Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Decapeptyl 3-month, 11.25 mgPowder and solvent for suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains the quantity of triptorelin (as triptorelin pamoate) to ensure that the minimum triptorelin quantity injected is 11.25mg.

Excipients:
Sodium < 1 mmol (23 mg)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for suspension for injection:
Sightly yellow lyophilised cake.

Solvent for suspension for injection:
Clear, colourless solution free of suspended particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prostatic carcinoma.
In the management of advanced prostatic carcinoma.

Genital and extragenital endometriosis.
Central precocious puberty (onset before 8 years in girls and 10 years in boys) -*see section 5.1*

4.2 Posology and method of administration

Prostatic carcinoma:
Male Adults only: one intramuscular or subcutaneous injection every three months.
In patients with metastatic castration-resistant prostate cancer not surgically castrated, receiving a GnRH agonist such as triptorelin and eligible to a treatment by abiraterone acetate, an inhibitor of androgen biosynthesis or enzalutamide, an inhibitor of signaling pathway of androgen receptors, the treatment by a GnRH agonist must be continued.

Endometriosis:
Female adults only: one intramuscular injection every three months.
The treatment must be started in the first five days of the menstrual cycle.
Treatment duration: this depends on the initial severity of the endometriosis and the changes observed in the clinical features (functional and anatomical) during treatment. In principle, the treatment should be administered for at least 3 months and for at most 6 months (*see section 4.8 Undesirable Effects*). It is not recommended to start a second treatment course with triptorelin or another GnRH analogue. In patients treated with GnRH analogues for endometriosis, the addition of an add-back therapy (ABT - an estrogen and progestogen) has been shown to reduce bone mineral density loss and vasomotor symptoms. Therefore, if appropriate, ABT should be co-administered with GnRH analogue taking into account the risks and benefits of each treatment.

Elderly patients:
No special requirements are needed in the elderly.

Central precocious puberty: (before 8 years in girls and 10 years in boys)

One intramuscular injection of Decapeptyl 3-month administered every 3 months.
The treatment of children with triptorelin should be under the overall supervision of the paediatric endocrinologist or of a paediatrician or 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 12 to 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.

Patients with liver disease or renal insufficiency:
No dosage reduction is required in patients with liver disease or renal insufficiency.

Decapeptyl 3-month must not be injected intravascularly.

Subcutaneous administration has not been studied in women and children.

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

4.3 Contraindications

Hypersensitivity to the active substance, GnRH (gonadotropin releasing hormone), its analogues or to any of the excipients listed in section 6.1 (see section 4.8 Undesirable effects).
This medication should never be used during pregnancy or the lactation period. Confirm that the patient is not pregnant or breast-feeding before starting the treatment.

4.4 Special warnings and precautions for use

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 an 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. anticonvulsants 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 3-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.

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

In men
Prostate cancer
Initially, Decapeptyl 3-month, 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 orchidectomy (surgical castration) should be considered. Careful monitoring is indicated during the first weeks of treatment, particularly in patients suffering from vertebral metastasis, 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.

Long-term androgen deprivation either by bilateral orchidectomy 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 3-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.

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.

In women
It should be confirmed that the patient is not pregnant before prescription of triptorelin

The use of GnRH agonists is likely to cause reduction in bone mineral density averaging 1% per month during a six-month treatment period. Every 10% reduction in bone mineral density is linked with about a two to three times increased fracture risk.

No specific data are available for patients with established osteoporosis or with risk factors for osteoporosis (e.g. chronic alcohol abusers, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis, malnutrition, e.g. anorexia nervosa). Since reduction in bone mineral density is likely to be more detrimental in these patients, treatment with triptorelin 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.

Endometriosis
GnRH agonist is not recommended for patients under the age of 18 years. Careful attention should be given to adolescent and young women (specially less than 16 years of age) who may not have reached maximum bone density.
In patients treated with GnRH analogues for endometriosis, the addition of ABT (an estrogen and progestogen) has been shown to reduce mineral density loss and vasomotor symptoms (see 'Posology and Method of Administration' section 4.2 for further information).

