SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Decapeptyl depot 22.5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains triptorelin embonate equivalent to 22.5 mg triptorelin. After reconstitution in 2 ml solvent, 1 ml of reconstituted suspension contains 11.25 mg of triptorelin.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Decapeptyl depot 22.5 mg is indicated for symptomatic treatment of advanced hormone-dependent prostate cancer. As an alternative treatment, if orchiectomy or the administration of oestrogens are not indicated or are unacceptable to the patient.

Decapeptyl 22.5 mg is also indicated for the treatment of central precocious puberty (CPP) in children 2 years and older with an onset of CPP before 8 years in girls and 10 years in boys.

4.2 Posology and method of administration

Posology

The usual dosage is one intramuscular injection of Decapeptyl depot 22.5mg every 24 weeks under medical supervision.

Paediatric population

Precocious puberty (before 8 years in girls and 10 years in boys)

The treatment of children with Decapeptyl 22.5 mg should be under the overall supervision of a paediatric endocrinologist or of a paediatrician or an endocrinologist with expertise in the treatment of central precocious puberty.

Treatment should be stopped around the physiological age of puberty in boys and girls and should not be continued in girls with a bone maturation of more than 12-13 years. There are limited data available in boys relating to the optimum time to stop treatment based on bone age, however it is advised that treatment is stopped in boys with a bone maturation age of 13-14 years.

Treatment monitoring

Prostate cancer

The efficacy of treatment can be monitored by measuring serum levels of testosterone and prostate specific agent (PSA) and by subjective evaluation (symptomatic improvement e.g. urinary symptoms, cancer pain etc)

Special dosage recommendations (refers to all dosages if not specified otherwise):

*Elderly patients***:** The dose does not have to be adapted to age.

The medicine is not indicated for post-menopausal women.

Hepatic or renal impairment: The dose does not have to be adjusted for patients suffering from limited hepatic or renal function.

Method of administration

As with other medicinal products administered by injection, the injection site should be varied periodically.

Once reconstituted, the suspension of Decapeptyl depot 22.5 mg should be intramuscularly injectedrelatively rapidly and uninterrupted manner in order to avoid any potential blockage of the needle.

Precautions to be taken before handling or administrating the medicinal product
Decapeptyl depot 22.5 mg is only intended for intramuscular use.

Since Decapeptyl depot 22.5 mg is a suspension of microgranules, inadvertent intravascular injection must be strictly avoided.

Decapeptyl depot 22.5 mg must be administered under the supervision of a physician.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to GnRH, its analogues or any of the excipients of the medicinal product listed in section 6.1 (see section 4.8).
Triptorelin is contraindicated during pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

The use of GnRH agonists may cause reduction in bone mineral density. In men, preliminary datasuggest that the use of a bisphosphonate in combination with an GnRH agonist may reduce bonemineral 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 bonemineral 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 (which may be severe) in patients undergoing treatment with GnRH agonists, such as triptorelin. Patients should be informed accordingly and treated appropriately if symptoms occur. Patients with known depression should be monitored closely during therapy.

Caution is required with intramuscular injection in patients treated with anticoagulants, due to the potential risk of haematomas at the site of injection.
The efficacy and safety of Decapeptyl depot 22.5 mg has been established via intramuscular route only. Subcutaneous administration is not recommended.

This medicine contains less than 1 mmol (23mg) sodium per dose, i.e., essentially “sodium-free”.

Prostate Cancer:

Initially, triptorelin, like other GnRH agonists, causes a 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 treatment, consideration should be given to the additional administration of a suitable anti- androgen to counteract the initial rise in serum testosterone levels and the worsening of clinical symptoms.

A small number of patients may experience a temporary worsening of signs and symptoms of their prostate cancer (tumour flare) and a 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 treatmentof these complications should be instituted, and in extreme cases an immediate orchiectomy (surgical castration) should be considered. Careful monitoring is indicated during the first weeksof treatment, particularly in patients suffering from vertebral metastases, at the risk of spinal cordcompression, and in patients with urinary tract obstruction.

