SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Decapeptyl Depot 11.25 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Decapeptyl Depot 11.25 mg. Each vial of *Decapeptyl Depot 11.25 mg* contains triptorelin embonate equivalent to 11.25 mg triptorelin. After reconstitution in 2 ml solvent, 1 ml of reconstituted suspension contains 5.625 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 11.25 mg is indicated for lowering of sexual hormones; treatment of advanced hormone-dependent prostate cancer

4.2 Posology and method of administration

Posology

The usual dosage is one intramuscular injection of *Decapeptyl Depot 11.25mg* every 12 weeks as under medical supervision.

Drug 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). Testosterone levels can be measured immediately before or after injection.

Patients with impaired hepatic function

No dosage adjustment is necessary for patients suffering from limited hepatic function.

Patients with impaired renal function

No dosage adjustment is necessary for patients suffering from limited renal function.

Elderly patients

No dosage adjustment is necessary.

Children and adolescents

The safety and efficacy of Decapeptyl Depot 11.25 mg have not been established in children and adolescents, it is not indicated for use in these populations.

Mode of administration

Since Decapeptyl Depot 11.25 mg is a suspension of microgranules, inadvertent intravascular injection must be strictly avoided.

Decapeptyl Depot 11.25mg may only be administered by doctors or medical personnel.

The injection site should be changed periodically.

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

4.3 Contraindications

Hypersensitivity to GnRH, its analogues or to any of the excipients listed in section 6.1 (see also section 4.8).

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).

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.

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 weeks of treatment, particularly in patients suffering from vertebral metastases, at the risk of spinal cord compression, and in patients with urinary tract obstruction.

After surgical castration triptorelin does not induce any further decrease in serum testosterone levels. 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 3 months (twelve 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 11.25 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 risk for metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.

Caution is required with intramuscular injection in patients treated with anticoagulants, due to the potential risk of haematomas at the site of injection.

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

Due to androgen deprivation, treatment with analogues of the GnRH can increase the risk of anaemia. This risk should be assessed in treated patients and monitored appropriately.

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. that it is essentially "sodium-free".

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 11.25 mg with medicinal products known to prolong the QT interval or medicinalproducts 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

Decapeptyl depot 11.25mg is not indicated for use in women.

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

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

Since patients suffering from locally advanced or metastatic, hormone-dependent prostate cancer are 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 causality is 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 treatment were reported. Most of these events are known to be related to biochemical or surgical castration.

The frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100, <1/10); 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 notknown*
Infections and infestations				nasopharyngitis	
Investigations		weight increase	alanine aminotransferase increased, aspartate - aminotransferase increased, blood creatinine increased, blood pressureincreased, blood urea increased, gamma-glutamyl transferase increased, weight decreased	blood alkaline phosphatase increased	
Blood and lymphatic system disorders			thrombocytosis		anaemia
Cardiac disorders			palpitations		QT prolongation* (see sections 4.4 and 4.5)
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 the eye, visual disturbances	
Ear and labyrinth disorders			Tinnitus, vertigo		
vascular disorders	hot flash	hypertension		hypotension	
Respiratory thoracic and mediastinal disorders			dyspnoea epistaxis	orthopnoea	

System Organ Class	*Very Common*	*Common*	*Uncommon*	*Rare*	*Additional post-marketing Frequency notknown*
Gastro-intestinal 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 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
Reproductive system and breasts disorders	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.

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.

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

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 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 tract will be evident with higher doses of Decapeptyl depot 11.25 mg. If overdose occurs, symptomatic management is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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. In males, 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), and testosterone.

However, chronic and continuous administration of triptorelin results in decreased LH and FSH secretion and suppression of testicular and ovarian steroidogenesis. A reduction of serum testosterone levels into the range normally seen in surgically castrated men occurs approximately2 to 4 weeks after initiation of therapy. This results in accessory sexual organ atrophy. These effects are generally reversible upon discontinuation of the medicinal product. In animals, administration of triptorelin resulted in the inhibition of growth of some hormone-sensitive prostate tumours in experimental models.