Used at the recommended dose, triptorelin causes constant hypogonadotrophic amenorrhoea. If genital haemorrhage occurs after the first month, plasma oestradiol levels should be measured and if levels are below 50 pg/mL, possible organic lesions should be investigated.

After withdrawal of treatment, ovarian function resumes and ovulation occurs approximately 5 months after the last injection. A non-hormonal method of contraception should be used throughout treatment including for 3 months after the last injection.

Since menses should stop during triptorelin treatment, the patient should be instructed to notify her physician if regular menstruation persists.

In paediatric population

Central precocious puberty

In girls, it should be confirmed that the patient is not pregnant before prescribing triptorelin.

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.

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

Information with regards to future fertility is still limited. In most girls, regular menses will start on average one year after ending the therapy.

Bone mineral density (BMD) may decrease during GnRH therapy for central precocious puberty. 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 treatment. The suggested theory is that the low concentrations of oestrogen during treatment with GnRH agonists weaken the epiphyseal 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 be supervised.

Prostate cancer

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Decapeptyl 3-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).

4.6 Fertility, pregnancy and lactation

Pregnancy

Triptorelin should 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, potentially fertile women should be examined carefully to exclude pregnancy. Non-hormonal methods of contraception should be employed during therapy until menses resume (see section 4.4).

Data currently available concerning the effects of this type of product during pregnancy are summarised below:

- Animal studies have not shown the product to have any teratogenic effects. No malformations are therefore expected in humans with this product as substances that cause malformations in humans have been found to be teratogenic in well-conducted animal studies.

- In clinical studies conducted to date, the use of GnRH analogues in a limited number of pregnant women has not resulted in any malformations or foetotoxicity. Nevertheless, further studies are required to study the consequences of exposure during pregnancy.

Lactation
Triptorelin should not be used during breast-feeding.

Fertility
There is no clinical evidence to suggest a causal connection between triptorelin and any subsequent abnormalities of oocyte development or pregnancy or outcome.

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 (possible undesirable effects of treatment), or resulting from the underlying disease.

4.8 Undesirable effects

Clinical trials experience
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 to < 1/10); uncommon (≥1/1000 to < 1/100); rare (≥1/10000 to < 1/1000); not known; (cannot be estimated from the available data).

System Organ Class	**Very common ≥ 1/10**	**Common ≥1/100 - <1/10**	**Uncommon ≥1/1000 - <1/100**	**Rare ≥1/10000 - <1/1000**	**Additional post-marketing AEs Frequency not known**
Infections and infestations				Nasopharyngitis	
Blood and lymphatic system disorders			Thrombocytosis		
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	Depression* Loss of libido Mood change*	Insomnia Irritability	Confusional state Decreased activity Euphoric mood	Anxiety
Nervous system disorders	Paraesthesia in lower limbs	Dizziness Headache	Paraesthesia	Memory impairment	

Eye disorders			Visual impairment	Abnormal sensation in eye Visual disturbance	
Ear and labyrinth disorders			Tinnitus Vertigo		
Cardiac Disorders			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 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
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	Breast pain Gynaecomastia 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
Investigations		Weight increased	Alanine aminotransferase increased Aspartate aminotransferase increased Blood creatinine increased Blood pressure increased Blood urea increased	Blood alkaline phosphatase increased	

			Gamma-glutamyl transferase increased Weight decreased		

* 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).

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

The use of GnRH agonists to treat prostate cancer may be associated with increased bone loss and may lead to osteoporosis and increases in the risk of bone fracture.

General tolerance in Women (see section 4.4)
As a consequence of decreased oestrogen levels, the most commonly reported adverse events (expected in 10% of women or more) were headache, libido decreased, sleep disorder, mood alterations, dyspareunia, dysmenorrhoea, genital haemorrhage, ovarian hyperstimulation syndrome, ovarian hypertrophy pelvic pain, abdominal pain, vulvovaginal dryness, hyperhidrosis, hot flushes and asthenia.

