1 NAME OF THE MEDICINAL PRODUCT

Diphereline® P.R. Powder and Solvent for Suspension for Injection 11.25 mg/vial

2 PRESENTATION AND FORM

Diphereline P.R. 11.25 mg, powder and solvent for suspension for injection for intramuscular and subcutaneous injection, 3-month prolonged release form. This pack contains a glass vial of powder, an ampoule of 2 mL solvent, 1 syringe and 3 needles.

3 COMPOSITION PER UNIT DOSE

Active ingredient
Triptorelin 11.25 mg* (as triptorelin pamoate)
*Taking into account the characteristics of the pharmaceutical form, each vial contains a quantity of triptorelin pamoate corresponding to 15 mg of triptorelin.

Excipients
Composition of the powder
D,L lactide-coglycolide polymer, mannitol, sodium carmellose and polysorbate 80
Composition of the solvent
Mannitol and water for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- **Prostate cancer**
  Treatment of locally advanced or metastatic, hormone-dependent prostate cancer.
  As adjuvant treatment to radiotherapy in patients with high-risk localised or locally advanced prostate cancer.

- **Endometriosis**

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

4.2 Posology and method of administration

Posology

- **Prostate cancer**

One intramuscular or subcutaneous injection of Diphereline P.R. 11.25 mg every 3 months.

Duration of the treatment: In high-risk localised or locally advanced hormone-dependent prostate cancer as concomitant to and following radiation therapy clinical data have shown that radiotherapy followed by long-term androgen deprivation therapy is preferable to radiotherapy followed by short-term androgen deprivation therapy (see section 5.1).
The treatment duration of androgen deprivation therapy recommended by medical guidances for patients with high-risk localised or locally advanced prostate cancer receiving radiotherapy is 2 – 3 years.
In patients who are not surgically castrated and treated with GnRH analogues for metastatic prostate cancer, treatment is usually continued upon development of castrate-resistant prostate cancer.

- **Endometriosis**

One intramuscular injection of Diphereline P.R. 11.25 mg every 3 months.
The subcutaneous administration has not been studied in women.

The treatment must be initiated in the first five days of the menstrual cycle.

Duration of the treatment: This depends on the initial severity of the endometriosis and the changes observed in the clinical features (functional and anatomical) during treatment. The treatment should not be administered for more than 6 months (see section 4.8). It is not recommended to undertake a second course of treatment by triptorelin or by 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.

- **Central precocious puberty**

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.

Children over 20 kg in body weight: One intramuscular injection of Diphereline P.R. 11.25 mg administered every 3 months.

Treatment should be stopped around the physiological age of puberty in boys and girls and it is recommended that treatment is not continued in girls with bone maturation of more than 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.

Diphereline P.R. 11.25 mg must not be injected intravascularly. The subcutaneous administration has not been studied in children.

Method of administration

See above in Posology section.

For reconstitution of Diphereline before use, see section 6.6.

NB: The prolonged release form must be injected in strict compliance with the instructions given in the package insert. Any incomplete injections resulting in the loss of suspension volumes greater than the volume generally remaining in the injection syringe must be reported.

4. 3 Contraindications

Hypersensitivity to active substance, to GnRH, its analogues or to any of the excipients listed in section 6.1 (see section 4.8).
Pregnancy and breast feeding.

4.4 Special warnings and precautions for use

In adults, the use of GnRH analogs may lead to bone loss which enhances the risk of osteoporosis. In men, preliminary data suggest that the use of a bisphosphonate in combination with a GnRH agonist may reduce bone mineral loss. Particular caution is necessary in patients with additional risk factors for osteoporosis (e.g. chronic alcohol abuse, smokers, long-term therapy with drugs that reduce bone mineral density, e.g. anticonvulsants or corticoids, family history of osteoporosis, malnutrition).

Rarely, treatment with GnRH agonists may reveal the presence of a previously unknown gonadotroph cell pituitary adenoma. These patients may present with a pituitary apoplexy characterised by sudden headache, vomiting, visual impairment and ophthalmoplegia.

