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. Powder and Solvent for Suspension for Injection 11.25 mg/vial, 3-month prolonged release form.
This pack contains a glass vial of powder, am ampoule of 2 mL solvent, 1 syringe and 3 needles.

2.1 Product description

Before reconstitution
Powder: Slightly yellow friable cake
Solvent: Colorless clear solution
After reconstitution
A homogenous white suspension

3 COMPOSITION PER UNIT DOSE

Active ingredient
Triptorelin 11.25 mg (as triptorelin pamoate)

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- **Prostate Cancer**

Treatment of locally advanced prostate cancer when used alone or as concomitant and adjuvant to radiotherapy.
Treatment of metastatic prostate cancer.
Patients who have not previously received hormone therapy show a more marked response to the treatment and response more frequently if the patient has not previously received another hormone treatment.

- **Genital and Extragenital Endometriosis (Stage I to stage IV)**

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 another GnRH analogue.

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

4.2 Posology and method of administration

Strictly comply with your doctor's prescription. Route of administration is intramuscular and subcutaneous. The powder should be suspended in the provided solvent immediately before injection by shaking the vial until a homogenous liquid is obtained. Injection should be strictly prepared by following precisely the instructions at the end of this package insert. Any incomplete injections resulting in the loss of suspension volumes greater than the volume generally remaining in the syringe must be reported.

Posology

- Prostate cancer

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

- Endometriosis

One intramuscular injection of Diphereline P.R. repeated every 3 months. The subcutaneous administration has not been studied in women. The treatment must be started in the first five days of the menstrual cycle.

Duration of 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

Children over 20 kg in body weight: One intramuscular injection of triptorelin PR 11.25 mg administered every 3 months.

The treatment of children with triptorelin should be under the overall supervision of a paediatric endocrinologist or of a paediatrician or endocrinologist with expertise in the treatment of precocious puberty.

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 a 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 to 14 years.

Triptorelin 11.25 mg must not be injected intravascularly. Subcutaneous administration has not been studied in women and children.

Method of administration

See above in Posology section.

4.3 Contraindications

Hypersensitivity to GnRH, its analogues or to any of the excipients listed in section 6.1 (see section 4.8).

Pregnancy and lactation period.

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 agonists, 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.

In men

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 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.

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 GnRH analogues 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.

In women

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

Pediatric 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 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 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 being possible undesirable effects of treatment, or resulting from the underlying disease.

4.8 Undesirable effects

General tolerance in men (see section 4.4)

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: initial increase in testosterone levels, followed by almost complete suppression of testosterone. These effects included hot flushes (50%), erectile dysfunction (4%) and decreased libido (3%).

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 swings	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	

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
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	ck 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 (including erythema, inflammation and pain) Oedema	Lethargy Oedema peripheral Pain Rigors Somnolence	Chest pain Dystasia Influenza like illness Pyrexia	Malaise

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Investigations		Weight increased	Alanine aminotransferase increased Aspartate aminotransferase increased Blood creatinine increased Blood pressure increased Blood urea increased Gamma-glutamyl transferase increased Weight decreased	Blood alkaline phosphatase increased 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 (see section 4.4).

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.

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). 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 changes 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	Angioneurotic oedema Urticaria

			Onychoclasis Pruritus Rash	
Musculoskeletal and connective tissue disorders		Arthralgia Muscle spasms Pain extremities	Back pain Myalgia	Muscular weakness
Reproductive system and breast disorders	Breast disorder Dyspareunia Dysmenorrhoea 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 agonists.
***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	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) Convulsions*
Eye disorders			Visual 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
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	

System organ class	Very common	Common	Uncommon	Not known
General disorders and administration site conditions		Injection site reaction (including injection site pain, injection site erythema, injection site inflammation)	Malaise	
Investigations		Weight increase		Blood prolactin increase Blood pressure 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 PROPOERTIES

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.

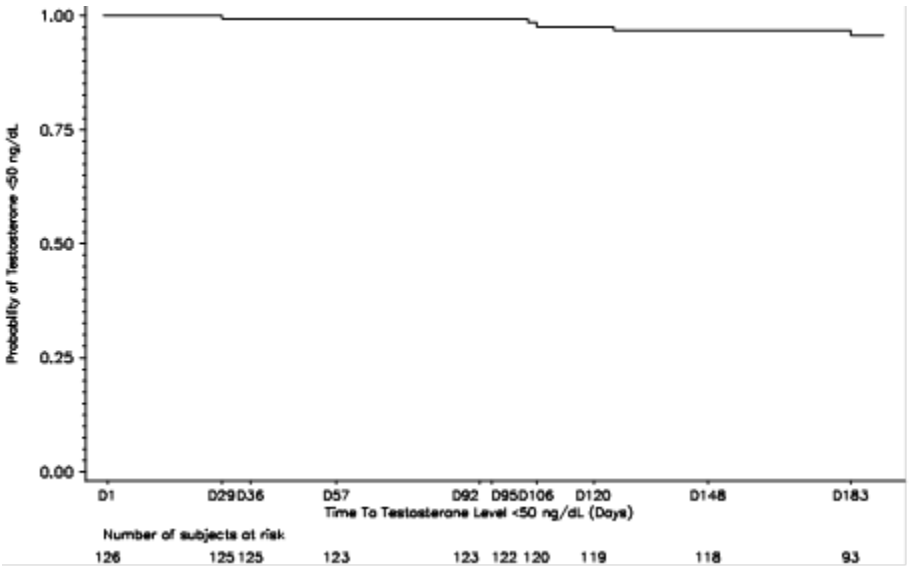
The administration Diphereline P.R 11.25 mg may initially increase blood LH and FSH levels and may consequently increase initial testosterone level (flare-up) in men and oestradiol level in women. Continuing the treatment decreases LH and FSH levels leading to decreased testosterone and oestradiol levels 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