The following adverse reactions, considered as at least possibly related to triptorelin treatment, were reported. Most of these 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 to < 1/10); uncommon (≥1/1000 to < 1/100); not known; (cannot be estimated from the available data).

System Organ Class	**Very common ≥ 1/10**	**Common ≥1/100 - <1/10**	**Uncommon ≥1/1000 - <1/100**	**Additional post-marketing AEs Frequency not known**
Immune system disorders		Hypersensitivity		Anaphylactic shock
Endocrine disorders				Pituitary apoplexy***
Metabolism and nutrition disorders			Decreased appetite Fluid retention	
Psychiatric disorders	Libido decreased Mood disorder Sleep disorder (including insomnia)	Depression* Nervousness	Affect lability Anxiety Depression** Disorientation	Confusional state
Nervous system disorders	Headache	Dizziness	Dysgeusia Hypoesthesia Syncope Memory impairment	

			Disturbance in attention Paraesthesia Tremor	
Eye disorders			Dry eye Visual impairment	Visual disturbance
Ear and labyrinth disorders			Vertigo	
Cardiac Disorders			Palpitations	
Vascular disorders	Hot flush			Hypertension
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis	
Gastrointestinal disorders		Abdominal pain Abdominal discomfort Nausea	Abdominal distension Dry mouth Flatulence Mouth ulceration Vomiting	Diarrhoea
Skin and subcutaneous tissue disorders	Acne Hyperhidrosis Seborrhoea		Alopecia Dry skin Hirsutism Onychoclasis Pruritus Rash	Angioneurotic oedema Urticaria
Musculoskeletal and connective tissue disorders		Arthralgia Muscle spasms Pain in extremities	Back pain Myalgia	Muscular weakness
Reproductive system and breast disorders	Breast disorder Dyspareunia Genital bleeding (including vaginal bleeding withdrawal bleed) Ovarian hyperstimulation syndrome Ovarian hypertrophy Pelvic pain Vulvovaginal dryness	Breast pain	Coital bleeding Cystocele Menstrual disorder (including dysmenorrhoea, metrorrhagia and menorrhagia) Ovarian cyst Vaginal discharge	Amenorrhoea
General disorders and administration site conditions	Asthenia	Injection site reaction (including pain, swelling, erythema and inflammation) Oedema peripheral		Malaise Pyrexia
Investigations		Weight increased	Weight decreased	Blood alkaline phosphatase increased Blood pressure increased

*Long term use: This frequency is based on class-effect frequencies common for all GnRH agonists

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

At the beginning of treatment, the symptoms of endometriosis may be exacerbated during the initial transient increase in plasma oestradiol levels. These symptoms are transient.
Vaginal bleeding including menorrhagia, metrorrhagia may occur in the month following the first injection.

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 to < 1/100); not known; (cannot be estimated from the available data).

Vaginal bleeding may occur in the month following the first injection.

System Organ Class	**Very common ≥ 1/10**	**Common ≥1/100 - <1/10**	**Uncommon ≥1/1000 - <1/100**	**Additional post-marketing AEs Frequency not known**
Immune system disorders		Hypersensitivity		Anaphylactic shock
Metabolism and Nutrition Disorders			Obesity	
Psychiatric disorders			Mood altered	Affect lability Depression Nervousness
Nervous system disorders		Headache		Idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4)
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 bleed, uterine haemorrhage, vaginal discharge, vaginal bleeding including spotting)		Breast pain	
General		Injection site	Malaise	

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

General
Increased lymphocytes 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

If overdose occurs, symptomatic management is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analogues of Gonadotropin-releasing hormone, ATC code: L02AE04: antineoplastic and immunomodulator.

Triptorelin is a synthetic decapeptide (D-Trp6 GnRH) analogue of natural GnRH. Studies in animals and man have shown that continued administration of triptorelin exerts, after a short initial stimulation, an inhibitory effect on the gonadotropin secretion with consequent suppression of testicular and ovarian function.