After surgical castration, triptorelin does not induce any further decrease in serum testosterone levels. Once castration levels of testosterone have been achieved by the end of the first month, serum testosterone levels are maintained for as long as the patients receive their injection every 6months (twenty-four weeks).

The effectiveness of treatment can be monitored by measuring serum levels of testosterone and prostate specific antigen.

Long-term androgen deprivation either by bilateral orchiectomy or administration of GnRH analogues is associated with increased risk of bone loss and 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) physicians should assess the benefit/risk profile including the potential for Torsades de pointes prior to initiating Decapeptyl depot 22.5 mg.

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 riskfor 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 normally restored after treatment is discontinued. The results of diagnostic tests of pituitary gonadal function conducted during treatment and after discontinuation of therapy with GnRH analogues may therefore be misleading.

Precocious puberty

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

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

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.

The therapy is a long-term treatment, adjusted individually. Decapeptyl depot 22.5mg should be administered as precisely as possible in regular 6 monthly periods. An exceptional delay of the injection date for a few days (169 ± 3 days) does not influence the results of the therapy.

After discontinuation of treatment the development of puberty characteristics will occur.

Information with regards to future fertility is still limited but future reproductive function and fertility appears to be unaffected by GnRH treatment. In most girls, regular menses will start on average one year after ending the therapy.

Bone mineral density may decrease during GnRH agonist therapy for central precocious puberty due to the expected effects of oestrogen suppression. 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 oestrogen 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.

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

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

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Decapeptyl depot 22.5 mg with medicinal products known to prolong the QT interval or medicinal products able to induce Torsades 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).

Paediatric Population

Interaction studies have only been performed in adults.

4.6 Pregnancy and lactation

Pregnancy

Decapeptyl depot 22.5 mg is indicated for adult men and children. There are very limited data on the use of triptorelin in pregnant women. Decapeptyl depot 22.5 mg is not indicated for use in females. It should be confirmed that the patient is not pregnant before prescription of Decapeptyl depot 22.5 mg.

Triptorelin must not be used during pregnancy since concurrent use of GnRH agonists is associated with a theoretical risk of abortion or foetal abnormality. Prior to treatment, potentiallyfertile women should be examined carefully to exclude pregnancy. Non-hormonal methods of contraception should be employed during therapy until menses return.

Animal studies have shown effects on reproductive parameters (see section 5.3 Preclinical safety data).

Lactation

Decapeptyl depot 22.5 mg is not indicated in lactating women.

4.7 Effects 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 should the patient experience dizziness, somnolence and visual disturbances being possible undesirable effects of treatment, or resulting from the underlying disease.

4.8 Undesirable effects

General tolerance in men

Since patients suffering from locally advanced or metastatic, hormone-dependent prostate cancerare generally old and have other diseases frequently encountered in this aged population, more than 90 % of the patients included in clinical trials reported adverse events, and often the causalityis difficult to assess. 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 expectedpharmacological effects. These effects included hot flushes and decreased libido.

With the exception of immuno-allergic (rare) and injection site (< 5%) reactions, all adverse events are known to be related to testosterone changes.

The following adverse reactions considered as at least possibly related to triptorelin treatmentwere reported. Most of these events are known to be related to biochemical or surgical castration.

The frequency of these side effects is classified as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (,1/10,000), uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); not known (cannot be estimated from the available data).

