

1 NAME OF THE MEDICINAL PRODUCT

Diphereline® P.R. 3.75 mg

2 PRESENTATION AND FORM

Diphereline P.R. 3.75 mg, powder and solvent for suspension for intramuscular injection, 28-day prolonged release form. This pack contains a glass vial of powder, an ampoule of 2 mL solvent, 1 syringe and 2 needles.

3 COMPOSITION PER UNIT DOSE

Active ingredient

Triptorelin 3.75 mg (as triptorelin acetate)

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 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 start a second treatment course with triptorelin or another GnRH analogue.

- **Treatment of uterine fibromyomas prior to surgery**

Associated with anaemia (haemoglobin less than or equal to 8 g/dl),

When a reduction in the size of the fibromyoma is necessary to facilitate or modify the surgical technique: endoscopic surgery, transvaginal surgery.

The treatment duration is restricted to 3 months.

- **Breast cancer**

As adjuvant treatment in combination with tamoxifen or an aromatase inhibitor, of endocrine responsive early stage breast cancer in women at high risk of recurrence who are confirmed as pre-menopausal after completion of chemotherapy (see sections 4.3, 4.4, 4.8 and 5.1).

- **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 strictly intramuscular.

The powder should be suspended in the provided solvent immediately before injection by shaking the vial until a homogeneous 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 injection of Diphereline P.R. 3.75 mg every 4 weeks.

- **Endometriosis**

One Diphereline P.R. 3.75 mg intramuscular injection repeated every 4 weeks. The treatment must be initiated in the first five days of the menstrual cycle.

Treatment duration: This depends on the initial severity of the endometriosis and the changes observed in the clinical features (functional and anatomical) during treatment. In principle, the treatment should not be administered for more than 6 months. 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 hormone replacement therapy 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.

- **Treatment of uterine fibromyomas prior to surgery**

One injection of Diphereline P.R. 3.75 mg repeated every 4 weeks. The treatment must be initiated in the first five days of the menstrual cycle. Duration of treatment must not exceed 3 months.

- **Breast cancer**

One intramuscular injection every 4 weeks in combination with tamoxifen or an aromatase inhibitor.

Triptorelin should be commenced after completion of chemotherapy, once pre-menopausal status has been confirmed.

The treatment with triptorelin must be initiated at least 6 - 8 weeks before starting aromatase inhibitor treatment. A minimum of two injections of triptorelin (with an interval of 4 weeks between injections) should be administered before commencement of aromatase inhibitor treatment.

During treatment with an aromatase inhibitor, triptorelin must not be interrupted to avoid rebound increases in circulating oestrogens in premenopausal women.

The recommended treatment duration for adjuvant treatment in combination with other hormonotherapy is up to 5 years.

- **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 under 20 kg in body weight: half (1/2) a dose by intramuscular route, every 4 weeks (28 days), i.e. administer half the volume of the reconstituted suspension.
- Children between 20 and 30 kg in body weight: two-thirds (2/3) of the dose by intramuscular route, every 4 weeks (28 days), i.e. administer two-thirds of the volume of the reconstituted suspension.
- Children over 30 kg in body weight: one intramuscular injection every 4 weeks (28 days), i.e. administer the full volume of reconstituted suspension.

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 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.

Method of administration

See above in Posology section.

Since Diphereline P.R. 3.75 mg is a suspension of microparticles, inadvertent intravascular injection must be strictly avoided.

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

4.3 Contraindications

Diphereline P.R. 3.75 mg should never be used during pregnancy and breast feeding. Confirm the patient is not pregnant before starting the treatment.

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

In the pre-menopausal breast cancer setting: Initiation of aromatase inhibitor treatment before adequate ovarian suppression with triptorelin has been achieved (see sections 4.2 and 4.4).

4.4 Special warnings and precautions for use

In adults, the use of GnRH agonists may cause reduction in bone mineral density 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 appropriately 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 a 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 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.

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

Androgen deprivation therapy may prolong the QT interval.

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.

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 physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Diphereline P.R. 3.75 mg.

In addition, from epidemiological data, it has been suggested 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 anemia. 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. 3.75 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 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 and pre surgery treatment of uterine fibromyomas

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).

