Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Decapeptyl 6-month 22.5 mg Powder and solvent for prolonged-release suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains triptorelin pamoate equivalent to 22.5 mg triptorelin.
After reconstitution in 2mL solvent, 1 mL of reconstituted suspension contains 11.25mg of triptorelin.
Contains sodium but less than 1mmol (23mg) sodium per vial.
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection
Powder: White to off-white powder.
Solvent: Clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Decapeptyl 6-month is indicated for the treatment of locally advanced or metastatic, hormone-dependent prostate cancer.
Decapeptyl 6-month is indicated for the treatment of central precocious puberty (CPP) in children 2 years and older (with an onset of CPP before 8 years in girls and 10 years in boys).

4.2 Posology and method of administration

Posology
The recommended dose of Decapeptyl 6-month is 22.5 mg of triptorelin (1 vial) administered every six months (twenty four weeks) as a single intramuscular injection.
In patients with metastatic castration resistant prostate cancer not surgically castrated receiving triptorelin and eligible for treatment with androgen biosynthesis inhibitors, treatment with triptorelin needs to be continued.

Patients with renal or hepatic impairment
No dosage adjustment is necessary for patients with renal or hepatic impairment.

Paediatric population
Central precocious puberty (before 8 years in girls and 10 years in boys)
The treatment of children with Decapeptyl 6-month 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.

Method of administration
As with other medicinal products administered by injection, the injection site should be varied periodically.
Once reconstituted, the suspension of Decapeptyl 6-month should be intramuscularly injected relatively rapidly and uninterrupted manner in order to avoid any potential blockage of the needle.
Precautions to be taken before handling or administering the medicinal product
Decapeptyl 6-month is only intended for intramuscular use
Since Decapeptyl 6-month is a suspension of microparticles, inadvertent intravascular injection must be strictly avoided.
Decapeptyl 6-month must be administered under the supervision of a physician.
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

Triptorelin is contraindicated during pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

The product should only be used under the supervision of an appropriate specialist having requisite facilities for regular monitoring of response.
The use of GnRH agonists may cause a reduction in bone mineral density. In men, preliminary data suggest that the use of a bisphosphonate in combination with a GnRH agonist may reduce bone mineral loss. No specific data is available for patients with established osteoporosis or with risk factors for osteoporosis (e.g. chronic alcohol abuse, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anti-convulsants or corticosteroids, family history of osteoporosis, malnutrition, e.g. anorexia nervosa). Particular caution is therefore necessary since reduction in bone mineral density is likely to be more detrimental in these patients. Treatment with Decapeptyl 6-month should be considered on an individual basis and only be initiated if the benefits of treatment outweigh the risk following a very careful appraisal. Consideration should be given to additional measures in order to counteract loss of bone mineral density.
Adjustment of antihypertensive therapy may be required in patients receiving such medication.
Rarely, treatment with GnRH agonists may reveal the presence of a previously unknown gonadotroph cell pituitary adenoma. These patients may present with a pituitary apoplexy characterised by sudden headache, vomiting, visual impairment and ophthalmoplegia.
There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as triptorelin. Patients should be informed accordingly and treated as appropriate if symptoms occur. 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 6-month has been established via intramuscular route only. The subcutaneous administration route is not recommended.
This medicine contains less than 1 mmol (23 mg) sodium per dose i.e. it is essentially 'sodum free'.

Prostate cancer
Initially, triptorelin, like other GnRH agonists, causes a transient increase in serum testosterone levels. As a consequence, isolated cases of transient worsening of signs and symptoms of prostate cancer may occasionally develop during the first weeks of treatment. During the initial phase of treatment, consideration should be given to the additional administration of a suitable anti-androgen to counteract the initial rise in serum testosterone levels and the worsening of clinical symptoms.
A small number of patients may experience a temporary worsening of signs and symptoms of their prostate cancer (tumour flare) and 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 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 the 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 6 months (twenty four weeks).
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 ratio including the potential for Torsade de pointes prior to initiating Decapeptyl 6-month.
In addition, from epidemiological data, it has been observed that patients may experience metabolic changes (e.g. glucose intolerance, fatty liver) and 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 of metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.
Increased lymphocyte count has been reported with patients undergoing GnRH agonist treatment. This secondary lymphocytosis is apparently related to GnRH induced castration and seems to indicate that gonadal hormones are involved in thymic involution.

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.