Clinical efficacy and safety

Administration of Decapeptyl depot 11.25 mg to patients with advanced prostate cancer as an intramuscular injection for a total of 3 doses (9 months) resulted in both achievement of castration levels of testosterone in 97.6% and 92.5% of patients receiving 3-month and 1-month formulations respectively, after four weeks and maintenance of castration levels of testosterone from month 2 through month 9 of treatment.

5.2. Pharmacokinetic properties

Absorption:

Following the administration of a single IM injection of Decapeptyl Depot 11.25mg to patients with prostate cancer, the mean t_{max} was 2 (2-6) hours and C_{max} was 37.1 (22.4-57.4) ng/ml.

Triptorelin did not accumulate over 9 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, medicinalproduct 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 destruction are either completely degraded within tissues or are rapidly and completely 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 as 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 renalelimination.

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 clearance is 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 11.25 mg is a sustainedrelease formulation, no dose adjustment is recommended in patients with renal or hepatic impairment.

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 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 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 microscopicchanges in the reproductive organs of male rats, dogs and monkeys. These were considered as a reaction to suppressed gonadal function caused by the pharmacological activity of the compound.The changes were partly reversed during recovery

After subcutaneous administration of 10 µg/kg to rats on days 6 to 15 of gestation, triptorelin did not elicit any embryotoxic, teratogenic or any other 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.

Mutagenicity. 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 GnRH 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), 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 11.25mg triptorelin,

1 ampoule containing 2 ml of solvent.

1 syringe and 2 needles **.**

6.6. Special precautions for disposal and other handling

1

The suspension for injection should be prepared immediatelly before use.

1. PREPARATION OF THE PATIENT BEFORE RECONSTITUTION

Prepare the patient by disinfecting his gluteus at the injection site. This operation needs to be performed first because once reconstituted, the drug should be injected immediately.

2. **PREPARATION OF THE INJECTION**.

Two needles are provided in the box:

- The reconstitution needle

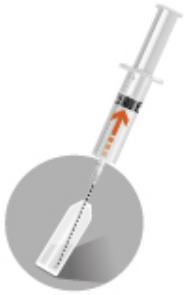
- The injection needle

The presence of bubbles on top of the lyophilisate is a normal appearance of the product.
The following steps must be completed in a continuous sequence.

2a

- Take out the ampoule containing the solvent. Tap any solution within the tip of the ampoule back to the main body of the ampoule.
- Screw the reconstitution needle onto the syringe (do not remove the needle cover at this point!)
- Break open the solvent ampoule with dot face up.
    - Remove the needle cover from the reconstitution needle.

Insert the needle in the ampoule and draw up all the solvent into the syringe.



- Put aside the syringe containing the solvent.

2b

- 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.
    - Take back the syringe containing the solvent again and insert the needle thorogh the rubber stopper vertically into the vial. Inject the solvent slowly so that it
    - if possible, it washes down the entire upper part of the vial.

2c

- Pull up the needle to above the liquid level. a
- Do not remove the needle from the vial. Reconstitute the suspension by swirling gently from side to side. Do not invert the vial.

- Make sure that the agitation is long enough (at least 30 seconds) to obtain an homogeneous and milky suspension.

- **Important: Check there is no unsuspended powder in the vial (if any powder clumps are present, continue swirling until they disappear)**

2d

- When the suspension is homogeneous, pull down the needle without inverting the vial, draw up all of the suspension. A small amount will remain in the vial and should be discarded. An overfill is included to allow for this loss.

- Remove the needle used for the reconstitution from the syringe. Screw on to the syringe needle for injections.
- Prime the needle to remove air from the syringe and inject immediately.

3. **INTRAMUSCULAR INJECTION**

- To avoid sedimentation, inject immediately into the disinfected area as quickly as possible (within 1 minute from reconstitution).

4. **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: DEBIOPHARM RESEARCH & MANUFACTURING S.A, SWITZERLAND

8. Name of registration holder:

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

9. Registration number: 135-83-31300

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