Used recommended dose, Diphereline P.R. 3.75 mg results in a constant hypogonadotropic amenorrhea. If genital haemorrhage occurs after the first month, plasma oestradiol levels should be measured and if levels are below 50 pg/ml, possible organic lesions should be investigated.

After withdrawal of treatment, ovarian function resumes and ovulation occurs approximately 2 months after the last injection.

A non-hormonal method of contraception should be used throughout treatment including for 1 month after the last injection.

It is recommended that during treatment of uterine fibroids, the size of the fibroid is determined regularly. There have been a few reports of bleeding in patients with submucous fibroids following GnRH analogue therapy. Typically, the bleeding has occurred 6 to 10 weeks after the initiation of therapy.

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

- Breast cancer

In order to ensure adequate ovarian suppression in pre-menopausal women, treatment with triptorelin should be administered for at least 6-8 weeks prior to commencement of an aromatase inhibitor, and monthly triptorelin injections should be administered on schedule and without interruption throughout aromatase inhibitor treatment.

Women who are pre-menopausal at breast cancer diagnosis and who become amenorrhoeic following chemotherapy may or may not have continued oestrogen production from the ovaries. Irrespective of menstrual status, pre-menopausal status should be confirmed following chemotherapy and before commencement of triptorelin, by blood concentrations of oestradiol and follicle-stimulating hormone (FSH) within the reference ranges for pre-menopausal women, in order to avoid unnecessary treatment with triptorelin in the event of a chemotherapy-induced menopause. Following commencement of triptorelin, it is important to confirm adequate ovarian suppression (gonadotrophin analogue-induced menopause) by serial assessment of circulating FSH, and oestradiol to assure a true postmenopausal status if this subset of women is to be considered for therapy with an aromatase inhibitor, in accordance with current clinical practice recommendations. Accordingly, ovarian suppression should be confirmed by low blood concentrations of FSH and oestradiol prior to starting aromatase inhibitor treatment and measurements should be repeated every three months during this combination therapy with triptorelin and an aromatase inhibitor.

This is to avoid aromatase inhibitor-induced rebound increase in circulating oestrogen, with consequential implications for the breast cancer. Of note, circulating FSH levels are lowered in response to gonadotrophin analogue-induced ovarian suppression (induced menopause), unlike in a natural menopause where FSH levels are elevated.

Triptorelin, when used as adjuvant therapy in combination with tamoxifen or an aromatase inhibitor, is associated with a high risk of osteoporosis. Osteoporosis has been reported with a higher frequency following the use of triptorelin in combination with aromatase inhibitor than in the combination with tamoxifen (39% vs 25%).

Bone mineral density should be assessed before starting treatment with triptorelin, especially in women who have multiple risk factors for osteoporosis. These patients should be closely monitored and treatment for, or prophylaxis of, osteoporosis should be initiated when appropriate.

Treatment of premenopausal women with endocrine responsive early stage breast cancer with triptorelin in combination with tamoxifen or an aromatase inhibitor should follow a careful individual appraisal of the risks and benefits.

Patients who have discontinued triptorelin treatment should also discontinue aromatase inhibitors within 1 month of the last triptorelin administration (28 days formulation).

The risk of musculoskeletal disorders (including joint or musculoskeletal pain) when triptorelin is used in combination with either an aromatase inhibitor or tamoxifen is approximately 89% with the AI and approximately 76% with tamoxifen.

Hypertension was reported as a targeted adverse event at a very common frequency with triptorelin in combination with either exemestane or tamoxifen (see section 4.8). Premenopausal women with breast cancer receiving triptorelin in combination with either exemestane or tamoxifen should have regular monitoring of cardiovascular risk factors and blood pressure.

Hyperglycaemia and diabetes were reported as targeted adverse events at a common frequency with triptorelin in combination with either exemestane or tamoxifen (see section 4.8). Premenopausal women with breast cancer receiving triptorelin in combination with either exemestane or tamoxifen should have regular monitoring of risk factors for diabetes with blood glucose monitoring on a regular basis and appropriate anti-diabetic treatment initiated, if appropriate, according to national guidelines.

Depression occurred in approximately 50% of patients treated with triptorelin in combination with either tamoxifen or exemestane in all treatment groups in the TEXT and SOFT studies, but less than 5% of patients had severe depression (grade 3-4). Patients should be informed accordingly and treated as appropriate if symptoms occur. Patients with known depression or depression history should be carefully monitored during therapy.

