1. Name of the medicinal product.

Decapeptyl ® 0.1

2. Qualitative and quantitative composition

1 disposable syringe with 1 ml solution for injection contains 100 ug triptorelin acetate, corresponding to 95.6 ug 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

IVF.

4.2 Posology and method of administration

Posology

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 0.1 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 0.1 and gonadotrophin is stopped and a single injection of 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 0.1 should be considered. The total duration of treatment is usually 4-7 weeks. When using Decapeptyl 0.1, luteal phase support should be provided according to the reproductive medical center's practice.

Special population

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).

Method of administration

Treatment with Decapeptyl 0.1 should be initiated under the supervision of a physician experienced in the treatment of infertility. Decapeptyl 0.1 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 6.6.

4.3 Contraindications

Decapeptyl 0.1 is contraindicated in cases of:
- 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
- Pregnancy and Lactation period

4.4 Special warnings and precautions for use

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 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).

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 months treatment period. Every 10% reduction in bone mineral density is linked with about a two to three times increased fracture risk.
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.

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

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 (which may be severe) in patients undergoing treatment with GnRH agonists, such as triptorelin. Patients should be informed accordingly and treated as appropriate if symptoms occur.

Mood changes, including depression have been reported. Patients with known depression should be monitored closely during therapy.

Ovarian stimulation should be done under strict medical supervision.

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. Despite this prolonged exposure, triptorelin is not expected to be present in circulation at the time of embryo transfer.

Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with Decapeptyl 0.1 is not advised in women with severe allergic conditions. Women of childbearing potential should be examined carefully before treatment to exclude pregnancy.

ART is associated with an increased risk of multiple pregnancies, pregnancy wastage, ectopic pregnancies and congenital malformations. These risks are also valid with usage of Decapeptyl 0.1 as adjunct therapy in controlled ovarian hyperstimulation. The use of Decapeptyl 0.1 in controlled ovarian hyperstimulation may increase the risk of ovarian hyperstimulation syndrome (OHSS) and ovarian cysts.

Follicular recruitment, induced by the use of GnRH analogues and gonadotrophins, 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.

Decapeptyl 0.1 contains sodium, but less than 1 mmol (23 mg) sodium per maximum dose.

4.5 Interactions with other medicinal products and other forms of interaction

Interactions of Decapeptyl 0.1 with other medicines have not been investigated for this indication.
The possibility of interactions with commonly used medicinal products, including histamine liberating products, cannot be excluded.
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 supervised.

4.6 Fertility, pregnancy and lactation.

Pregnancy

Decapeptyl 0.1 is not indicated during pregnancy. Pregnancy must be excluded before initiation of fertilization treatment. 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 fertilisation treatment, there is no clinical evidence to suggest a causal connection between triptorelin and any subsequent abnormalities of oocyte development or pregnancy or outcome.
Very limited data on the use of triptorelin during pregnancy do not indicate an increased risk of congenital malformations. Studies in animals have shown reproductive toxicity (see section 5.3). Based on the pharmacological effects disadvantageous influence on the pregnancy and the offspring cannot be excluded.

Lactation

Decapeptyl 0.1 is not indicated for use during lactation.

4.7 Effects on ability to drive and use machine.

No studies on the effects on the ability to drive and use machines have been performed. However, due to its pharmacological profile Decapeptyl 0.1 is likely to have no or negligible influence on the patient's ability to drive and use machines.

4.8 Undesirable effects

Frequently (≥ 2%) reported adverse events during treatment with Decapeptyl 0.1 in clinical trials, either before or during co-administration with gonadotrophins, are listed in the table below. The most frequent adverse events are headache (27%), vaginal bleeding/spotting (24%), abdominal pain (15%), injection site inflammation (12%) and nausea (10%).

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

At the beginning of treatment with Decapeptyl 0.1, the combination with gonadotrophins may result in ovarian hyperstimulation syndrome. Ovarian enlargement, dyspnoea, pelvic and/or abdominal pain may be observed (refer to section 4.4 Special Warnings and Precautions for Use). Genital haemorrhage including menorrhagia and metrorrhagia may occur at the beginning of treatment with Decapeptyl 0.1.