An opened, not controlled and multicentric phase 3 clinical trial involving 126 patients with advanced prostate cancer has been conducted during 6 months in order to assess the efficacy of subcutaneous administration of Diphereline P.R. 11.25 (one administration every 3 months). 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]) (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 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, median PSA levels were reduced by 64.2% at Month 1 and by 96% at Month 6 (secondary endpoint). Median PSA values remained within normal range (0–4 ng/mL) from Month 2 until the end of the study.

In patients with locally advanced prostate cancer several randomized long-term clinical trials provide evidence for the benefit of androgen deprivation therapy (ADT) in combination with radiotherapy (RT) compared to RT alone (RTOG 85-31, RTOG 86-10, EORTC 22863, D'Amico et al., JAMA, 2008).

A randomized phase III of 970 patients with prostate cancer locally advanced (T2c-T4) 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 (CI-sided 95, 71% = 1.79; 95.71% CI = [1.09; 1.85], p = 0.65 for noninferiority and 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 (CI 95% [1.14 to 2.57], p = 0.002). Overall quality of life using QLQ-C30 did not diff er significantly between the two groups (P= 0.37). The post hoc analysis in the subgroup triptorelin also show the advantage of the long term treatment versus the short term treatment on overall mortality (relative risk 1.28; 95.71% CI = [0.89; 1.84], p = 0.38 and p = 0.08 respectively for noninferiority post-hoc tests and for difference between treatment groups).
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.

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

Endometriosis
Continued administration of Diphereline P.R. 11.25 mg induces suppression of oestrogen 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 Tmax of 4.5h) and triptorelin is constantly released during the period of 91 days. Residual concentrations of triptorelin (Cmin) 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 Shelf life

Do not exceed the expiry date indicated on the pack.

6.2 Storage condition

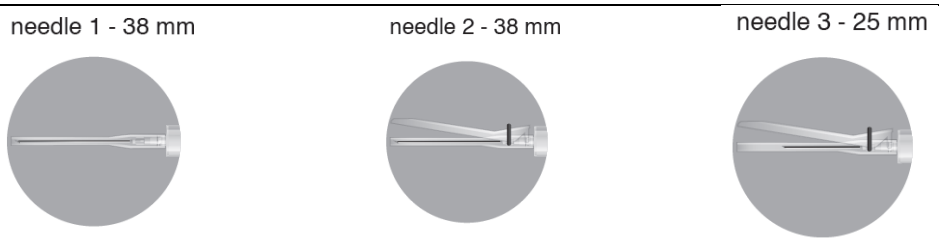
To be stored below 30°C, keep away from heat.
Keep out of reach of children.

The following information is only for healthcare professionals.

INSTRUCTIONS FOR USE

Read carefully the leaflet before injection.

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. 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 – PREPARTION 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) onto 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 ampule and draw up all the solvent into the syringe. Put aside the syringe containing the solvent.

2b

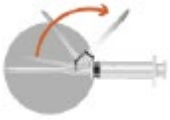
- Take out the vial containing the powder; Tap any powder which has accumulated at the top of the vial back to the bottom of the vial.
- Remove the plastic tap on the top of vial.
- Take back the syringe containing the solvent and insert the needle through the rubber stopper vertically into the vial. 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 and reconstitute the suspension by shaking horizontally.
- 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 and 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 the Needle 1 used for the reconstitution from the syringe. Screw onto the syringe corresponding to the type of injection:
  - For **intramuscular** injection, **needle 2** (long needle with safety device) or
  - For **subcutaneous** injection in **men only**, **needle 3** (short needle with safety device).
- Move the safety sheath away from the needle and towards the syringe barrel. The safety sheath remains in the position you set.



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- Remove the needle protection from the needle.
- Prime the needle to remove air from the syringe and inject immediately.

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<tr><td colspan="2">3 – INJECTION</td></tr>
<tr><td>

To avoid sedimentation, inject immediately into the disinfected area as quickly as possible (within 1 minute from reconstitution).

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

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Men, women, children (intramuscular)

Men only (subcutaneous)

</td></tr>
<tr><td colspan="2">4 – AFTER USE</td></tr>
<tr><td>

- Activation of the safety system using a 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.
- Dispose the needles in designated sharp container.

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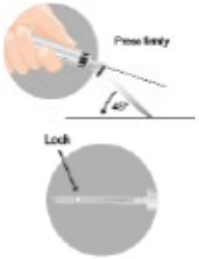
Method A

Or

Method B



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PRODUCT REGISTRATION HOLDER

Zuellig Pharma Malaysia Sdn Bhd

NAME AND ADDRESS OF MANUFACTURER

IPSEN PHARMA BIOTECH
Chemin Departmental No. 402 – 83870 Signes – France

DATE OF REVISION

April 2025