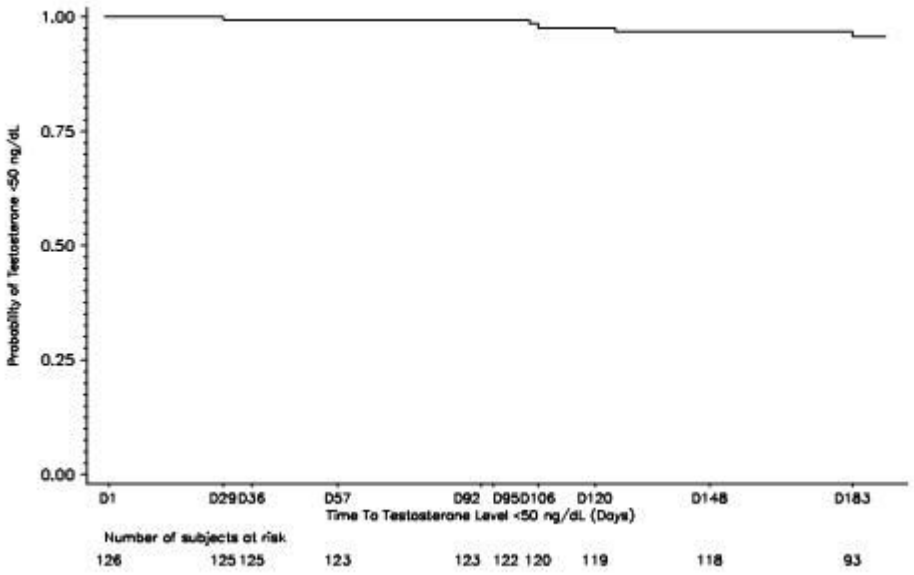
The first administration of Decapeptyl 3-month stimulates the release of pituitary gonadotropins with a transient increase in testosterone levels ('flare-up'). Prolonged administration leads to a suppression of gonadotropins and a fall in plasma testosterone to castrate levels after approximately 20 days and which continues for as long as the product is administered.

A transient increase in acid phosphatases may be observed in men at the beginning of treatment.

Prostate cancer
In men, administration via subcutaneous route or intramuscular route achieved similar results (about 20 days to achieve castration level and castration still maintained 3 months after administration). Studies performed with triptorelin 11.25 mg administered intramuscularly in patients with locally advanced or metastatic prostate cancer showed at 3 months 94.9% - 100% of patients to be at castration level (<50 ng/dl). The mean testosterone levels at month 3 varied between 24 +- 2 ng/dl and 26 +- 20 ng/dl.

Administration of Decapeptyl 3-month to patients with advanced prostate cancer as a subcutaneous injection for a total of 2 doses (6 months) resulted in both achievement of castrate levels of testosterone during the first month and maintenance of castration at Month 6. After four weeks 97.6% of subjects were castrated (testosterone levels <50 ng/dL) (95% CI: [93.2; 99.5]) and castration was maintained at Month 6 in 96.6% of subjects (95%CI: [91.6; 99.1]). The probability for a subject to be castrated within the first month of treatment and to remain castrated at each measurement up to 6 months was 96% (95%CI [0.92, 0.99]) (see Figure 1).

Figure 1: Kaplan-Meier Plot for Probability of Testosterone < 50 ng/dL from Day 29 through Day 183 after subcutaneous administration



Decapeptyl 11.25 mg is effective in achieving testosterone suppression (see Table 1).

Table 1 Serum Testosterone Levels after subcutaneous administration

	Mean ± SD (ng/dl)
Baseline	341.68 ±150.19
Month 1	18.43 ± 16.75
Month 3	10.69 ± 7.42
Month 6	8.40 ±5.98

In addition, the proportion of subjects with a testosterone level <20 ng/dL was explored. From Month 2 to Month 6, the proportion of subjects with a serum testosterone levels <20 ng/dL was above 90%. The probability of testosterone <20 ng/dL to Month 6 was 90% (95% CI: [0.85, 0.95]) in the ITT population. Median PSA levels fell significantly after the first administration of triptorelin. PSA levels were reduced by 64.2% at Month 1 and by 96.0% at Month 6. Median PSA values remained within normal range (0-4 ng/mL) from Month 2 until the end of the study.

