מקרא צבעים

מידע חדש המהווה החמרה – **XX**

התאמה לתנאי רישום בישראל – **XX**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

~~Decapeptyl Depot~~Decapeptyl depot 22.5 mg ~~powder and solvent for suspension for injection.~~

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

~~**Decapeptyl Depot 22.5 mg.**~~ 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**~~**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

Decapeptyl depot 22.5 mg. The usual dosage is one intramuscular injection of ~~Decapeptyl Depot~~Decapeptyl depot 22.5~~0~~mg every 24 weeks under medical supervision.

~~Since Decapeptyl Depot~~Decapeptyl depot ~~22.50 mg is a suspension of microgranules, intravascular injection must be strictly avoided.~~

~~Decapeptyl Depot~~Decapeptyl depot ~~22.5 mg may only be administered by doctors or medical personnel.~~

~~The injection site should be varied periodically.~~

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 variedperiodically.

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 injectionmust 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 ~~LH-RH, triptorelin, other~~ GnRH, its analogues or any of the excipients of the medicinal product listed in section 6.1 (see ~~paragraph~~ section ~~6~~4.~~1~~8). ~~If the tumor is not hormone-dependent or after surgical castration.~~

~~In patients with spinal cord compression caused by metastases of their prostate cancer.~~ 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 unknowngonadotroph cell pituitary adenoma. These patients may present with a pituitary apoplexycharacterised 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".

~~*Allergic reactions*: Allergic reactions have been observed in rare cases shortly after the injection of Decapeptyl depot~~Decapeptyl depot ~~22.5 mg. Rare cases of anaphylactic shock and angioneurotic oedema have been reported after the administration of triptorelin. In such cases, treatment with Decapeptyl depot~~Decapeptyl depot ~~22.5 mg should be discontinued immediately and appropriate measures taken.~~

~~Paraesthesia and severe migraine are rare. Treatment should be discontinued in serious or recurring cases.~~

~~*Patients taking anticoagulants:* In view of the risk of bruising at the injection site, particular caution is indicated in patients being treated with anticoagulants.~~

~~Mood disorders/Depression: Mood disorders, including depressive episodes (some of which were severe), have been reported during treatment with triptorelin. Patients suffering from depression (or with a history of depression) should therefore be monitored closely during treatment.~~

~~Pituitary apoplexy:~~
~~Rare cases of pituitary apoplexy (a clinical syndrome resulting from pituitary infarction) have been described after the administration of LH-RH agonists. A pituitary adenoma had been diagnosed in the majority of cases. Most of these cases occurred within 2 weeks and in some cases within one hour, of the first injection. The pituitary apoplexy was characterized by sudden headache, vomiting, visual impairment, ophthalmoplegia, altered mental status and, occasionally, cardiovascular collapse.~~
~~Immediate medical intervention is essential.~~
~~For this reason, a GnRH agonist should not be administered to patients with a known pituitary adenoma.~~

Prostate Cancer:

~~Like other GnRH agonists, causes a transient increase in serum testosterone levels within the first week after the initial injection of the sustained release formulation. This increase may also occur if the interval between 2 injections exceeds 1 month for Decapeptyl Depot~~Decapeptyl depot ~~3.75mg, 12 weeks for Decapeptyl Depot~~Decapeptyl depot ~~11.25 mg and 24 weeks for Decapeptyl Depot~~Decapeptyl depot ~~22.5 mg. In contrast with the decline in testosterone level that an orchiectomy produces, this initial increase in circulating testosterone levels may result in a temporary worsening of signs and symptoms of prostate cancer in a small percentage of patients (<5%)~~
~~This is usually manifested by exacerbated cancer pain, mainly in the form of neuropathy, haematuria and bone pain, which can be managed symptomatically. Aggravation of disease symptoms, e.g. obstruction of the ureter or bladder sphincter, or spinal cord compression due to metastases, may occur in isolated cases and may be associated with paralysis or a fatal outcome.~~

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 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 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).

~~If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted, and in extreme cases an immediate orchiectomy should be considered. Careful monitoring is therefore indicated during the first weeks of treatment, particularly in patients suffering from vertebral metastases and/or urinary tract obstruction.~~

~~During the initial phase of treatment, consideration should be given to the concomitant administration of an anti-androgen to counteract the initial rise in serum testosterone levels and any worsening of clinical symptoms.~~

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), 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.

