may occur. This is generally reversible within 6-9 months after treatment discontinuation (see section 4.4 Warnings and Precautions for use).

Women – Uterine Myoma & Endometriosis

Summary of safety profile

As a consequence of decreased oestrogen levels, the most commonly reported adverse events were headache, libido decreased, sleep disorder, mood altered, dyspareunia, dysmenorrhoea, genital haemorrhage, pelvic pain, abdominal pain, vulvovaginal dryness, hyperhidrosis, hot flushes and asthenia.

Tabulated summary of adverse reactions

The following adverse reactions, considered as at least possibly related to triptorelin treatment, were reported.

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Frequency not known*
Immune system disorders		Hypersensitivity	Anaphylactic reaction	
Psychiatric disorders	Libido decreased, mood altered, sleep disorder	Depression**, depressed mood		Confusional state, anxiety
Nervous system disorders	Headache		Paraesthesia	Dizziness
Eye disorders			Visual impairment	Vision blurred
Ear and labyrinth disorders				Vertigo
Vascular disorders	Hot flush			
Respiratory, thoracic and mediastinal disorders	Abdominal pain	Nausea		Abdominal discomfort, diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Hyperhidrosis			Angioedema, pruritus, rash, urticaria
Musculoskeletal and connective tissue disorders	Bone pain	Myalgia, arthralgia	Back pain	Bone disorder, muscle spasms, muscular weakness
Reproductive system and breast disorders	Vulvovaginal dryness, vaginal haemorrhage, dyspareunia, dysmenorrhoea, pelvic pain			Heavy menstrual bleeding, intermenstrual bleeding, breast pain, amenorrhoea
General disorders and administration site conditions	Asthenia	Fatigue, irritability, Injection site pain, injection site reaction		Pyrexia, malaise, injection site reactions (HLT)[l]
Investigations			Blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, alanine aminotransferase increased, blood cholesterol increased	Blood pressure increased, weight increased, weight decreased

* Frequencies of these adverse events cannot be estimated from the available data.

** This frequency is based on class-effect frequencies common for all GnRH agonists.
[I] The injection site reactions High Level Term (HLT) includes several injection site reaction. Terms that have been reported in post-marketing experience with triptorelin acetate.

Description of selected adverse reactions
At the beginning of treatment, the symptoms of endometriosis including pelvic pain and dysmenorrhoea may be exacerbated due to the initial transient increase in plasma oestradiol levels. These symptoms are transient and usually disappear in one or two weeks.

Genital haemorrhage including menorrhagia and metrorrhagia may occur in the month following the first injection.

Slight trabecular bone loss may occur. This is generally reversible within 6-9 months after treatment discontinuation (see section 4.4 Warnings and Precautions for use).

Women – ART

Summary of the safety profile
The most commonly reported adverse event was headache. When used for infertility treatment ovarian hyperstimulation syndrome (see section {Warnings and Precautions for use}), ovarian enlargement, pelvic and/or abdominal pain may be observed.

No anaphylactic reactions have been seen in clinical trials, and only very few cases of hypersensitivity have been reported from post-marketing use.

Tabulated summary of adverse reactions
Based on the frequency of adverse drug reactions reported in clinical trials with DECAPEPTYL® CR in females for downregulation and prevention of premature LH surges (N=466).

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Frequency not known*
Immune system disorders				Hypersensitivity
Psychiatric disorders			Mood altered**, depression**, sleep disorder	Libido decreased, anxiety, confusional state
Nervous system disorders	Headache			Dizziness
Eye disorders				Vision blurred, visual impairment
Ear and labyrinth disorders				Vertigo
Vascular disorders		Hot flush		
Respiratory, thoracic and mediastinal disorders				Dyspnoea
Gastrointestinal disorders		Nausea, abdominal pain	Diarrhoea, vomiting	Abdominal discomfort
Skin and subcutaneous tissue disorders			Hyperhidrosis, pruritus, rash, urticaria	Angioedema