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.

Endometriosis
The treatment suppresses oestradiol secretion in women and thus enables resting of ectopic endometrial tissue.

Central precocious puberty
One, non-comparative, open label study was undertaken in children with central precocious puberty to assess the efficacy of Decapeptyl 3-month to suppress pubertal development as defined by onset of development of sex characteristics before the age of 8 years for girls and 9 years for boys and a pubertal response of LH to luteinizing hormone releasing hormone (LHRH) ≥7 IU/L.

Sixty four patients (54 girls and 10 boys) were enrolled and received the first injection, with 61 (51 girls and 10 boys) receiving all four injections and completing study visits up to month 12.
53 children (45 girls (83%) and 8 boys (80%)) had suppressed LH response (LH ≤ 3 IU/L) to LHRH challenge, three months after the injection. At 6 months the corresponding proportions were 51 girls (94%) and 9 boys (90%) and at 12 months 49 girls (91%) and 7 boys (70%).

Stabilisation of the height standard deviation score was observed in 35/51 (69%) and 7/10 (70%) boys at month 12. Stabilisation of the difference in bone age – chronological age and a decrease in the growth velocity were also observed at month 12.

Most patients (51/54 girls and 10/10 boys) achieved a regression or stabilisation of their secondary sex characteristics: all girls had stable or decreased breast development at month 12 (69% regression) and all boys had decreased or stable genital development at month 12 (70% regression).

Nine children (14%) experienced side-effects, four patients with local reaction at the injection site and five patients with withdrawal bleeding. Two patients experienced injection site pain.

5.2 Pharmacokinetic properties

Following intramuscular injection of Decapeptyl 3-month in patients (men and women), a peak in plasma triptorelin is observed approximately 3 hours after injection. After a phase of decrease, which continues during the first month, the circulating triptorelin levels remain stable until day 90.

The pharmacokinetic properties following subcutaneous injection of Decapeptyl
3-month in men are similar to those observed after intramuscular injection: the plasma concentration peak of triptorelin is rapidly achieved after the administration (median Tmax ranged from 2.0 to 4.5 h, whatever the route of administration subcutaneous or intramuscular) and triptorelin is continuously released over the 91-day period. Three months after subcutaneous or intramuscular administration, the residual levels of triptorelin (Cmin) were similar (0.062 ng/ml for subcutaneous route, 0.032-0.063 ng/ml for intramuscular route).

5.3 Preclinical safety data

In-vitro and animal toxicology studies have not shown any specific toxic potential for triptorelin. The observed effects are related to the pharmacological properties of triptorelin on the endocrine system.

The resorption of Decapeptyl 3-month is complete in 120 days.

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

D,L lactide coglycolide polymers
Mannitol,
Sodium carmellose
Polysorbate 80
Water for injections

6.2 Incompatibilities

Not applicable. The product is not intended for admixture.

6.3 Shelf life

3 years. The product should be used immediately after reconstitution. Any remaining product should be discarded.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

Powder for suspension for injection:
Type I, clear, slightly tinted glass vial (4ml)

Solvent for suspension for injection:
Type I, clear glass ampoule (2ml)

Box containing 1 vial and 1 ampoule with 1 syringe and 3 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 suspension should be injected immediately using the specific injection needle:

- The 38 mm length needle (20 G) with safety device for **intramuscular** injection in the gluteal muscle (patients treated for prostate cancer, endometriosis or central precocious puberty)
- The 25 mm length needle (20 G) with safety device for **subcutaneous** injection in abdomen or thigh (only patients treated for prostate cancer).

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 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

PA0869/003/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2 October 1998

Date of last renewal: 2 October 2008

10 DATE OF REVISION OF THE TEXT