~~Effects on diagnostic methods~~

Administration of ~~At therapeutic doses,~~ 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 ~~within 4 to 12 weeks~~ after discontinuation of therapy with GnRH analogues ~~LH-RH agonists~~ may therefore be misleading.~~erroneous~~.

~~*Risk of diabetes/cardiovascular risk:* An increased risk of diabetes mellitus and/or cardiovascular event has been reported in men treated with GnRH agonists. It is therefore advisable to monitor patients with hypertension, hyperlipidaemia or cardiovascular disorders for this risk while they are undergoing treatment with triptorelin.~~

~~*Effect on the QT/QTc interval:* Since long-term androgen deprivation may prolong the QT interval, it is advisable to monitor patients with a prolonged QT interval, electrolyte abnormalities or heart failure. The concomitant use of triptorelin with drugs that are known to prolong the QT interval or to be capable of inducing torsades de pointers, such as antiarrhythmics in class IA (e.g. quinidine, disopyramide) or class III(e.g. amiodarone, sotalol) should be carefully assessed (see section 4.5).~~

~~*Osteoporosis/bone density*. The administration of synthetic LH-RH analogues for the treatment of prostate cancer may cause bone loss and possibly osteoporosis, thus increasing the risk of bone fracture. This may also lead to an incorrect diagnosis of bone metastases. Particular caution is necessary in patients with additional risk factors for osteoporosis (e.g. chronic alcohol abuse, smoking, malnutrition, a positive family history of osteoporosis or long-term treatment with drugs that reduce bone mineral density, e.g. corticoids or anticonvulsants).~~

~~An elevated lymphocyte count has been reported in patients receiving treatment with GnRH agonists. This secondary lymphocytosis is evidently related to LH-RH induced castration and seems to indicate that gonadal hormones are involved in thymic involution.~~

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~~ 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.

4.5 Interaction with other medicinal products and other forms of interaction

~~Paricular caution is required~~ when triptorelin is co-administered with drugs affecting pituitary secretion of gonadotrophins, caution should be taken and it is recommended that ~~and monitoring of~~ the patient's hormonal status

should be supervised.

~~is recommended.~~

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.

~~Cytochrome P450 (CYP) enzymes are unlikely to be involved in the metabolism and elimination of triptorellin. Moreover, in vitro data has been shown that triptorelin is neither an inhibitor nor an inducer of CYP and that is not a substrate or an inhibitor of P-glycoprotein (P-gp) either. Drug interaction with triptorelin are therefore unlikely.~~

4.6 Pregnancy and lactation

Pregnancy

Decapeptyl depot 22.5 mg is indicated for adult men and children. There are very limited data on theuse 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 isassociated 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.

~~Decapeptyl depot~~Decapeptyl depot ~~22.50mg is not indicated for use in 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.

~~Although no studies have investigated this subject, certain undesirable effects such as apathy, epileptic seizures and abnormal vision may impair reflexes and the ability to drive and use tools or machines.~~

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 expected pharmacological 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.

~~General information~~

~~Allergic reactions have been observed in isolated cases shortly after the injection of triptorelin, but these regressed with conventional treatment.~~

~~Prostate cancer~~

~~An exacerbation of cancer pain may occur 7 to 10 days after the first injection as a result of the transient increase in testosterone levels (see section 4.4). This pain usually regress as the cancer responds to treatment. Temporary treatment with an anti-androgen may be considered.~~

~~The most commonly observed undesirable effects during triptorelin treatment where attributable to its expected physiological effects: initial increase in testosterone level, followed by almost complete suppression of testosterone. These effects, which were observed very frequently, included hot flushes, facial, flushing (particularly at the start treatment), impotence and decreased libido.~~

~~The following undesirable effects, for which a causal connection with the treatment was at least considered possible have been reported, although a causal connection is often difficult to determine in patients with metastatic cancer.~~

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 beestimated from the available data).