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare***	***Additional post-marketing Frequency not known***
Infections and infestations				Nasopharyngitis	
Neoplasms		Temporary tumour flare			
Blood and lymphatic system disorders			Thrombocytosis		
Cardiac disorders			Palpitations		QT prolongation* (see sections 4.4 and 4.5)
Investigations		Weight increase	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatinine increased, Blood pressure increased, Blood urea increased Gamma-glutamyl transferase increased Weight decreased	Blood alkaline phosphatase increased	

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare***	***Additional post-marketing Frequency not known***
Immune system disorders		Hypersensitivity		Anaphylactic reaction	Anaphylactic shock
Endocrine disorders					Pituitary apoplexy**
Metabolism and nutrition disorders			Anorexia Diabetes mellitus Gout Hyperlipidaemia Increased appetite		
Psychiatric disorders	Libido decreased	Loss of libido Depression* Mood changes*	Insomnia, Irritability	Confusional state, Decreased activity, Euphoric mood	Anxiety
Nervous system disorders	Paraesthesia in lower limbs	Dizziness Headache	Paraesthesia	Memory impairment	
Eye disorders			Visual impairment	Abnormal sensation in eye, visual disturbance	
Ear and labyrinth disorders			Tinnitus, Vertigo		
vascular disorders	Hot flash	Hypertension		Hypotension	
Respiratory tract			Dyspnoea, Epistaxis	Orthopnoea	
Gastrointestinal disorders		Dry mouth, Nausea	Abdominal pain Constipation, Diarrhoea, Vomiting	Abdominal distension, Dysgeusia, Flatulence	
Skin and subcutaneous tissue disorders	Hyperhidrosis		Acne, Alopecia, Erythema, Pruritus Rash, Urticaria	Blister, Purpura	Angioneurotic oedema
Musculo-skeletal and connective Tissue disorders	Back pain	Musculoskeletal pain, Pain in extremity	Arthralgia, Bone pain, Muscle cramp, Muscular weakness, Myalgia	Joint stiffness, Joint swelling, Musculoskeletal stiffness, Osteoarthritis	
Renal and urinary disorders			Nocturia, Urinary retention		Urinary incontinence

System Organ Class	*Very Common*	*Common*	*Uncommon*	*Rare*	*Additional post-marketing Frequency not known*
Reproductive system and breasts	Erectile dysfunction (including ejaculation failure, ejaculation disorder)	Pelvic plain	Gynaecomastia, Breast pain, Testicular atrophy, Testicular pain		
General disorders and administration site conditions	Asthenia	Injection site reaction (including erythema inflammation and pain) Oedema	Lethargy, Oedema peripheral, Pain, Rigors, Somnolence	Chest pain, Dysstasia, Influenza like illness, Pyrexia	Malaise

*This frequency is based on class-effect frequencies common for all GnRH agonists
**Reported following initial administration in patients with pituitary adenoma

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 by an increase in urinary symptoms (< 2%) and 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, either urethral obstruction or spinal cord compression by metastasis have occurred. 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 Special 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 increases the risk of bone fracture. This may also lead to an incorrect diagnosis of bone metastases.

Patients receiving long-term treatment with GnRH analogue in combination with radiation therapy may have more side effects, mostly gastrointestinal and related to radiotherapy.

General tolerance in children (see section 4.4)

The frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000, < 1/100).

System Organ Class	*Very Common Treatment related AEs*	*Common Treatment related AEs*	*Uncommon Treatment related AEs*	*Additional Post-marketing Frequency unknown*
Eye disorders			Visual impairment	Visual disturbance
Gastrointestinal disorders		Abdominal pain	Vomiting, Constipation, Nausea	
General disorders and administration site conditions		Injection site reaction (including injection site pain, injection site erythema and injection site inflammation)	Malaise	

System Organ Class	***Very Common Treatment related AEs***	***Common Treatment related AEs***	***Uncommon Treatment related AEs***	***Additional Post-marketing Frequency unknown***
Immune system disorders		Hypersensitivity		Anaphylactic shock
Investigations		Weight increased		Blood pressure increased, Blood prolactin increased
Metabolism and nutrition disorders			Obesity	
Musculoskeletal and connective tissue disorders			Neck pain	Myalgia
Nervous system disorders		Headache		Idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4)
Psychiatric disorders			Mood altered	Affect lability, Depression, Nervousness
Reproductive system and breast disorders	Vaginal bleeding (including vaginal haemorrhage, withdrawal bleed, uterine haemorrhage, vaginal discharge, vaginal bleeding including spotting)		Breast pain	
Respiratory, thoracic and mediastinal disorders			Epistaxis	
Skin and subcutaneous tissue disorders		Acne	Pruritus , Rash, Urticaria	Angioneurotic oedema
Vascular disorders		Hot flush		Hypertension