Central 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 6-month should be administered as precisely as possible in regular 6 monthly periods. An exceptional delay of the injection date for a few days (169 ± 3 days) does not influence the results of the therapy.
After discontinuation of treatment, the development of puberty characteristics will occur.
Information with regards to future fertility is still limited but future reproductive function and fertility appears to be unaffected by GnRH treatment. In most girls, regular menses will start on average one year after ending the therapy.
Bone mineral density may decrease during GnRH agonist therapy for central precocious puberty due to the expected effects of oestrogen suppression. However, after cessation of treatment subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected by treatment.
Slipped capital femoral epiphysis can be seen after withdrawal of GnRH agonist treatment. The suggested theory is that the low concentrations of oestrogen during treatment with GnRH agonists weaken the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.
Idiopathic intracranial hypertension
Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in paediatric patients receiving triptorelin. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, vision disturbances and tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of triptorelin should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

When triptorelin is co-administered with drugs affecting pituitary secretion of gonadotropins, caution should be exercised 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 6-month with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade 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 Fertility, pregnancy and lactation

Pregnancy
Decapeptyl 6-month is indicated for adult men and children. There are very limited data on the use of triptorelin in pregnant women.

It should be confirmed that the patient is not pregnant before prescription of Decapeptyl 6-month.
Triptorelin must not be used during pregnancy since concurrent use of GnRH agonists is associated with a theoretical risk of abortion or fetal abnormality. Prior to treatment, potential fertile 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 6-month is not indicated in lactating women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, the ability to drive and use machines may be impaired should the patient experience dizziness, somnolence and visual disturbances being possible undesirable effects of treatment, or resulting from the underlying disease.

4.8 Undesirable effects

General tolerance in Men (see section 4.4)
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 (≥1/10 000, < 1/1000); not known (cannot be estimated from the available data).

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare***	***Additional post-marketing Frequency not known***
Infections and infestations	**1.**			Nasopharyngitis	
Blood and lymphatic system disorders	**2.**		Thrombocytosis		
Immune system disorders	**3.**	Hypersensitivity		Anaphylactic reaction	Anaphylactic shock
Endocrine disorders	**4.**				Pituitary apoplexy**
Metabolism and nutrition disorders	**5.**		Anorexia Diabetes mellitus Gout Hyperlipidaemia Increased appetite		
Psychiatric disorders	Libido decreased **6.**	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	**7.**		Visual impairment	Abnormal sensation in eye Visual disturbance	
Ear and labyrinth disorders	**8.**		Tinnitus Vertigo		
Cardiac disorders	**9.**		Palpitations		QT prolongation* (see sections 4.4 and 4.5)
Vascular disorders	Hot flush	Hypertension		Hypotension	
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis	Orthopnoea	
Gastrointestinal disorders		Dry mouth	Abdominal pain	Abdominal	

		Nausea	Constipation Diarrhoea Vomiting	distension Dysgeusia Flatulence	
General disorders and administration site conditions	Asthenia	Injection site reaction (including erythema inflammation and pain) Oedema	Lethargy Oedema peripheral Pain Rigours Somnolence	Chest pain Dysstasia Influenza-like illness Pyrexia	Malaise
Skin and subcutaneous tissue disorders	Hyperhidrosis		Acne Alopecia Erythema Pruritus Rash Urticaria	Blister Purpura	Angioneurotic oedema
Musculoskeletal and connective tissue disorders	Back pain	Musculoskeletal pain Pain in extremity	Arthralgia Bone pain Muscle cramp Muscular weakness Myalgia	Joint stiffness Joint swelling Musculoskeletal stiffness Osteoarthritis	
Renal and urinary disorders			Nocturia Urinary retention		Urinary incontinence
Reproductive system and breast disorders	Erectile dysfunction (including ejaculation failure, ejaculation disorder)	Pelvic pain	Gynaecomastia Breast pain Testicular atrophy Testicular pain		
Investigations		Weight increased	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	

* 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/or 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.

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); not known (cannot be estimated from the available data).

System Organ Class	***Very Common Treatment related AEs***	***Common Treatment related AEs***	***Uncommon Treatment related AEs***	***Additional post-marketing Frequency not known***
Immune system disorders		Hypersensitivity		Anaphylactic shock
Metabolism and nutrition disorders			Obesity	
Psychiatric disorders			Mood altered	Lability affected Depression Nervousness
Nervous system disorders		Headache		Idiopathic intracranial hypertension (pseudotumor cerebri) (see section4.4)
Eye disorders			Visual impairment	Visual disturbance
Vascular disorders		Hot flush		Hypertension
Respiratory, thoracic and mediastinal disorders			Epistaxis	
Gastrointestinal disorders		Abdominal pain	Vomiting Constipation Nausea	
Skin and subcutaneous tissue disorders		Acne	Pruritus Rash Urticaria	Angioneurotic oedema
Musculoskeletal and connective tissue disorders			Neck pain	Myalgia
Reproductive system and breast disorders	Vaginal bleeding (including vaginal haemorrhage, withdrawal bleeding, uterine haemorrhage, vaginal discharge, vaginal bleeding including spotting)		Breast pain	
General disorders and		Injection site reaction	Malaise	

administration site conditions		(including injection site pain, injection site erythema and injection site inflammation)		
Investigations		Weight increased		Blood pressure increased Blood prolactin increased

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

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance: Website: www.hpra.ie.