There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonist, such as triptorelin. Patients should be informed accordingly and treated appropriate if symptoms occur. Patients with known depression should be monitored closely during therapy.

Convulsions have been reported with GnRH analogues, particularly in women and children. Some of these patients had risk factors for seizures (such as history of epilepsy, intracranial tumours or co-medication with drugs known to present a risk of seizure reactions). Convulsions have also been reported in patients in the absence of such risk factors.

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

Caution should be given to patients treated with anti-coagulants as haematoma may potentially appear at the injection site.

<u>In men</u>

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 metastasis, at the risk of spinal cord compression, and in patients with urinary tract obstruction. For the same reason, particular care should be taken when beginning treatment in patients with premonitory signs of spinal cord compression.

After surgical castration, triptorelin does not induce any further decrease in serum testosterone levels.

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 Diphereline P.R. 11.25 mg.

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

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

Administration of triptorelin in therapeutic doses result 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.

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

The effectiveness of treatment can be monitored by measuring serum levels of testosterone and prostate specific antigen.

<u>In women</u>

It should be confirmed that patient is not pregnant before prescription of Diphereline P.R. 11.25 mg.

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 is available for patients with established osteoporosis or with risk factors for osteoporosis (e.g. chronic alcohol abuses, 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 section 4.2).

The administration, of Diphereline P.R. 11.25 mg results in 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.

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

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.

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 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 *(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 medicaments and other forms of interaction

When triptorelin is used in combination with drugs that modify the secretion of pituitary gonadotropins, special precautions must be taken and it is recommended to close monitored with hormone assays.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of triptorelin 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

Pregnancy should be excluded before Diphereline P.R. 11.25 mg is prescribed.

Triptorelin should not be used during pregnancy since concurrent use of GnRH agonists is associated with a theoretical risk of abortion or foetal 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.

Breast-feeding

Triptorelin should not be used during breastfeeding.

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 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 erectile dysfunction 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 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 (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000). No frequency can be determined for the adverse reactions reported after marketing. Consequently, they are reported with "frequency not known".

System Organ Class	Very common	Common	Uncommon	Rare	Frequency not known
Infections and infestations				Nasopharyngitis	
Blood and lymphatic system disorders		Anaemia	Thrombocytosis		
Immune system disorders		Hypersensitivity		Anaphylactic reaction	Anaphylactic shock

Metabolism and nutrition disorders			Anorexia, diabetes mellitus, gout, hyperlipidaemia, increased appetite		
Psychiatric disorders	Libido decreased	Depression*, loss of libido, 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	
Endocrine disorders					Pituitary apoplexy**
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		Nausea, dry mouth	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	Gynaecomastia, breast pain, testicular atrophy, testicular pain		
General disorders and administration site conditions	Asthenia	Injection site reaction (including erythema, inflammation and pain), oedema	Lethargy, oedema peripheral, pain, rigors, somnolence	Chest pain, dystasia, influenza like illness, pyrexia	Malaise
Investigations		Weight increased	Alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, blood pressure increased, blood urea increased, gamma-glutamyl transferase, weight decreased	Blood alkaline phosphatase increased, body temperature 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 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.

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.

An increase in lymphocytes has been reported in patients treated with GnRH analogues. This secondary lymphocytosis is apparently related to castration induced by GnRH and suggests that gonadal hormones are involved in thymic involution.

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

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 altered, 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 (≥ 1/1,000 to < 1/100). No frequency can be determined for the adverse reactions reported after marketing. Consequently, they are reported with frequency "not known".