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare ~~or very rare~~***	***Additional post-marketing Frequency not known~~Unknown~~***
Infections and infestations		~~Urinary tract infections~~		Nasopharyngitis	
Neoplasms		Temporary tumour flare			
Blood and lymphatic system disorders			Thrombocytosis ~~anaemia~~	~~lymphadenopathy~~	
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 ~~or very rare~~*	*Additional post-marketing Frequency not known~~Unknown~~*
Immune system disorders		Hypersensitivity	~~Hypersensitivity reactions (see also Section 4.4)~~	Anaphylactic reaction	Anaphylactic shock
Endocrine disorders	~~reduced size of genitalia (12.2%)~~				Pituitary apoplexy**
Metabolism and nutrition disorders		~~Anorexia, elevated alkaline phosphatase, hyperuricaemia~~	Anorexia Diabetes mellitus Gout Hyperlipidaemia Increased appetite ~~Hyperglycaemia, elevated urea nitrogen, , elevated blood urea nitrogen not originating from proteins, weight gain~~		
Psychiatric disorders	Libido decreased	Loss of libido Depression* Mood changes*~~decreased libido, depression~~	Insomnia Irritability~~Nervousness, amnesia, euphoria~~	Confusional state Decreased activity Euphoric mood	Anxiety
Nervous system disorders	Paraesthesia in lower limbs	Dizziness Headache ~~bouts of severe insomnia~~	Paraesthesia~~somnolence, loss of consciousness~~	Memory impairment ~~migraine dysgeusia, spinal cord compression, hypoaesthesia, convulsion~~	
Eye disorders		~~eye pain, conjunctivitis~~	Visual impairment	Abnormal sensation in eye ~~Abnormal vision,~~ visual ~~field~~ disturbance, ~~papilloedema~~	
Ear and labyrinth disorders			Tinnitus Vertigo		
~~Cardio~~vascular disorders	Hot flash	Hypertension	~~Hypotension deep vein thrombosis,~~	Hypotension ~~myocardial ischemia~~	

System Organ Class	*Very Common*	*Common*	*Uncommon*	*Rare ~~or very rare~~*	*Additional post-marketing Frequency not known~~Unknown~~*
			~~pulmonary embolism~~		
Respiratory tract		~~cough, dyspnea, pharyngitis~~	Dyspnoea Epistaxis ~~Rhinitis~~	Orthopnoea	
Gastrointestinal disorders		Dry mouth Nausea ~~abdominal pain, constipation diarrhoea, dyspepsia~~	Abdominal pain Constipation Diarrhoea Vomiting ~~tenesmus, gastro-oesophageal reflux~~	Abdominal distension Dysgeusia Flatulence	
~~Hepatobiliary disorders~~		~~abnormal liver function~~	~~cholestatic hepatitis~~		
Skin and subcutaneous tissue disorders	Hyperhidrosis	~~Rash~~	Acne Alopecia Erythema Pruritus Rash Urticaria~~Increased sweating, Alopecia, pruritus ani, eczema, bullous eruption~~	Blister Purpura ~~urticaria, photosensitivity reactions~~	Angioneurotic oedema
Musculoskeletal and connective Tissue disorders	Back pain ~~Bone pain (25.8%)~~	Musculoskeletal pain Pain in extremity~~Back pain leg pain, arthralgia, myalgia muscle cramp in the lower limbs,~~	Arthralgia Bone pain Muscle cramp Muscular weakness Myalgia ~~Osteoarthritis Muscle weakness~~	Joint stiffness Joint swelling Musculoskeletal stiffness Osteoarthritis ~~pathological fractures~~	
Renal and urinary disorders		~~Dysuria, urinary retention~~	Nocturia Urinary retention ~~Frequent micturition, urethral disorders, urinary incontinence, kidney pain, hematuria, abnormal renal function~~		Urinary incontinence

System Organ Class	*Very Common*	*Common*	*Uncommon*	*Rare ~~or very rare~~*	*Additional post-marketing Frequency not known~~Unknown~~*
Reproductive system and breasts	Erectile dysfunction (including ejaculation failure, ejaculation disorder)	Pelvic plain ~~Impotence~~ ~~Gynecomastia~~ ~~Breast pain~~	Gynaecomastia Breast pain Testicular atrophy Testicular pain~~functional disorders of the prostate or testicles mastitis~~		
General disorders and administration site conditions	Asthenia~~Hot flushes (70.4%)~~	Injection site reaction (including erythema inflammation and pain) Oedema~~Pain, fatigue, chest pain, asthenia, peripheral oedema, pain at the injections site~~	Lethargy Oedema peripheralPain Rigors Somnolence ~~malaise, aggravation of postoperative problems, inflammation and other reactions at the injection site~~	Chest pain Dysstasia Influenza like illness Pyrexia ~~perineal pain~~	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.