Musculoskeletal and connective tissue disorders			Arthralgia, muscle spasms, Musculoskeletal pain, myalgia	Muscular weakness
Reproductive system and breast disorders		Breast pain, dysmenorrhoea	Metrorrhagia, Ovarian cyst, Vaginal discharge	Ovarian Hyperstimulation syndrome[I] Dyspareunia, genital haemorrhage, menorrhagia, ovarian enlargement, pelvic pain, vulvovaginal dryness, amenorrhoea
General disorders and administration site conditions		Injection site inflammation, Injection site pain	Asthenia, malaise	Injection site reactions (HLT)[II], pyrexia
Investigations				Weight increased, blood pressure increased

* Frequencies of these adverse events cannot be estimated from the available data.

** This frequency is based on class-effect frequencies common for all GnRH agonists.

[I] In clinical trials with Deca CR used for Controlled Ovarian Stimulation, Ovarian Hyperstimulation Syndrome (OHSS) was observed in patients only after administration of gonadotrophins.

[II] The injection site reactions High Level Term (HLT) includes several injection site reaction terms that have been reported in post-marketing experience with triptorelin acetate.

Children – Precocious Puberty

Summary of the safety profile

Cases of slipped capital femoral epiphysis have been reported during use with triptorelin.

Tabulated summary of adverse reactions

The following adverse reactions, considered as at least possibly related to triptorelin treatment, were reported.

MedDRA System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Frequency not known*
Immune system disorders			Anaphylactic reaction	Hypersensitivity
Psychiatric disorders	Mood altered**, depression**			Affect lability, nervousness
Nervous system disorders				Headache, dizziness, idiopathic intracranial hypertension (pseudotumor cerebri)[I]
Eye disorders				Vision blurred, visual impairment
Vascular disorders				Hot flush
Respiratory, thoracic and mediastinal disorders				Epistaxis, dyspnoea
Gastrointestinal disorders			Nausea, vomiting	Abdominal pain, abdominal discomfort
Skin and				Erythema, angioedema,

subcutaneous tissue disorders				rash, urticaria, alopecia, pruritus
Musculoskeletal and connective tissue disorders				Myalgia, arthralgia, epiphysiolysis
Reproductive system and breast disorders			Vaginal discharge, vaginal haemorrhage	Genital haemorrhage
General disorders and administration site conditions				Pain, injection site reactions (HLT)[II], malaise, pyrexia
Investigations				Blood pressure increased, weight increased

* Frequencies of these adverse events cannot be estimated from the available data.
** This frequency is based on class-effect frequencies common for all GnRH agonists.
[I] See section {Warnings and precautions for use}.
[II] The injection site reactions High Level Term (HLT) includes several injection site reaction terms that have been reported in post-marketing experience with triptorelin acetate.

4.9 Overdose
There is insufficient experience of overdosing with triptorelin to draw conclusions on possible adverse effects. Considering the package form and the pharmaceutical form, overdosing is not expected. If overdose occurs, symptomatic management is indicated.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Gonadotropin releasing hormone analogues; ATC code: L02AE04

<u>General</u>
Triptorelin is a synthetic decapeptide analogue of the natural gonadotrophin-releasing hormone (GnRH). GnRH is a decapeptide, which is synthesised in the hypothalamus and regulates the biosynthesis and release of the gonadotrophins LH (luteinising hormone) and FSH (follicle stimulating hormone) by the pituitary. Triptorelin stimulates the pituitary more strongly to secretion of LH and FSH than a comparable dose of gonadorelin, whereas the duration of action is longer. The increase of LH and FSH levels will initially lead to an increase of serum testosterone concentrations in men or serum estrogen concentrations in women. Chronic administration of a GnRH agonist results in an inhibition of pituitary LH- and FSH-secretion.

<u>Men – Prostate Cancer; Women - Uterine Myoma and Endometriosis</u>
This inhibition leads to a reduction in steroidogenesis, by which the serum estradiol concentration in women and the serum testosterone concentration in men fall to within the postmenopausal or castrate range, respectively, i.e. a hypogonadotrophic hypogonadal state. Plasma DHEAS (dihydroepiandrostenedion sulphate) levels are not influenced. Therapeutically, this leads to a decrease in growth of testosterone-sensitive prostate tumours in men, and to reduction of endometriosis foci and estrogen-dependent uterus myomas in women. Regarding uterine myoma, maximal benefit of treatment is observed in women with anemia (hemoglobin inferior or equal to 8 g/dl).