General

Increased lymphocytes count has been reported with patients undergoing GnRH analogue treatment. This secondary lymphocytosis is apparently related to GnRH induced castration and seems to indicate that gonadal hormones are involved in thymic involution.

Reporting suspected adverse reactions after authorization 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

The pharmaceutical properties of Decapeptyl depot 22.5mg and its mode of administration make accidental or intentional overdose unlikely. There is no human experience of overdose. Animal tests suggest that no effect other than the intended therapeutic effects on sex hormone concentration and on the reproductive system will

be evident with higher doses of Decapeptyl depot 22.5 mg. If overdose occurs, symptomatic management is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1Pharmacodynamic properties

Pharmacotherapeutic group:

Hormones and related agents, gonadotropin releasing hormone analogues.

ATC code: L02AE04

Mechanism of action and pharmacodynamic effects

Triptorelin, a GnRH agonist, acts as a potent inhibitor of gonadotrophin secretion when given continuously and in therapeutic doses. Animal and human studies show that after administrationof triptorelin there is an initial and transient increase in circulating levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone in males and oestradiol in females.

However, chronic and continuous administration of triptorelin results in decreased LH and FSH secretion and suppression of testicular and ovarian steroidogenesis.

In men with prostate cancer:

A reduction of serum testosterone levels into the range normally seen in surgically castrated men occurs approximately 2 to 4 weeks after initiation of therapy. Decapeptyl depot 22.5 mg is designed todeliver 22.5 mg of triptorelin over a 6-month period. Once the castration levels of testosterone have been achieved by the end of the first month, serum testosterone levels are maintained for aslong as the patients receive their injection every twenty-four weeks.

This results in accessory sexual organ atrophy. These effects are generally reversible upon discontinuation of the medicinal product. The effectiveness of treatment can be monitored by measuring serum levels of testosterone and prostate specific antigen. As shown during the clinicaltrial programme, there was a 97% median relative reduction in PSA at Month 6 for Decapeptyl depot 22.5 mg.

In animals, administration of triptorelin resulted in the inhibition of growth of some hormone-sensitive prostate tumours in experimental models.

Clinical efficacy and safety in prostate cancer

Administration of Decapeptyl depot 22.5 mg to patients with advanced prostate cancer as an intramuscular injection for a total of 2 doses (12 months) resulted in both achievement of castration levels of testosterone in 97.5% of patients after four weeks and maintenance of castration levels of testosterone in 93.0% of the patients from Month 2 through Month 12 of treatment.

Clinical efficacy and safety in children with precocious puberty

In a non-comparative clinical study, 44 children with central precocious puberty (39 girls and 5 boys) were treated with a total of two intramuscular injections of Decapeptyl 22.5 mg over 12 months (48 weeks). Suppression of stimulated LH concentrations to prepubertal levels was achieved in 95.5% of subjects by month 3, and in 93.2 % and 97.7% of subjects at months 6 and 12, respectively.

The consequence is a regression or stabilisation of secondary sex characteristics and slowing down of accelerated bone maturation and growth.

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

5.2. Pharmacokinetic properties

Absorption:

Following a single IM injection of Decapeptyl Depot 22. 5mg in patients with prostate cancer, tmax was 3 (2-12) hours and Cmax (0-169 days) was 39.9 (19.1-107.0)ng/ml.

Triptorelin did not accumulate over 12 months of treatment.

