SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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 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

Decapeptyl 22.5 mg. The usual dosage is one intramuscular injection of Decapeptyl Depot 22. 50mg every 24 weeks under medical supervision.

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

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.

4.3 Contraindications

Hypersensitivity to LH-RH, triptorelin, other GnRH analogues or any of the excipients (see paragraph 6.1).
If the tumor is not hormone-dependent or after surgical castration.
In patients with spinal cord compression caused by metastases of their prostate cancer.

4.4 Special warnings and precautions for use

*Allergic reactions***:** Allergic reactions have been observed in rare cases shortly after the injection of 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 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 3.75mg, 12 weeks for Decapeptyl Depot 11.25 mg and 24 weeks for 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.

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.

Effects on diagnostic methods

At therapeutic doses, triptorelin 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 LH-RH agonists may therefore be 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 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, and monitoring of the patient's hormonal status is recommended.
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

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

4.7 Effects on ability to drive and use machines

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 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), unknown (the exact frequency cannot be indicated because it is based

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare or very rare***	***Unknown***
Infections		Urinary tract infections			
Neoplasms		Temporary tumour flare			
Blood and lymphatic system disorders			anaemia	lymphadenopathy	
Immune system disorders			Hypersensitivity reactions		

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare or very rare***	***Unknown***
			(see also Section 4.4)		
Endocrine disorders	reduced size of genitalia (12.2%)				
Metabolism and nutrition disorders		Anorexia, elevated alkaline phosphatase, hyperuricaemia	Hyperglycaemia, elevated urea nitrogen, diabetes meilitus, elevated blood urea nitrogen not originating from proteins, weight gain		
Psychiatric disorders		mood changes, decreased libido, depression	Nervousness, amnesia, euphoria		
Nervous system disorders		headache, bouts of severe dizziness, insomnia	praesthesia somnolence, loss of consciousness	migraine dysgeusia, spinal cord compression, hypoaesthesia, convulsion	
Eye disorders		eye pain, conjunctivitis		Abnormal vision, vsual field disturbance, papilloedema	
Ear			Tinnitus		
Cardiovascular disorders		Hypertension	Hypotension deep vein thrombosis, pulmonary embolism	myocardial ischemia	
Respiratory tract		cough, dyspnea, pharyngitis	Rhinitis		

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare or very rare***	***Unknown***
Gastrointestinal disorders		abdominal pain, nausea, constipation diarrhoea, dyspepsia	Vomiting tenesmus, gastro-oesophageal reflux		
Hepatobiliary disorders		abnormal liver function	cholestatic hepatitis		
Skin and subcutaneous tissue disorders		Rash	Increased sweating, Alopecia, pruritus ani, eczema, bullous eruption	urticaria, photosensitivity reactions	
Musculoskeletal disorders	Bone pain (25.8%)	Back pain leg pain, arthralgia, myalgia muscle cramp in the lower limbs,	Osteoarthritis Muscle weakness	pathological fractures	
Renal and urinary disorders		Dysuria, urinary retention	Frequent micturition, nocturia, urethral disorders, urinary incontinence, kidney pain, hematuria, abnormal renal function		
Reproductive system and breasts		Impotence Gynecomastia Breast pain	functional disorders of the prostate or testicles mastitis		
General disorders and administration site conditions	Hot flushes (70.4%)	Pain, fatigue, chest pain, asthenia, peripheral oedema, pain at	malaise, aggravation of postoperative problems, inflammation and other	perineal pain	

System Organ Class	*Very Common*	*Common*	*Uncommon*	*Rare or very rare*	*Unknown*
		the injections site	reactions at the injection site		

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

System Organ Class	*Very Common Treatment related AEs*	*Common Treatment related AEs*	*Uncommon Treatment related AEs*	*Additional Post-marketing Frequency unknown*
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

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. Animal tests suggest that no effect other than the intended therapeutic effects on sex hormone concentration and on the reproductive system will 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

Mode of action

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, 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

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 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 57th to the 337rd day.

117 of the 120 patients treated with 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 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 22. 5mg. Following the administration of a single IM injection of Decapeptyl Depot 22. 5mg to patients with prostate cancer, the mean t_{max} was 3 (2-12) hours and C_{max} (0-169 days) was 40.0 (22.2-76.8)ng/ml. No clinically significant accumulation was observed following the second injection.

Distribution:

After intravenous bolus administration, triptorelin is distributed according to a 3-compartment model; with half-lives are approximately 6 minutes, 45 minutes, and 3 hours. The steady state volume of distribution is approximately 30 l.

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

Metabolism:

No metabolites of triptorelin has not been determined in humans. However, human pharmacokinetic data show that C-terminal fragments produced by tissue degradation are either completely destroyed within tissues, rapidly and definitively destroyed in plasma, or cleared by the kidneys.

Elimination:

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

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

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.

5.3 Preclinical safety data

The acute toxicity of triptorelin is very low. The observed effects are essentially related to the exacerbation of the pharmacological effects of triptorelin.

In chronic toxicity studies, triptorelin induced macro- and microscopic changes in the reproductive organs of male rats and dogs when administered at clinically relevant doses. These effects are believed to reflect the suppressed gonadal function caused by the pharmacological activity of the active ingredient. The 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 foetotoxic effects. 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 mice, triptorelin did not show any oncogenic effect 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

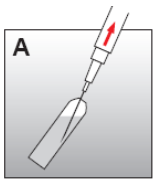
The suspension for injection should be prepared immediatelly before use.

Preparation for injection.

Two needles are provided in the box:

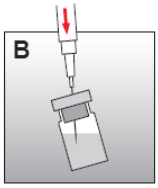
- The reconstitution needle
- The injection needle

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

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Injection

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

After use

- Dispose the needle 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

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