System Organ Class	Very common	Common	Uncommon	Frequency not known
Immune system disorders		Hypersensitivity		Anaphylactic shock
Metabolism and nutrition disorders			Decreased appetite, fluid retention	
Psychiatric disorders	Sleep disorder (including insomnia), mood altered, libido decreased	Depression*, nervousness	Affect lability, anxiety, depression**, disorientation	Confusional state
Nervous system disorders	Headache	Dizziness	Dysgeusia, hypoesthesia, syncope, memory impairment, disturbance in attention, paraesthesia, tremor	Convulsions****
Eye disorders			Dry eye, visual impairment	Visual disturbance
Endocrine disorders				Pituitary apoplexy***
Ear and labyrinth disorders			Vertigo	

Cardiac disorders			Palpitations	
Vascular disorders	Hot flush			Hypertension
Respiratory, thoracic and mediastinal disorders			Dyspnoea, epistaxis	
Gastrointestinal disorders		Nausea, abdominal pain, abdominal discomfort	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 extremities	Back pain, myalgia	Muscular weakness
Reproductive system and breast disorders	Breast disorder, dyspareunia, genital bleeding (including vaginal bleeding, privation haemorrhage), 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		Pyrexia, malaise
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 agonist.

***Reported following initial administration in patients with pituitary adenoma.

****During post-market experience, convulsions have been reported in patients receiving GnRH analogues, including triptorelin.

At the beginning of treatment, the symptoms of endometriosis including pelvic pain, dysmenorrhoea may be exacerbated very commonly (≥ 10%) during the initial transient increase in plasma oestradiol levels. These symptoms are transient and usually disappear in one or two weeks.

Genital haemorrhage including menorrhagia, metrorrhagia may occur in the month following the first injection.

Long-term use of GnRH analogues may lead to bone loss which is a risk factor of osteoporosis.

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 (⩾ 1/1,000 to < 1/100). No frequency can be estimated for the adverse reactions reported after marketing. Consequently they are reported with frequency "not known".

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

System Organ Class	Very common	Common	Uncommon	Frequency not known
Immune system disorder		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) Convulsions*
Eye disorders			Vision impairment	Visual disturbance
Vascular disorders		Hot flushes		Hypertension
Respiratory, thoracic and mediastinal disorders			Epistaxis	
Gastrointestinal disorders		Abdominal pain	Vomiting, constipation, nausea	
Skin and subcutaneous tissue disorders		Acne	Pruritis, urticaria, rash	Angioneurotic oedema

System Organ Class	Very common	Common	Uncommon	Frequency not known
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 disorders and administration site conditions		Injection site reaction (including injection site pain, injection site erythema and injection site inflammation	Malaise	
Investigations		Weight increased		Blood pressure increased, blood prolactin increased

*During post-market experience, convulsions have been reported in patients receiving GnRH analogues, including triptorelin.

Long term tolerance in children population
The long-term clinical trial 2-54-52014-159 (NCT00909844) included 35 patients, age ranging from 4 to 10.4 years, who had received up to 4 years of treatment with Diphereline P.R. 11.25 mg. More than half of patients (20 patients: 57.1%) reported at least one adverse event during the study, of which the most frequent were abdominal pain (17.1%), injection site pain (11.4%), headache and hot flush (each 8.6%). Overall, the safety profile was similar as seen in the other central precocious puberty studies.

4.9 Overdose

If overdose occurs, symptomatic management is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Gonadotrophin-releasing hormone analogue
ATC code: L02AE04

Mechanism of action

Triptorelin is a synthetic decapeptide analogue of natural GnRH (gonadotrophin-releasing hormone).

Studies conducted in both humans and animals have shown that after initial stimulation, the prolonged administration of triptorelin inhibits gonadotrope secretion with consequent suppression of testicular and ovarian function.

