## 1. NAME OF THE MEDICINAL PRODUCT
DECAPEPTYL® Injection 0.1 mg/ml

## 2. QUALITATIVE AND QUANTITAVE COMPOSITION
Each pre-filled syringe of 1 ml solution for injection contains 100 micrograms triptorelin acetate equivalent to 95.6 micrograms triptorelin free base.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM
Solution for injection
Clear colourless solution.

## 4. CLINICAL PARTICULARS
### 4.1 Therapeutic indications

Women - ART
DECAPEPTYL® is indicated for downregulation and prevention of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation for assisted reproductive technologies (ART).

### 4.2 Posology and method of administration
General
The dosage regimen of DECAPEPTYL® is 0.1 mg given once daily as a 1 mL subcutaneous injection.

Women - ART
Treatment with DECAPEPTYL® should be initiated under the supervision of a physician experienced in the treatment of infertility. Treatment can be started in the early follicular phase (day 2 or 3 of the menstrual cycle) or in the mid-luteal phase (day 21-23 of the menstrual cycle or 5-7 days before expected start of menses). Controlled ovarian hyperstimulation with gonadotrophins should be started after approximately 2-4 weeks of DECAPEPTYL® treatment. Ovarian response should be monitored clinically (including ovarian ultrasound alone or preferably in combination with measurement of oestradiol levels) and the dose of gonadotrophins adjusted accordingly. When a suitable number of follicles have reached an appropriate size, treatment with DECAPEPTYL® and gonadotrophin is stopped and a single injection of human chorionic gonadotrophin (hCG) is administered to induce the final follicular maturation. If downregulation is not confirmed after 4 weeks (determined by ultrasound documentation of a shedded endometrium alone or preferably in combination with measurement of oestradiol levels), discontinuation of DECAPEPTYL® should be considered. The total duration of treatment is usually 4-7 weeks.

When using DECAPEPTYL®, luteal phase support should be provided. Luteal phase support should be given according to the reproductive medical centre's practice.

In view of the possible effect on bone density, DECAPEPTYL therapy without add-back therapy should not exceed duration of 6 months (see section 4.4 Special warnings and precautions for use).

*Patients with renal or hepatic impairment*
No specific dose recommendations are given for subjects with renal or hepatic impairment. A clinical study indicated that the risk of accumulation of triptorelin in patients with severe liver and renal impairment is small (see section 5.2 Pharmacokinetic properties).

*Paediatric population*
There is no relevant use of DECAPEPTYL® in the paediatric population.

Method of administration
DECAPEPTYL® is intended for subcutaneous injection once daily into the lower abdominal wall. Following the first administration, it is advised that the patient be kept under medical supervision for 30 minutes to ensure there is no allergic/pseudo-allergic reaction to the injection.

Facilities for the treatment for such reactions should be immediately available. The following injections may be self-administered as long as the patient is made aware of the signs and symptoms that may indicate hypersensitivity, the consequences of such a reaction and the need for immediate medical intervention. The injection site should be varied to prevent lipoatrophy. For instructions for use and handling, see section 6.7 Other handling information.

**4.3 Contraindications**
General
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to gonadotrophin-releasing hormone (GnRH) or any other GnRH analogue.

Women – ART
- 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 bisphosphonate in combination with an GnRH agonist may reduce bone mineral loss. Particular caution is necessary in patients with additional major 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).

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 characterised by sudden headache, vomiting, visual impairment and ophthalmoplegia.

There is an increased risk of incident 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.

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 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.

Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with DECAPEPTYL® is not advised in women with severe allergic conditions. Women of childbearing potential should be examined carefully before treatment to exclude pregnancy.

Women – ART
It should be confirmed that the patient is not pregnant before prescription of triptorelin.

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® as adjunct therapy in controlled ovarian hyperstimulation. The use of DECAPEPTYL® in controlled ovarian hyperstimulation 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 ovarian hyperstimulation syndrome (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 e.g. with rest, intravenous infusion of electrolyte solutions or colloids and heparin.

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 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 properties).

**4.5 Interaction with other medicinal products and other forms of interaction**
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. 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 data). Based on the pharmacological effects, disadvantageous, influence on the pregnancy and the offspring cannot be excluded and DECAPEPTYL® 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 or 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 Effects on ability to drive and use machines**
No studies on the effects of the ability to drive and use machines have been performed. However, due to its pharmacological profile DECAPEPTYL® is likely to have no or negligible influence on the patient's ability to drive and use machines.

**4.8 Undesirable effects**

Summary of safety profile
The most frequent adverse events are headache (27%), vaginal bleeding/spotting (24%), abdominal pain (15%), injection site inflammation (12%) and nausea (10%). Ovarian cysts have been reported to occur commonly (1%) during the initial phase of treatment with DECAPEPTYL®.

Mild to severe hot flushes and hyperhidrosis may occur which do not usually require discontinuation of therapy.

At the beginning of treatment with DECAPEPTYL®, the combination with gonadotrophins may result in ovarian hyperstimulation syndrome. When used for infertility treatment, ovarian hyperstimulation syndrome (see section 4.4 Special Warnings and Precautions for Use), ovarian enlargement, dyspnoea, pelvic and/or abdominal pain may be observed. Genital haemorrhage including menorrhagia and metrorrhagia may occur at the beginning of treatment with DECAPEPTYL®.