<u>Women – ART</u>
The triptorelin-induced downregulation of the pituitary can prevent the LH surge and thereby premature ovulation and/or follicular luteinization. The use of the downregulation with GnRH agonist reduces the cycle cancellation rate and improves the pregnancy rate in ART cycles.

<u>Children – Precocious Puberty</u>

In children suffering from CPP, triptorelin treatment leads to a suppression of the secretion of gonadotropins, estradiol, and testosterone to prepubertal levels. This results in arrest or even regression of pubertal signs and an increase in adult height prediction in CPP patients.

5.2 Pharmacokinetic properties

After intramuscular administration of DECAPEPTYL® CR, the plasma concentrations of triptorelin are determined by the (slow) degradation of the poly-(d,l lactide coglycolide) 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 a triptorelin depot-formulation (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 the 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 I.M. 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.

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.

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.

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

Special populations

In patients with renal or hepatic impairment, triptorelin has a mean terminal half-life of 7-8 hours compared to 3-5 hours in healthy subjects. The clinical studies indicated that the risk of accumulation of triptorelin in patients with severe liver and renal impairment is small.

5.3 Preclinical safety information

Short- and long-term nonclinical studies reveal no special hazards for humans. Changes in organ weights and lowering of plasma hormone concentrations) were related to the pharmacological effect of triptorelin.

Life-long exposure to triptorelin had no carcinogenic effect on mice and caused species specific pituitary adenomas in rats. The rat finding was considered to be related to a rodent specific pharmacological effect of triptorelin and of no relevance to humans; no signs of mutagenicity, clastogenicity or carcinogenicity were recorded for triptorelin.

Reproductive toxicity studies in rats, rabbits and monkeys showed no toxic effects of treatment with triptorelin on fertility, embryo-fetal and pre- and postnatal development. Triptorelin is not teratogenic but there are indications for delayed fetal development and parturition in rats.

Single I.M. or S.C. injection of DECAPEPTYL® CR or its suspension agent produced delayed foreign body reactions at the injection site. Within 8 weeks, these late reactions were nearly reversed after I.M. injection but only slightly reversed after S.C. injection. Local tolerance of DECAPEPTYL® CR after I.V. injection was limited.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

One pre-filled syringe with powder contains:
Poly-(d,l lactide coglycolide)
Propyleneglycol dicaprylocaprate

One pre-filled syringe with one ml suspension agent contains:
polysorbate 80
Dextran 70
Sodium chloride
Sodium dihydrogen phosphate dihydrate
Sodium hydroxide
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product should not be mixed with other medicinal products.

6.3 Shelf-life

3 years
Reconstituted suspension must be applied immediately after preparation as per instructions.

6.4 Storage conditions

Stored at 2°C - 8 °C (in a refrigerator).
Keep the container in the outer carton.

6.5 Nature and contents of container

Powder: Pre-filled syringe
Solvent: Pre-filled syringe
Pre-filled syringes (borosilicate glass type I, clear) with a connector (polypropylene), rubber stopper (plunger stopper, type I) and injection needle for intramuscular injection.

Pack sizes:

1 pre-filled syringe (powder) plus
1 pre-filled syringe (solvent)