~~Rare cases of pituitary apoplexy have been described during post marketing phase (see Section 4.4)~~

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	
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		
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 ~~triptorelin~~ 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.

~~occur, even at elevated doses of triptorelin. Any overdosage should be treated symptomatically.~~

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Hormones and related agents, gonadotropin releasing hormone analogues.

ATC code: L02AE04

Mechanism ~~**Mode**~~ **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 administration of 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 to deliver 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.

~~Replacing the amino acid glycine by D-tryptophan at position 6 of gonadorelin produces an agonist with a more powerful biological activity than the naturally occurring gonadotropin - releasing hormone (GnRH, LH-RH). This enhanced effect may be attributable to an increased affinity for the pituitary receptors and to slower inactivation in the target tissues.~~

~~Pharmacodynamics~~

~~After single-dose or intermittent administration, LH-RH stimulates the release of LH and FSH from the pituitary. With continuous administration however, as is the case with the delayed release that occurs after injection of Decapeptyl Depot~~Decapeptyl depot~~, a "paradoxical" effect is observed: plasma levels of LH, FSH, testosterone and oestrogen/progesterone fall to castration level within about 2-4 weeks following a transient increase at the start of the treatment.~~

~~The derivatives triptorelin pamoate and triptorelin acetate are equivalent in respect of their pharmacodynamics and toxicity and are interchangeable.~~

Clinical efficacy

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.

~~Decapeptyl Depot~~Decapeptyl depot ~~22. 5mg was investigated in South Africa in a open-label, uncontrolled clinical trial involving 120 patients with advanced prostate cancer, 64% of whom were Caucasian, 23% black and 13% of other ethnic origins. The men were aged between 51 and 96 years (average age 71 years). These patients received either Decapeptyl Depot~~Decapeptyl depot ~~22.5mg (n=120) every 168 days, with a total of 2 doses (max treatment period: 336 days). The primary efficacy criteria were the achievement of castration level after 29 days and its maintenance from the 57~~th ~~to the 337~~rd ~~day.~~

~~117 of the 120 patients treated with Decapeptyl Depot~~Decapeptyl depot ~~22.5mg (97.5%) had achieved serum testosterone levels equivalent to castration level (≤1.735 nmol/l) by day 29.~~

~~93% of the patients treated with Decapeptyl Depot~~Decapeptyl depot ~~22.5 mg maintained serum testosterone levels equivalent to castration level from day 57 to day 337.~~

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:

~~Decapeptyl Depot~~Decapeptyl depot ~~22. 5mg.~~ *Following ~~the administration of~~ a single IM injection of Decapeptyl Depot 22. 5mg ~~to~~ in patients with prostate cancer, ~~the mean~~ t_{max} was 3 (2-12) hours and C_{max} (0-169 days) was ~~40~~39.~~0~~ 9 (~~22~~19.~~21~~-~~76~~107.~~80~~)ng/ml.*

Triptorelin did not accumulate over 12 months of treatment.

~~No clinically significant accumulation was observed following the second injection.~~

Distribution:

Results of pharmacokinetic investigations conducted in healthy men indicate that ~~After~~ after intravenous bolus administration, triptorelin is distributed and eliminated according to a 3-compartment model; and corresponding~~with~~ 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.

~~The steady state volume of distribution is approximately 30 l.~~

~~Triptorelin does not bind to plasma proteins at clinically relevant concentrations.~~

Biotransformation:

~~*Metabolism:*~~

~~No~~ metabolites of triptorelin ~~has~~ 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 ~~and definitively destroyed~~ in plasma, or cleared by the kidneys.

~~*Biotransformation:*~~

~~Metabolites of triptorelin have not been determined in humans. However, human pharmacokinetic data suggest that C-terminal fragments produced by tissue degradation are either completely degraded 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 ~~unmetabolised~~ triptorelin.

which increased to 62 % in subjects with hepatic impairment. Since creatinine clearance (Clcreat) 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.