During treatment with triptorelin some adverse reactions showed a general pattern of hypo-oestrogenic events related to pituitary-ovarian blockade such as sleep disorder, headache, mood altered, vulvovaginal dryness, dyspareunia and libido decreased.

Breast pain, muscle spasms, arthralgia, weight increased, nausea, abdominal pain, abdominal discomfort, asthenia and episodes of blurred vision and visual disturbances may occur during treatment with DECAPEPTYL®.

Single cases of allergic reactions, localized or generalized, have been reported after injection of DECAPEPTYL®. No anaphylactic reactions have been seen in clinical trials.

Tabulated summary of adverse reactions

Based on the frequency of adverse drug reactions reported in clinical trials with DECAPEPTYL® in females for downregulation and prevention of premature LH surges (N=2,095).

| **MedDRA System Organ Class** | **Very common (≥ 1/10)** | **Common (≥ 1/100 to < 1/10)** | **Uncommon (≥ 1/1000 to < 1/100)** | **Rare (>1/10,000 to <1/1,000)** | **Frequency Not known*** |
|---|---|---|---|---|---|
| Infections and infestations | | Upper respiratory tract infection, pharyngitis | | | |
| Immune system disorders | | | Hypersensitivity | | |
| Psychiatric disorders | | | Mood altered**, depression** | Fear | Sleep disorder, libido decreased |
| Nervous system disorder | Headache | Dizziness | | | |
| Eye disorders | | | | | Visual impairment, vision blurred |
| Vascular disorders | | Hot flush | | | |
| Respiratory, thoracic and mediastinal disorders | | | | Dyspnoea | |

| MedDRA System Organ Class | Very common (≥ 1/10) | Common (≥ 1/100 to < 1/10) | Uncommon (≥ 1/1000 to < 1/100) | Rare (>1/10,000 to <1/1,000) | Frequency Not known* |
|---|---|---|---|---|---|
| Gastrointestinal disorders | Abdominal pain, Nausea | Abdominal distension, vomiting | | | Abdominal discomfort |
| Skin and subcutaneous tissue disorders | | | Hyperhidrosis, Rash | Pruritus, Blister | Angioedema, Urticaria |
| Musculoskeletal & connective tissue disorders | | Back pain | Musculoskeletal pain | | Muscle spasms, arthralgia |
| Pregnancy puerperium and perinatal conditions | | Abortion | | | |
| Reproductive system and breast disorders | Vaginal haemorrhage | Pelvic pain, ovarian hyperstimulation syndrome, dysmenorrhoea, ovarian cyst*** | Breast pain | Vaginal discharge | Ovarian enlargement menorrhagia, metrorrhagia, vulvovaginal dryness, dyspareunia |
| General disorders and administration site conditions | Injection site inflammation | Injection site erythema, Injection site pain, injection site reactions (HLT)[1], fatigue, influenza like illness | | Injection site discolouration, injection site irritation, cyst | Asthenia |
| Investigations | | | | | 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.
*** Ovarian cysts may occur during the initial phase of treatment with GnRH agonist. They are usually asymptomatic and nonfunctional.
[1] 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**

Overdose in humans may result in a prolonged duration of action. In case of overdose, DECAPEPTYL® treatment should be (temporarily) discontinued.

No adverse reaction has been reported as a consequence of overdose.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotropin releasing hormone analogues, ATC code: L02AE04

General

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 gives a greater stimulation of the pituitary to secrete LH and FSH than a comparable dose of gonadorelin, and has a longer duration of action. 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. The exact duration of action of DECAPEPTYL® has not been established, but pituitary suppression is maintained for at least 6 days after stopping administration. After discontinuation of DECAPEPTYL®, a further drop in circulating LH levels should be expected, with LH levels returning to baseline after approximately 2 weeks.

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.

### 5.2 Pharmacokinetic properties

The pharmacokinetic data suggest that after subcutaneous administration of DECAPEPTYL® the systemic bioavailability of triptorelin is close to 100%. The elimination half-life of triptorelin is approximately 3-5 hours, indicating that triptorelin is eliminated within 24 hours. Metabolism to smaller peptides and amino acids primarily occurs in the liver and kidneys. Triptorelin is predominantly excreted in the urine.

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 data

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 but 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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride
Acetic acid, glacial (for pH adjustment)
Water for injections

**6.2 Incompatibilities**
In the absence of compatibility studies, the medicinal product must not be mixed with other medicinal products.

**6.3 Shelf life**
3 years.

**6.4 Special precautions for storage**
Store in a refrigerator (2 - 8 °C). Do not freeze. Store in the original package in order to protect from light.

**6.5 Nature and contents of container**
Solution for injection in single use pre-filled disposable borosilicate type 1 glass syringes with integrated needle and rigid needle shield. The syringe is closed with a chlorobutyl rubber stopper with a polystyrene plunger rod.

Pack sizes:
7 x 1 ml pre-filled syringes 0.1mg/1ml

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

**6.7 Other handling information**
Inject the entire contents of a pre-filled disposable syringe subcutaneously. Single-use only.

**Manufacturer**
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