3 pre-filled syringes (powder) plus
3 pre-filled syringes (solvent)

ss

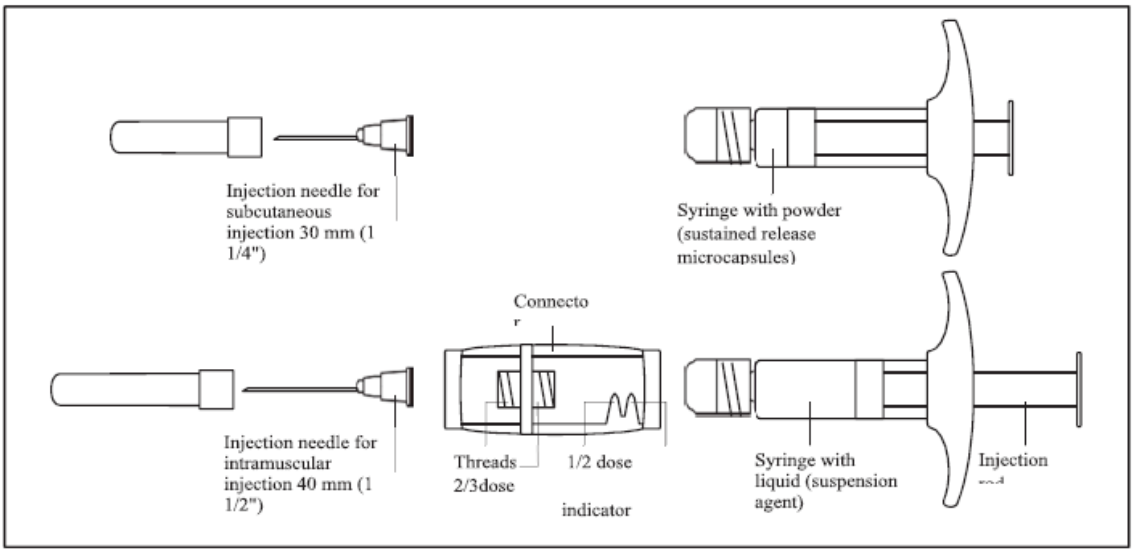
No special requirements for disposal. Any unused product or waste material should be disposed in accordance with local requirements.

6.7 Other handling information - INSTRUCTIONS FOR USE

⚠ **Important Information**:

1. Store DECAPEPTYL® CR in the packaging in the refrigerator.
2. Make sure to inject DECAPEPTYL® CR immediately after reconstitution.

Overview of the DECAPEPTYL® CR components:



1. Preparation

To ensure correct preparation of the suspension, the following instructions must be strictly followed:

Ⓐ

- Take the package of DECAPEPTYL® CR from the refrigerator.
- Open the connector package and take out the connector.

⚠ **Make sure not to touch the threads in the connector.**

Ⓑ

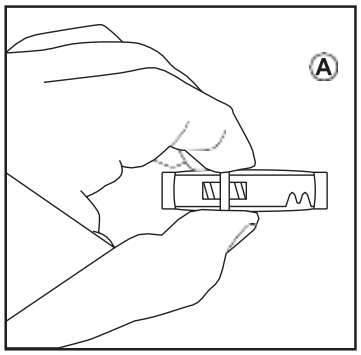
- Twist the cap off the syringe with powder. Hold the syringe with the tip pointing upwards to prevent spilling any powder.

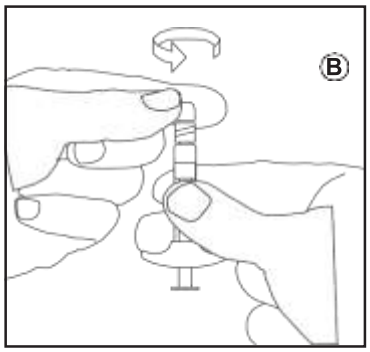
⚠ **Make sure not to push the injection rod.**

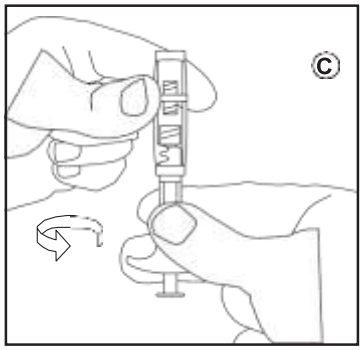
Ⓒ

- Screw the syringe with the powder onto one of the threads in the connector until it comes to a stop.

⚠ **Always attach the syringe with powder to the connector before attaching the syringe with liquid**







Ⓓ

- Twist the cap off the syringe with the liquid. Hold the syringe with the tip pointing upwards to prevent spilling any liquid.