Particular attention should also be paid to the exemestane and tamoxifen prescribing information for relevant safety information when administered in combination with triptorelin.

Chemotherapy can induce temporary amenorrhoea or a permanent loss of ovarian function due to cytotoxic damage of gonadal tissue. Retention of pre-menopausal status following completion of chemotherapy should be confirmed as recommended by clinical guidelines by blood concentrations of oestradiol and FSH within the reference ranges for pre-menopausal women.

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 gonadal 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 agonist 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 agonist treatment. The suggested theory is that the low concentrations of oestrogen during treatment with GnRH agonists weaken the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.

Idiopathic intracranial hypertension (*pseudotumor cerebri*) has been reported in paediatric patients receiving triptorelin. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, vision disturbances and tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of triptorelin should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

When triptorelin is 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 is prescribed including before use infertility treatment.

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

Pregnancy should be excluded before Diphereline is prescribed including before use infertility treatment.

When triptorelin is used in this setting, 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 by 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 in clinical trials 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$). No frequency can be determined for the adverse reactions reported after marketing. Therefore, 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*	Irritability Insomnia	Confusional state, decreased activity, euphoric mood	Anxiety
Nervous system disorders	Paraesthesia in lower limbs	Dizziness Headache	Paraesthesia	Memory impairment	
Endocrine disorders					Pituitary apoplexy**
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	Diarrhoea, vomiting, constipation, abdominal pain	Abdominal distension, dysgeusia, flatulence,	
Skin and subcutaneous tissue disorders	Hyperhidrosis		Pruritus, rash, acne, alopecia, urticaria, Erythema	Blister, Purpura	Angioneurotic oedema,

System Organ Class	Very common	Common	Uncommon	Rare	Frequency not known
Musculoskeletal and connective tissue disorders	Back pain	Musculoskeletal pain, Pain in extremity	Arthralgia, Bone pain, myalgia, muscle cramp, muscular weakness	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,	Testicular atrophy, breast pain, gynecomastia, testicular pain		
General disorders and administration site conditions	Asthenia	Injection site reaction (including erythema, inflammation and pain) fatigue, Oedema	Lethargy, Oedema peripheral, pain, rigors, somnolence	Chest pain, dysstasia, influenza like illness, pyrexia	Malaise
Investigation		Weight increased	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatinine increased, Blood pressure increased, Blood urea increased, Gamma-glutamyl transferase increased, Weight decreased	Blood alkaline phosphatase increased	

*This frequency is based on class-effect frequencies common for all GnRH agonists.

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

Triptorelin causes a transient increase in circulating testosterone levels within the first week after the initial injection of the sustained release formulation. With this initial increase in circulating testosterone levels, a small percentage of patients ($\leq 5\%$) may experience a temporary worsening of signs and symptoms of their prostate cancer (tumour flare), usually manifested by an increase in urinary symptoms and metastatic pain 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 changes, 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$). No frequency can be determined for the adverse reactions reported after marketing. Therefore, they are classified 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 flushes			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, Onychoclasia, Pruritus, Rash	Angioneurotic oedema, , urticaria
Musculoskeletal and connective tissue disorders		Arthralgia, muscle spasms, Pain in extremities	Back pain, Myalgia	Muscular weakness

System Organ Class	Very Common	Common	Uncommon	Frequency not known
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 bleeding (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 ($\geq 10\%$) 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.

When used to treat infertility, the combination with gonadotrophins may result in ovarian hyperstimulation syndrome. Ovarian hypertrophy, pelvic and/or abdominal pain may be observed.

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

Breast Cancer

The most commonly observed adverse reactions associated with triptorelin treatment for up to 5 years in combination with either tamoxifen or an aromatase inhibitor in the TEXT and SOFT studies were hot flush, musculoskeletal disorder, fatigue, insomnia, hyperhidrosis, vulvovaginal dryness and depression.

The frequencies of the adverse reactions reported with triptorelin in combination with tamoxifen (N = 2325) or exemestane (N = 2318) are shown in the following table. The classifications are as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$).