Distribution:

Results of pharmacokinetic investigations conducted in healthy men indicate that after intravenous bolus administration, triptorelin is distributed and eliminated according to a 3-compartment model; and corresponding half-lives are approximately 6 minutes, 45 minutes, and 3 hours.

The volume of distribution at steady state of triptorelin following intravenous administration of 0.5 mg triptorelin acetate is approximately 30 l in healthy male volunteers. Since there is no evidence that triptorelin at clinically relevant concentrations binds to plasma proteins, medicinal product interactions involving binding-site displacement are unlikely.

Biotransformation:

Metabolites of triptorelin have not been determined in humans. However, human pharmacokinetic data show that C-terminal fragments produced by tissue degradation are either completely destroyed within tissues or are rapidly further degraded in plasma or cleared by the kidneys.

Elimination:

Triptorelin is eliminated by both the liver and kidneys. Following intravenous injection of 0.5 mg triptorelin, 42 % of the dose was excreted in urine in the form of intact triptorelin.

which increased to 62 % in subjects with hepatic impairment. Since creatinine clearance (Cl_{creat}) in healthy volunteers was 150 ml/min and only 90 ml/min in subjects with hepatic impairment, this indicates that the liver is a major site of triptorelin elimination. In these healthy volunteers, the true terminal half-life of triptorelin was 2.8 hours and total clearance of triptorelin 212 ml/min, the latter being dependent on a combination of hepatic and renal elimination.

Other special populations:

Following intravenous administration of 0.5 mg triptorelin to subjects with moderate renal insufficiency (Cl_{creat} 40 ml/min), triptorelin had an elimination half-life of 6.7 hours, 7.81 hours in subjects with severe renal insufficiency (Cl_{creat} 8.9 ml/min) and 7.65 hours in patients with impaired hepatic function (Cl_{creat} 89.9 ml/min).

The effects of age and race on triptorelin pharmacokinetics have not been systematically studied.However, pharmacokinetic data obtained in young healthy male volunteers aged 20 to 22 years with an elevated creatinine clearance (approximately 150 ml/min) indicated that triptorelin was eliminated twice as fast in the young population. This is related to the fact that triptorelin clearanceis correlated to total creatinine clearance, which is well known to decrease with age.

Because of the large safety margin of triptorelin and since Decapeptyl depot 22.5 mg is a sustained release formulation, no dose adjustment is recommended in patients with renal or hepaticimpairment.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetics/pharmacodynamics relationship of triptorelin is not straightforward to assess, since it is non-linear and time-dependent. Thus, after acute administration in naive subjects, triptorelin induces a dose-dependent increase of LH and FSH responses.

When administered as a sustained release formulation, triptorelin stimulates LH and FSH secretion during the first days post dosing and, in consequence, testosterone secretion. As shown by the results of the different bioequivalence studies, the maximal increase in testosterone is reached after around 4 days with an equivalent C_{max} which is independent from the release rate oftriptorelin. This initial response is not maintained despite continuous exposure to triptorelin and is followed by a progressive and equivalent decrease of testosterone levels. In this case too, the extent of triptorelin exposure can vary markedly without affecting the overall effect on testosterone serum levels.

5.3 Preclinical safety data

The toxicity of triptorelin towards extragenital organs is low. The observed effects were mainly related to the exacerbation of the pharmacological effects of triptorelin.

In chronic toxicity studies at clinically relevant doses, triptorelin induced macro- and microscopic changes in the reproductive organs of male rats, dogs and monkeys. These were considered as a reaction to the suppressed gonadal function caused by the pharmacological activity of the active ingredient. The changes were partly reversed during recovery phase.

After subcutaneous administration of 10 µg/kg to rats on days 6 to 15 of gestation, triptorelin did not elicit any embryotoxic, teratogenic, or anyother effects on the development of the offspring (F1 generation) or their reproductive performance. At 100 µg/kg, a reduction in maternal weight gain and an increased number of resorptions were observed.