⚠ **Make sure not to push the injection rod.**

Ⓔ

- Screw the syringe with the liquid onto the other thread in the connector until it comes to a stop.

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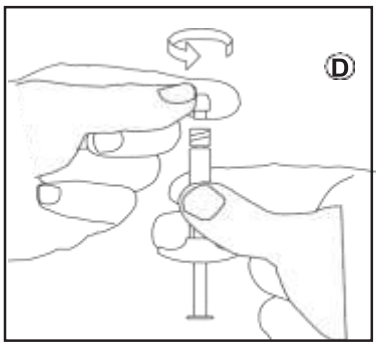
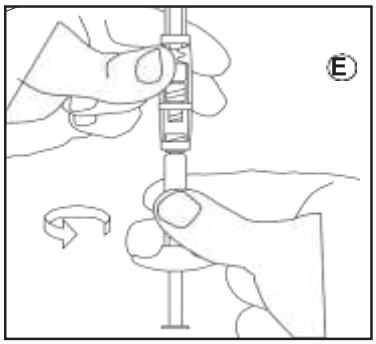
TURN OVER



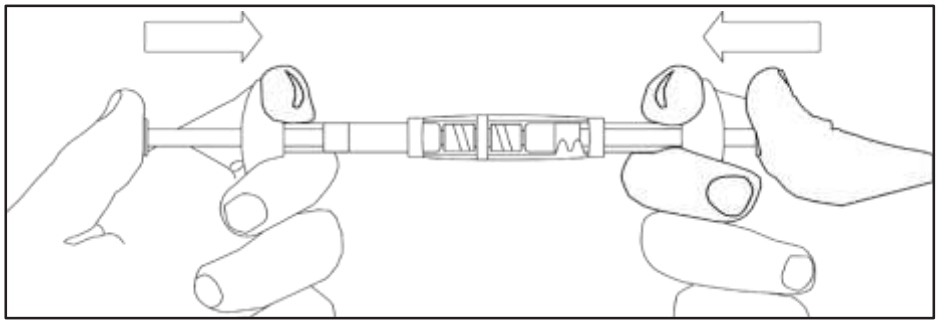


The following information is intended for healthcare professionals only:

2. Reconstitution

To mix the suspension:

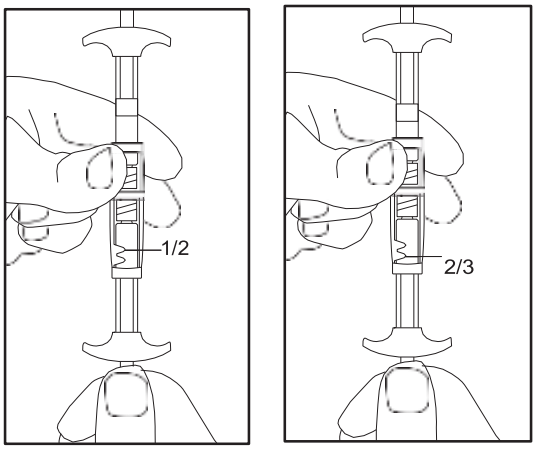
- Inject all the liquid into the syringe with the powder.
- Slowly push the suspension back and forth into the two syringes until it is homogenously milky white to faintly yellow. Take care to hold the syringes straight; do not bend.



1/2 or 2/3 doses for children:

Use the dose indicators on the connector to measure 1/2 or 2/3 doses:

- Make sure that the suspension is in the syringe connected to the side of the connector **without** dose indicators.
- Turn the syringes to a vertical position with the syringe containing the suspension at the top.
- Wait some seconds to let the foam separate.
- Slowly pull the injection rod of the empty syringe downwards until the suspension reaches the 1/2 or 2/3 indicator.



1/2 DOSE 2/3 DOSE

3. Injection

- Screw the syringe with the suspension ready for injection off the connector.
- Screw the injection needle onto the syringe.
- Inject the suspension immediately.

DECAPEPTYL® CR is for single use only and any unused suspension should be discarded.

Manufacturer
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Wittland 11, 24109 Kiel, Germany

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