1. Name of the medicinal product

Diphereline P.R. 22.5 mg

Powder and solvent for suspension for injection.

2. Qualitative and quantitative composition

Each vial contains triptorelin embonate equivalent to 22.5 mg triptorelin. After reconstitution in 2 ml solvent, 1 ml of reconstituted suspension contains 11.25mg of triptorelin. For a full list of excipients see section 6.1

3. Pharmaceutical form

Powder and solvent for suspension for intramuscular injection (I.M), 6-month prolonged release form.
Powder: White to off-white powder. Solvent: Clear solution.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of patients with locally advanced, non-metastatic prostate cancer, as an alternative to surgical castration.

Treatment of metastatic prostate cancer.

As adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.

As neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.

As adjuvant treatment to radical prostatectomy in patients with locally advanced prostate cancer at high risk of disease progression.

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 Diphereline P.R. 22.5 is 22.5 mg of triptorelin (1 vial) administered every six months (twenty four weeks) as a single intramuscular injection.

In patients treated with GnRH analogues for metastatic prostate cancer, treatment is usually continued upon development of castrate-resistant prostate cancer.

Reference should be made to relevant guidelines.

DipherelineP.R. is also available as a 1-month treatment (Diphereline P.R. 3.75mg) and as a 3-month treatment (Diphereline P.R. 11.25 mg).

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 Diphereline P.R. 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.

Method of administration

As with other medicinal products administered by injection, the injection site should be varied periodically.

Once reconstituted, the suspension of Diphereline P.R. 22.5 mg 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

Diphereline P.R. 22.5 mg is only intended for intramuscular use.

Since Diphereline P.R. 22.5 mg is a suspension of microparticles, inadvertent intravascular injection must be strictly avoided.

Diphereline P.R. 22.5 mg must be administered under the supervision of a physician.

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

4.3 Contraindications

Hypersensitivity to GnRH, 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 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 Diphereline P.R. 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.

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 Diphereline P.R. 22.5 mg has been established via intramuscular route only. The subcutaneous administration is not recommended.

This medicine contains less than 1 mmol (23 mg) sodium per dose i.e it is essentially 'sodium 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 orchidectomy (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 orchidectomy or administration of GnRH agonists 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 Diphereline P.R. 22.5 mg.

In addition, from epidemiological data, it has been observed that patients may experience metabolic changes (e.g. glucose intolerance), or an increased risk of cardiovascular disease during androgen deprivation therapy. However, prospective data did not confirm the link between treatment with GnRH analogues and an increase in cardiovascular mortality. Patients at high risk of metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and their glucose, cholesterol and blood pressure adequately monitored during androgen deprivation therapy.

Metabolic changes may be more severe in these high-risk patients. Patients at high risk of metabolic or cardiovascular disease and receiving androgen deprivation therapy should be monitored at appropriate intervals not exceeding 3 months.

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 agonists 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. Diphereline P.R. 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
Drugs which raise prolactin levels should not be prescribed concomitantly as they reduce the level of GnRH receptors in the pituitary.

When Diphereline P.R. 22.5 mg 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 Diphereline P.R. 22.5 mg 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

Diphereline P.R. 22.5 mg 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 Diphereline P.R. 22.5 mg.

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

Diphereline P.R. 22.5 mg 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				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	Loss of libido Depression* Mood changes*	Insomnia Irritability	Confusional state Decreased activity Euphoric mood	Anxiety
Nervous system disorders	Paraesthesia in lower limbs	Dizziness Headache	Paraesthesia	Memory impairment	
Eye disorders			Visual impairment	Abnormal sensation in 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	
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 increase	Alanine aminotransferase increased Aspartate aminotransferase increased Blood creatinine increased Blood pressure increased Blood urea increased Gamma-glutamyl transferase increased Weight decreased	Blood alkaline phosphatase increased	

* 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.

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

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		
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 administration site conditions		Injection site reaction (including injection site pain, injection site erythema and	Malaise	

		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.

4.9 Overdose
The pharmaceutical properties of Diphereline P.R. 22.5 mg 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 Diphereline P.R. 22.5 mg. If overdose occurs, this should be managed symptomatically.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group:

Hormones and related agents, gonadotropin releasing hormone agonists.

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 luteinising 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 after bilateral orchidectomy occurs approximately 2 to 4 weeks after initiation of therapy. Diphereline P.R. 22.5 mg is designed to deliver 22.5 mg of triptorelin over a 6-month period. Once the castration levels of testosterone have been achieved by the end of the first month, serum testosterone levels are maintained for as long as the patients receive their injection according to the recommended posology.

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 Diphereline P.R. 22.5 mg.

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 Diphereline P.R. 22.5 mg to patients with advanced prostate cancer as an intramuscular injection for a total of 2 doses (48 weeks) resulted in both achievement of castration levels of testosterone in 97.5% of patients after four weeks and maintenance of castration levels of testosterone in 93.0% of the patients from Month 2 through Month 12 of treatment.

In a phase III randomized clinical trial including 970 patients with locally advanced prostate cancer (mainly T2c-T4 with some T1c to T2b patients with pathological regional nodal disease) of whom 483 were assigned to short-term androgen suppression (6 months) in combination with radiation therapy and 487 to long-term therapy (3 years), a non-inferiority analysis compared the short-term to long-term concomitant and adjuvant hormonal treatment with triptorelin (62.2%) or goserelin (30.1%). The 5-year overall mortality was 19.0% and 15.2%, in the short-term and long-term groups, respectively. The observed Hazard Ratio of 1.42 with an upper one-sided 95.71% CI of 1.79 or two-sided 95.71% CI of 1.09; 1.85 (p = 0.65 for non-inferiority), demonstrate that the combination of radiotherapy plus 6 months of androgen deprivation therapy provides inferior survival as compared with radiotherapy plus 3 years of androgen deprivation therapy. Overall survival at 5 years of long-term treatment and short-term treatment shows 84.8% survival and 81.0%, respectively.