~~Total triptorelin clearance is about 200 ml/min, and its terminal half-life is 2.8 hours.~~

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.

~~*Kinetics in special populations:*~~

~~*Age*: The influence of age on triptorelin pharmacokinetics has not been systematically studied. However, pharmacokinetic data obtained in young healthy male volunteers aged between 20 and 22, and with an elevated creatinine clearance (approx..150 ml/min) indicate that triptorelin is eliminated twice as fast in the young. This is attributable to the fact that creatinine clearance decrease with age.~~

~~*Renal function*: Impaired renal function leads to a delay in triptorelin elimination. The half-life was 6.7 hours in patinets with moderate renal insufficiency (mean creatinine clearance of 40 ml/min) and 7.8 hours in patients with severe renal insufficiency (mean creatinine clearance of 8.9 ml/min).~~

~~*Hepatic function*: The half-life of triptorelin in patients with impaired hepatic function was 7.65 hours. The portion of unmetabolised triptorelin excreted in urine increased to 62% in these patients, indicating that the liver plays an important role in eliminating triptorelin.~~

~~*Ethnicity*. The influence of race on triptorelin pharmacokinetics have not been studied.~~

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 shownby 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 of triptorelin. 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 ~~acute~~ toxicity of triptorelin towards extragenital organs is ~~very~~ low. The observed effects were mainly ~~are essentially~~ 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, ~~and~~ dogs and monkeys~~when administered at clinically relevant doses~~. These were considered as a reaction to~~effects are believed to reflect~~ the suppressed gonadal function caused by the pharmacological activity of the active ingredient. The changes~~lesions~~ were partly reversed during recovery phase.

After subcutaneous administration of 10 µg/kg to rats on days 6 to 15 of gestation ~~(compared to clinical dose of 3.75mg every 4 weeks in humans)~~, triptorelin did not elicit any embryotoxic, teratogenic, or anyother~~foetotoxic~~ 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*.

~~When administered to~~In mice, ~~triptorelin did not show any~~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.

~~At the dose equivalent to 8 times the recommended human therapeutic dose (based on body surface area), animal studies showed adverse effects on organogenesis in rats (maternal toxicity and embryotoxicity). Isolated cases of hydroureter have been observed in young rats exposed in utero to high doses of trptorelin.~~

~~In the context of medically assisted procreation, triptorelin has often been used in controlled studies to suppress endogenous gonadotropins and oestrogens.~~

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

	~~**Decapeptyl Depot 22.5 mg**~~
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 ~~3.75mg/11.25mg/~~22.5 mg triptorelin ~~(respectivelly)~~,

1 ampoule with solvent containing 2 ml water for injection.

1 syringe and 2 needles **.**

6.6. Special precautions for disposal and other handling

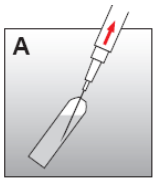
The suspension for injection should be prepared immediatelly before use.

1. Preparation for injection.

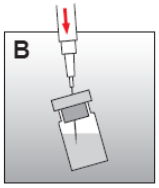
Two needles are provided in the box:

- The reconstitution needle
- The injection needle

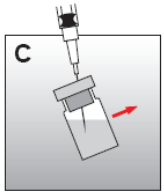
- Tap any solution that may be present in the tip of the ampoule back into the main reservoir of the solvent ampoule.
- Screw the reconstitution needle onto the syringe (do not remove the needle guard at this point!)
- Break open the solvent ampoule (breakpoint facing your body).
- Remove the needle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

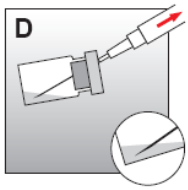


- Pull up the needle to above the level of the liquid and gently swirl the vial to produce a homogeneous, milky suspension for injection (Fig.C). Make sure there is no powder left in the vial, and if nessesary, continue swirling the vial until the powder has completely disappeared. N.B.: Do not mix the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

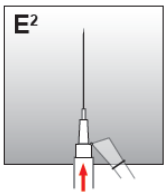


- Then draw up all of the suspension for injection into the syringe (Fig. D).

- 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).



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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 3800, Israel.

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

This leaflet was revised in February 2022 according to MOH guidelines.
~~*The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in august 2017*~~