4.9 Overdose

The pharmaceutical properties of Decapeptyl 6-month and its mode of administration make accidental or intentional overdose unlikely. There is no experience of overdose from clinical trials. 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 6-month. If overdose occurs, this should be managed symptomatically.

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 Gonadotropin 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 6-month isdesigned 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 as long 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 clinical trial programme, there was a 97% median relative reduction in PSA at Month 6 for Decapeptyl 6-month.
In animals, administration of triptorelin resulted in the inhibition of growth of some hormone-sensitive prostate tumours in experimental models.

Clinical efficacy in prostate cancer

Administration of Decapeptyl 6-month 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 (Week 48) of treatment.
In patients with metastatic castration-resistant prostate cancer, clinical studies have shown the benefit from the addition of androgen biosynthesis inhibitors, such as abiraterone acetate to GnRH analogues, such as triptorelin.

Clinical efficacy and safety in children with central 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 6-month over 12 months (48 weeks). Suppression of stimulated LH concentrations to prepubertal levels was achieved in 95.5% of subjects by month 3, and in 93.2 % and 97.7% of subjects at months 6 and 12, respectively.
The consequence is a regression or stabilisation of secondary sex characteristics and slowing down of accelerated bone maturation and growth.
In girls, initial ovarian stimulation at treatment initiation, followed by the treatment-induced oestrogen increase, may lead, in the first month, to uterine 'withdrawal' bleeding of mild or moderate intensity.

5.2 Pharmacokinetic properties

Absorption:
Following a single intramuscular injection of Decapeptyl 6-month in patients with prostate cancer, t_{max} was 3 (2-12) hours and C_{max} (0-169 days) was 40.0 (22.2-76.8) ng/mL.
In children with precocious puberty $t_{max}$was 4 (2-8) hours and C_{max}(0-169 days) was 39.9 (19.1-107.0) ng/ml.
Triptorelin did not accumulate over 12 months of treatment.
Distribution:
Results of pharmacokinetic investigations conducted in healthy men indicate that after intravenous bolus administration, triptorelin is distributed and eliminated according to a 3-compartment model and corresponding half-lives are approximately 6 minutes, 45 minutes, and 3 hours.
The volume of distribution at steady state of triptorelin following intravenous administration of 0.5mg triptorelin acetate is approximately 30L in healthy male volunteers. Since there is no evidence that triptorelin at clinically relevant concentrations binds to plasma proteins, medicinal productinteractions involving binding-site displacement are unlikely.
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 the kidneys. Following intravenous administration of 0.5mg triptorelin to healthy male volunteers, 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 150mL/min and only 90mL/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 212mL/min, the latter being dependent on a combination of hepatic and renal elimination.
Other special populations:
Following intravenous administration of 0.5mg triptorelin to subjects with moderate renal insufficiency (Cl_{creat} 40mL/min), triptorelin had an elimination half-life of 6.7 hours, 7.81 hours in subjects with severe renal insufficiency (Cl_{creat} 8.9mL/min) and 7.65 hours in patients with impaired hepatic function (Cl_{creat} 89.9mL/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 6-month is a sustained release 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 microscopic changes 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 10µg/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 100µg/kg, a reduction in maternal weight gain and an increased number of resorptions were observed.

Triptorelin is not mutagenic *in vitro* or *in vivo*. In mice, no oncogenic effect has been shown with triptorelin at doses up to 6000µg/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

4 years.
Use immediately after reconstitution.

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

Powder vial: 6 mL septum transparent light brown vial (type I glass) with bromobutyl stopper and aluminium cap with dark green flip-off cover.
Solvent ampoule: transparent, colourless ampoule (type I glass) containing 2 mL of sterile solvent for suspension.

Box of:
1 vial, 1 ampoule and 1 blister containing 1 injection syringe and 2 injection needles.

6.6 Special precautions for disposal and other handling

The suspension for injection must be reconstituted using an aseptic technique and only using the ampoule of solvent for injection.
The instructions for reconstitution hereafter and in the leaflet must be strictly followed.
The solvent should be drawn into the syringe provided using the reconstitution needle (20 G, without safety device) and transferred to the vial containing the powder. The suspension should be reconstituted by swirling the vial gently from side to side for long enough until a homogeneous, milky suspension is formed. Do not invert the vial.
It is important to check there is no unsuspended powder in the vial. The suspension obtained should then be drawn back into the syringe, without inverting the vial. The reconstitution needle should then be changed and the injection needle (20 G, with safety device) used to administer the product.
As the product is a suspension, the injection should be administered immediately after reconstitution to prevent precipitation.
For single use only.
Used needles, any unused medicinal product or suspension or other waste materials should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Ipsen Pharmaceuticals Limited
Blanchardstown Industrial Park
Blanchardstown
Dublin 15
Ireland

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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