Triptorelin is not mutagenic *in vitro* or *in vivo*.

In mice, no oncogenic effect has been shown with triptorelin at doses up to 6000 µg/kg after 18 months of treatment. A 23-month carcinogenicity study in rats has shown an almost 100 % incidence of benign pituitary tumours at each dose level, leading to premature death. The increased incidence in pituitary tumours in rats is a common effect associated with LH-RH agonist treatment. The clinical relevance of this is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder	poly (d,l-lactide-co-glycolide) 72/25 cooh, Poly (dl-lactide-co-glycolide) 85/15 lauryl ester, mannitol, carmellose sodium, polysorbate 80
Solvent	water for injections

6.2. Incompatibilities

In the absence of compatibility studies, this 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

Use immediately after reconstitution.

6.4. Special precautions for storage

Store bellow 25ºC.

For storage conditions of the reconstituted medicinal product see section 6.3.

6.5. Nature and contents of container

1 vial with powder containing 22.5 mg triptorelin,

1 ampoule with solvent containing 2 ml water for injection.

1 syringe and 2 needles **.**

6.6. Special precautions for disposal and other handling

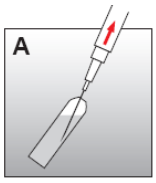
The suspension for injection should be prepared immediatelly before use.

1. Preparation for injection.

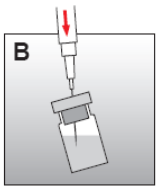
Two needles are provided in the box:

- The reconstitution needle
- The injection needle

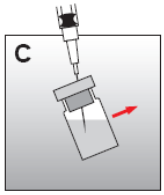
- Tap any solution that may be present in the tip of the ampoule back into the main reservoir of the solvent ampoule.
- Screw the reconstitution needle onto the syringe (do not remove the needle guard at this point!)
- Break open the solvent ampoule (breakpoint facing your body).
- Remove the needle guard from the reconstitution needle and draw up all the solvent into the syringe. (Fig.A).



- Put aside the syringe containing the solvent.
- Take out the vial containing the powder. Tap any powder which has accumalated at the top of the vial back to the bottom of the vial.
- Remove the plastic cap from the top of the vial.
- Pick up the syringe containing the solvent again and insert the needle thorogh the rubber stopper of the vial and slowly inject the solvent so that it flows down the edge of the vial over a wide area (Fig.B).

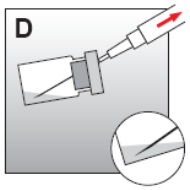


- Pull up the needle to above the level of the liquid and gently swirl the vial to produce a homogeneous, milky suspension for injection (Fig.C). Make sure there is no powder left in the vial, and if nessesary, continue swirling the vial until the powder has completely disappeared. N.B.: Do not mix the suspension by repeatedly filling and emptying the syringe!

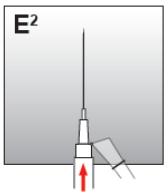


- Then draw up all of the suspension for injection into the syringe (Fig. D).

- As the product is a suspension, the injection should be administered immediately after reconstitution to prevent precipitation.



- Remove the reconstitution needle. Firmly screw the injection needle onto the syringe (screw it on tightly). Only touch the colored hub.
- Remove the needle cover from the injection needle.
- Expel any air from the syringe (Fig.E2).



2. Injection

- Inject the suspension for injection relatively rapidly and in a steady and uninterrupted manner into the muscles.

3. After use

- Dispose of the needles in a designated sharps container.
- For single use only. Any unused suspension must be discared

7. Name of manufacturer

Debio Pharam Researches and Manufacturing SA, Swtzerland

8. Name of registration holder:

Ferring pharmaceuticals LTD, 8 Hashita Street, Industrial Park, Caesarea 3088900, Israel.

9. **Registration number:** 154-61-34193

This leaflet was revised in May 2023 according to MOH guidelines.