Overall quality of life using QLQ-C30 did not differ significantly between the two groups (p= 0.37).

Neoadjuvant triptorelin prior to radiotherapy has been shown to significantly reduce prostate volume.

The use of a GnRH agonist may be considered after radical prostatectomy in selected patients considered at high risk of disease progression. There are no disease-free survival data or survival data with triptorelin in this setting.

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 Diphereline P.R. 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:

Following a single intramuscular injection of Diphereline P.R. 22.5 mg 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 0.5 mg triptorelin is approximately 30L in healthy male volunteers. Since there is no evidence that triptorelin at clinically relevant concentrations binds to plasma proteins, medicinal product interactions involving binding-site displacement are unlikely.

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 0.5 mg 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 0.5 mg 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} 89.9 mL/min).

The effects of age and race on triptorelin pharmacokinetics have not been systematically studied. However, pharmacokinetic data obtained in young healthy male volunteers aged 20 to 22 years with an elevated creatinine clearance (approximately 150mL/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 Diphereline P.R. 22.5 mg 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 compound did not demonstrate any specific toxicity in animal toxicological studies. The effects observed are related to the pharmacological properties of triptorelin on the endocrine system.

Triptorelin is not mutagenic *in vitro* or *in vivo*. In mice, no oncogenic effect has been shown with triptorelin at doses up to 6000 µg/kg after 18 months of treatment. A 23 month carcinogenicity study in rats has shown an almost 100 % incidence of benign pituitary tumours at each dose level, leading to premature death. The increased incidence in pituitary tumours in rats is a common effect associated with GnRH agonist treatment. The clinical relevance of this is not known.

6. Pharmaceutical particulars

6.1 List of excipients

Powder:

poly (d,l-lactide-co-glycolide)
mannitol
carmellose sodium
polysorbate 80

Solvent:

water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be reconstituted with other medicinal products.

6.3 Shelf life

3 years.

Use immediately after reconstitution.

From a microbiological point of view, the ready-for-use suspension for injection should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C

6.4 Special precautions for storage

Do not store above 30°C. For storage conditions after reconstitution of the medicinal product see section 6.3.

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.

Any unused medicinal product, needles or other waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder

Zuellig Pharma Ltd Bangkok, Thailand.

8. Marketing Authorization Number

1C 15033/66 (N)

9. Date of first authorization / Renewal of the authorization

June 2023

10. Date of revision of the text

Sep 2022 (Base upon UK SmPC dated April 2022)

1 - PREPARATION OF THE PATIENT BEFORE RECONSTITUTION OF THE MEDICINAL PRODUCT

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

2 - PREPARATION OF THE INJECTION

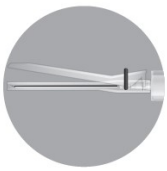
Two needles are provided in the box :

- **Needle 1** : a long needle (38mm) without safety device to be used for reconstitution
- **Needle 2** : a long needle (38mm) with safety device to be used for injection

needle 1 - 38 mm

20 Gauge

needle 2 - 38 mm



20 Gauge

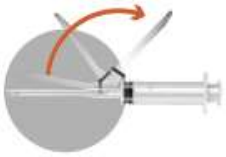
The presence of bubbles on top of the lyophilisate is a normal appearance of the product.

2a Take out the ampoule containing the solvent. Tap any solution within the tip of the ampoule back to the main body of the ampoule. Screw Needle 1 (without safety device) on to the syringe. Do not remove the needle protection yet. Break open the ampoule with dot face up. Remove the needle protection from Needle 1. Insert the needle in the ampoule and draw up all the solvent into the syringe. Put aside the syringe containing the solvent.	
2b Take out the vial containing the powder; Tap any powder which has accumulated at the top of the vial back to the bottom of the vial. Remove the plastic tap on the top of vial. Take back the syringe containing the solvent and insert the needle through the rubber stopper vertically into the vial. Inject the solvent slowly, so that, if possible, it washes down the entire upper part of the vial.	
2c Pull up Needle 1 above the liquid level. Do not remove the needle from the vial. Reconstitute the suspension by swirling gently from side to side. Do not invert the vial. Make sure that the agitation is long enough to obtain an homogeneous and milky suspension. **Important : Check there is no unsuspended powder in the vial (if any powder clumps are present, continue swirling until they disappear)**	

2d

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

Grasp the coloured hub to disconnect the needle. Remove Needle 1 used for the reconstitution from the syringe. Screw on to the syringe Needle 2.
Move the safety sheath away from the needle and towards the syringe barrel. The safety sheath remains in the position you set.
Remove the needle protection from the needle.
Prime the needle to remove air from the syringe and inject immediately.



3 – INTRAMUSCULAR INJECTION

To avoid precipitation, inject immediately intramuscularly, after disinfection.

4 – AFTER USE

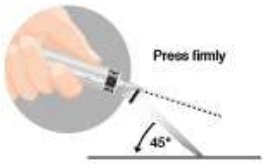
Activation of the safety system using a one-handed technique,
Note : Keep your finger behind the tab at all times

Method A or

There are two alternatives to activate the safety system.

Method A : push the tab forward with your finger
or

Method B : push the sheath to a flat surface
In both cases press down with a firm quick motion until a distinct audible click is heard.
Visually confirm that the needle is fully engaged under the lock.
Used needles, any unused suspension or other waste material should be disposed of in accordance with local requirements.



Method B