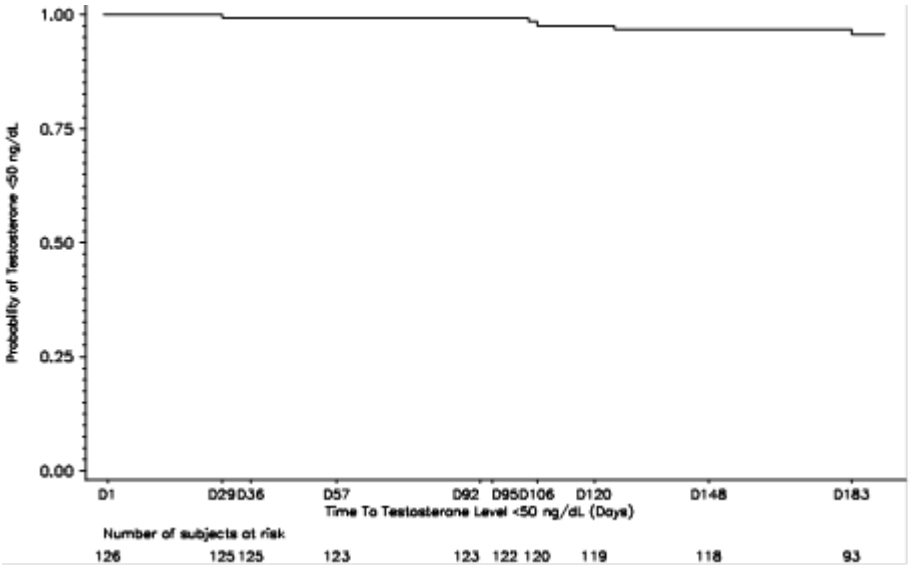
The administration of Diphereline P.R. 11.25 mg may initially increase blood LH and FSH levels and may consequently increase initial testosterone level (flare-up) in men and oestradiol level in women. Continuing the treatment decreases LH and FSH levels leading to decreased testosterone and oestradiol levels similar to those observed after castration within about 20 days after the injection and for as long as the active substance is released.

Clinical efficacy and safety

Prostate Cancer

One open-label, uncontrolled, multicenter, 6-month phase 3 study involving 126 patients with locally advanced or metastatic prostate cancer was conducted to assess the efficacy of subcutaneous administration of Diphereline P.R. 11.25 mg administered on day 1 and day 92 (one administration every 3 months). Four weeks after the first injection, 123 out of 126 subjects (97.6%) were castrated (testosterone levels < 50 ng/dL) (95% CI: 93.2; 99.5) and castration was maintained till end of study at Day 183 in 115 out of 119 subjects (96.6%) (95% CI: 91.6; 99.1) (coprimary endpoints). 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 0.96 (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



During the treatment by triptorelin, the median prostate-specific antigen (PSA) levels were reduced by 64.2% at Day 29 and by 96% at Day 183 (secondary endpoint). Median PSA values remained within normal range (0 – 4 ng/mL) from Month 2 Day 57 until the end of the study.

A randomized phase III study (EORTC 22961) of 970 patients with prostate cancer locally advanced (mainly T2c-T4 with some T1C to T2B patients with pathological regional nodal disease) has investigated whether radiation therapy associated with short term androgen deprivation therapy (6 months, n = 483) was non-inferior to radiotherapy associated with long term androgen deprivation therapy (3 years, n = 487). The GnRH agonist was triptorelin (62.2%) or other GnRH agonists (37.8%) and the trial was not further stratified by the type of agonist.

Overall, total mortality at 5 years was 19.0% and 15.2% respectively in the "short term hormonal treatment" and "long term hormonal treatment" groups, with a relative risk of 1.42 (95% CI: 1.08, 1.86; p = 0.0082) for post-hoc test of difference between groups of treatment). The 5-year mortality specifically related to the prostate was 4.78% and 3.2% respectively in the "short term hormonal treatment" and "long term hormonal treatment" groups, with a relative risk of 1.71 (95% CI: 1.14 to 2.57, p = 0.002).

Evidence for the indication of high-risk localised prostate cancer is based on published studies of radiotherapy combined with GnRH analogues. Clinical data from five published studies were analyzed (EORTC 22863, RTOG 85-31, RTOG 92-02, RTOG 86-10, and D'Amico et al., JAMA, 2008), which all demonstrate a benefit for the combination of GnRH analogue with radiotherapy. Clear differentiation of the respective study populations for the indications locally advanced prostate cancer and high-risk localised prostate cancer was not possible in the published studies.