Ovarian cysts have been reported to occur commonly (1%) during the initial phase of treatment with Decapeptyl 0.1.

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 0.1.

Single cases of allergic reactions, localized or generalized, have been reported after injection of Decapeptyl 0.1.

MedDRA System Organ Class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥ 1/1,000 to <1/100)**	**Not known (frequency cannot be estimated from the available data)**
Infections and infestations		Upper respiratory tract infection, pharyngitis		
Immune system disorders				Hypersensitivity
Psychiatric disorders			Mood changes, depression	Sleep disorder, libido decreased
Nervous system disorder	Headache	Dizziness		
Eye disorders				Visual impairment, vision blurred
Vascular disorders		Hot flushes		
Respiratory, thoracic and mediastinal disorders				Dyspnoea
Gastrointestinal disorders	Abdominal pain, nausea	Abdominal distension, vomiting		Abdominal discomfort
Skin and subcutaneous tissue disorders				Hyperhidrosis, pruritus, rash, angioedema, urticaria
Musculoskeletal and connective tissue disorders		Back 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		Ovarian enlargement, menorrhagia, metrorrhagia, vulvovaginal dryness, dyspareunia, breast pain
General disorders and administration site conditions	Injection site inflammation	Injection site pain, injection site reaction, fatigue, influenza like illness		Asthenia, injection site erythema
Investigations				Weight increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Overdose in humans may result in prolonged duration of action. In case of overdose, Decapeptyl 0.1 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: Gonadotrophin-releasing hormone analogues, ATC code: L02AE04

Triptorelin (acetate) is a synthetic decapeptide and an analogue of the natural hypothalamus hormone GnRH. Triptorelin has a longer duration of action than the natural GnRH and has a biphasic effect at the pituitary level. After an initial large sudden increase in LH and FSH levels (flare-up), circulating LH und FSH levels decrease due to the pituitary GnRH receptor desensitization, with a consequent marked reduction in the gonadal production. The exact duration of action of Decapeptyl 0.1 has not been established, but pituitary suppression is maintained for at least 6 days after stopping administration. After discontinuation of Decapeptyl 0.1, a further drop in circulating LH levels should be expected, with LH levels returning to baseline after approximately 2 weeks.

The Decapeptyl 0.1 -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 and improves the pregnancy rate in ART cycles.

5.2 Pharmakokinetic properties

The pharmacokinetic data suggest that after subcutaneous administration of Decapeptyl 0.1 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 and therefore will not be present in circulation at the time of embryo transfer. Metabolism to smaller peptides and amino acids primarily occurs in the liver and kidneys. Triptorelin is predominantly excreted in the urine.

The clinical studies indicated that the risk of accumulation of triptorelin in patients with severe liver and renal impairment is small (i.e. half-life of approximately 8 hours in these patients).

5.3 Preclinical safety data.

In rats treated over a long period of time with triptorelin, an increase in pituitary tumors has been detected. LHRH analogues are known to induce pituitary tumors in rodents due to the rodent specific regulation of the endocrine system which is different from the

regulation in humans. The influence of triptorelin on pituitary abnormalities in humans is unknown and the observation in rats is considered not to be relevant to humans.
Triptorelin is not teratogenic but there are indications for delayed fetal development and parturition in rats.

Preclinical data reveal no special hazard to humans based on repeat dose toxicity and genotoxicity studies.

6. Pharmaceutical particulars

6.1 List of excipients: Sodium chloride, Acetic acid 99 %, Water for injection

6.2 Incompatibilities

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

6.3 Shelf-life: The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (+2 °C - +8 °C). Do not freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

1 ml solution in a pre-filled syringe (glass) with plunger stopper (chlorobutyl rubber), plunger rod (polystyrene), integrated needle and rigid needle shield in the pack size of 7.

6.6 Special precautions for disposal

Inject the entire contents of a pre-filled disposable syringe subcutaneously. Single-use only. No special requirements for disposal.

7. Marketing authorisation holder

Ferring Pharmaceuticals Ltd., 8 Hashita Street, Industrial Park, Caesarea 3088900
Israel

8. Registration number: 136-67-24855

This leaflet was revised in July 2022 according to MOH guidelines.