In patients with metastatic prostate cancer castration-resistant, clinical studies have shown the benefit of adding androgen biosynthesis inhibitors such as abiraterone acetate or inhibitors of signaling pathway of androgen receptors such as enzalutamide to the treatment by a GnRH analog, such as triptorelin.

Endometriosis

Prolonged treatment with Diphereline P.R. 11.25 mg suppresses oestradiol secretion and thus enables resting of ectopic endometrial tissue in women.

Pediatric population – precocious puberty

The inhibition of hypophyseal gonadotrophic hyperactivity in both sexes manifests as suppression of oestradiol or testosterone secretion, as a lowering of the LH peak and as improved Height Age/Bone Age ratio.

Initial gonadic stimulation may cause slight genital haemorrhages requiring medroxyprogesterone or cyproterone acetate treatment.

In the long-term clinical trial 2-54-52014-159 (NCT00909844), 34 girls and 1 boy, with central precocious puberty (CPP) have been treated with triptorelin pamoate 11.25 mg every 3 months for a period of up to 4 years. Treatment ended when the investigator decided the patient had completed his/her treatment, that is to say at about 11 years in girls and 13 in boys (usually after 1-3 years of treatment). At that timepoint, 31/34 (91%) of girls had maintained stabilization or regression of Tanner breast pubertal stage.

5.2 Pharmacokinetic properties

Following intramuscular injection of Diphereline P.R. 11.25 mg in patients (men and women), a peak plasma concentration of triptorelin is observed about 3 hours after injection. After a declining concentration phase, which continues during the first month, circulating triptorelin levels remain constant until the end of the third month following the injection.

In the study conducted with subcutaneous administration in men, peak plasma concentration of triptorelin is rapidly reached after injection (median T_{max} of 4.5h) and triptorelin is constantly released during the period of 91 days. Residual concentrations of triptorelin (C_{min}) were 0.063 ng/ml three months after subcutaneous administration.

5.3 Preclinical safety data

The molecule did not demonstrate any specific toxicity in animal toxicological studies. The effects observed are related to the pharmacological properties of the substance on the endocrine system.

The resorption of the product 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 Incompatibilities

Not applicable.

6.2 Shelf life

3 years.
After reconstitution, it is to be used immediately.

6.3 Special precautions for storage

Do not store above 30°C.
For storage conditions after reconstitution of the medicinal product, see section 6.2.

6.4 Nature and contents of container

Powder in vial (glass type I) + 2 mL of solvent in ampoule (glass) with syringe and needles. Box containing 1 vial and 1 ampoule with 1 syringe and 3 needles.

6.5 Special precautions for disposal and handling

The powder should be suspended in the specific solvent immediately before injection by shaking the vial gently until a milky homogeneous liquid is obtained (The instructions for reconstitution hereafter and in the leaflet must be strictly followed.).

For single use only. Any unused suspension should be discarded.

The powder is to be suspended in 2 mL of mannitol solution:

Using the reconstitution needle (without safety device), one of the injection needles, all of the solvent is drawn up into the injection syringe supplied and transferred to the vial containing the powder. The vial should be gently shaken to completely disperse the powder to obtain a homogenous, milky suspension. The suspension obtained is then drawn back into the injection syringe. The injection needle should be changed and the suspension should be injected immediately using the specific needle:

- the 38 mm length needle (20 G) with safety device for intramuscular injection in the gluteal muscle (men, women, children)
- the 25 mm length needle (20 G) with safety device for subcutaneous injection in abdomen or thigh (only in men).

The suspension should be discarded if it is not administered immediately after reconstitution. See also section 6.2.

Used injection needles should be disposed in a designated sharp container. Any remaining product should be discarded.

Used needles, unused suspension or other waste material should be disposed of in accordance with local requirements.

FOLLOWING INFORMATION IS ONLY FOR HEALTHCARE PROFESSIONALS

INSTRUCTIONS FOR USE

Read carefully the leaflet before injection.

1 – PREPARATION OF THE PATIENT BEFORE RECONSTITUTION

The skin at the site of injection needs to be disinfected first because once reconstituted the drug should be injected immediately.
The injection site is

- for **WOMEN** and **CHILDREN**: the buttock (**intramuscular** administration)
- for **MEN ONLY:** the buttock (**intramuscular** administration) or the abdomen or thigh (**subcutaneous** administration)

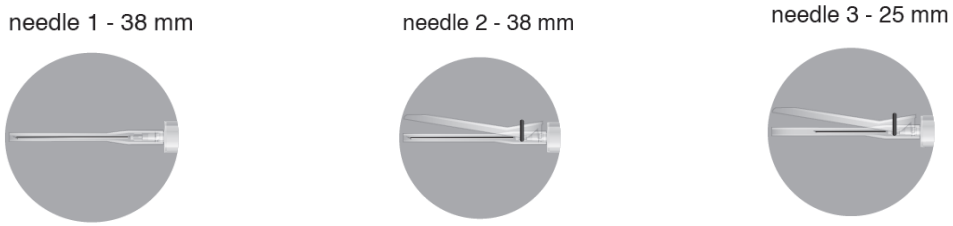
2 – PREPARATION OF THE INJECTION

Three needles are provided in the box, ONLY TWO are to be used:

Needle 1: a long needle (38 mm) without safety device to be used for reconstitution in all cases

Needle 2: a long needle (38 mm) with safety device to be used for intramuscular injection (Men, Women, Children)

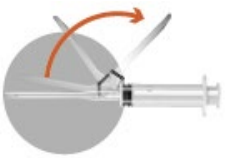
Needle 3: a short needle (25 mm) with safety device to be used for subcutaneous injection (Men only)



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

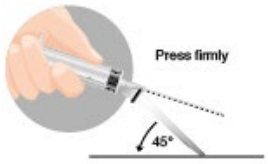
2a

- Take out the ampoule containing the solvent. Tap any solution within the tip of the ampoule back to the main body of the ampoule.
- Screw 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 (at least 30 seconds) to obtain an homogeneous and milky suspension. • **Important: Check there is no unsuspended powder in the vial (if any powder clumps are present, continue swirling until they disappear).**	
2d • When the suspension is homogeneous, pull down the needle without inverting the vial, draw up all of the suspension. A small amount will remain in the vial and should be discarded. An overfill is included to allow for this loss. • Grasp the coloured hub to disconnect the needle. Remove Needle 1 used for the reconstitution from the syringe. Screw onto the syringe corresponding to the trype of injection: - For intramuscular injection: Screw on to the syringe Needle 2. - For subcutaneous injection: Screw on to the syringe Needle 3. • 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 – INJECTION	
To avoid sedimentation, inject immediately into the disinfected area as quickly as possible (within 1 minute from reconstitution).	**Men, women, children**

<table>
<tr><td>WOMEN, CHILDREN
• with Needle 2 (long needle) intramuscular injection into the gluteal muscle.

MEN
• with Needle 2 (long needle) intramuscular injection into the gluteal muscle or
• with Needle 3 (short needle) subcutaneous injection into abdomen wall or lateral aspects of thigh. Grasp the skin of abdomen or thigh, elevate the subcutaneous tissue and insert the needle with an angle between 30 and 45 degrees</td><td>(intramuscular)
 
Men only (subcutaneous)
  </td></tr>
<tr><td colspan="2">4 – AFTER USE</td></tr>
<tr><td>• Activation of the safety system at one-handed technique,
• Note: Keep your finger behind the tab at all times
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.</td><td> 
Method A or
 
Method B</td></tr>
</table>

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