System Organ Classes	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1000
Immune system disorders		Hypersensitivity		
Metabolism and nutrition disorders		Diabetes mellitus (glucose intolerance) Hyperglycaemia		
Psychiatric disorders	Insomnia Libido decreased Depression			
Nervous system disorders			Cerebral ischaemia Central nervous system haemorrhage	
Cardiac disorders			Myocardial Ischaemia	QT prolongation
Vascular disorders	Hot flush Hypertension	Embolism		
Gastrointestinal disorders	Nausea			
Skin and subcutaneous tissue disorders	Hyperhidrosis			
Musculoskeletal and connective tissue disorders	Musculoskeletal disorder Osteoporosis	Fracture		
Renal and urinary disorders	Urinary incontinence			
Reproductive system and breast disorders	Dyspareunia Vulvovaginal dryness			
General disorders and administration site conditions	Fatigue	Injection site reaction		

The ADRs identified above should be used in addition to the triptorelin ADRs identified in men and women in tables above to fully describe the ADR profile for the use of OFS in combination with either exemestane or tamoxifen.

Osteoporosis has been reported with a higher frequency with the use of triptorelin in combination with exemestane than in the combination with tamoxifen (39% versus 25%) (see section 4.4).

Musculoskeletal disorder and fractures were also more commonly reported in the combination with exemestane than in the combination with tamoxifen (89% versus 76% and 6.8% versus 5.2%, respectively).

Hypertension has been reported as a targeted adverse event at a very common frequency with triptorelin in combination with either exemestane or tamoxifen (23% and 22% respectively).

Hyperglycaemia and diabetes have been reported as targeted adverse events at a common frequency with triptorelin in combination with either exemestane or tamoxifen (hyperglycaemia: 2.6% and 3.4% respectively; diabetes: 2.3% and 2.3% respectively).

General tolerance in children (see section 4.4)

The frequency of the adverse reactions is classified as follows: very common ($\geq 1/10$); common ($\geq 1/100$ 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 reaction		Anaphylactic shock
Metabolism and nutrition disorders			Obesity	
Psychiatric disorders			Mood altered	Affect lability, Depression, Nervousness
Nervous system disorders		Headache		Idiopathic intracranial hypertension (<i>pseudotumor cerebri</i>) (see section 4.4) Convulsions*
Eye disorders			Vision impairment	Visual disturbance
Vascular disorders		Hot flush		Hypertension
Respiratory, thoracic and mediastinal disorders			Epistaxis	
Gastrointestinal disorders		Abdominal pain	Vomiting, Constipation, Nausea	
Skin and subcutaneous tissue disorders		Acne	Pruritus, Rash, Urticaria	Angioneurotic oedema
Musculoskeletal and connective tissue disorders			Neck pain	Myalgia
Reproductive system and breast disorders	Vaginal bleeding (including vaginal haemorrhage, withdrawal bleed, uterine haemorrhage, vaginal discharge, vaginal bleeding including spotting)		Breast pain	
General disorders and administration site conditions		Injection site reaction (including injection site pain, injection site erythema and injection site inflammation)	Malaise	
Investigations		Weight increased		Blood prolactin increased, Blood pressure increased

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

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: L 02 A E04: antineoplastic and immunomodulator.

Mechanism of action

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

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

Further studies in animals have suggested another mechanism of action: direct effects on the gonads by decreasing the sensitivity of peripheral receptors to GnRH.

Clinical efficacy and safety

Prostate cancer

The administration of a daily dose of triptorelin may initially increase LH and FSH blood levels (flare up) and consequently increase testosterone levels. Continuing the treatment decreases LH and FSH to concentrations that result in castration levels of steroids within 2-3 weeks and for as long as the product is administered.

The treatment may improve functional and objective symptoms.

A randomized phase III study 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).

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 non-inferiority post-hoc tests and for difference between treatment groups).

This study shows that the combination of radiotherapy and long term androgen deprivation therapy (3 years) is preferable to a combination of radiotherapy and short term androgen deprivation therapy (6 months).

Endometriosis

Prolonged treatment with triptorelin suppresses oestradiol secretion and thus enables resting of ectopic endometrial tissue.

Uterine fibromyomas

Studies conducted have shown a regular and pronounced decrease in the volume of certain uterine fibromyomas. This decrease is maximum during the third month of treatment.

Triptorelin treatment may induce amenorrhea after the first month of treatment in most patients. It may correct a possible anaemia resulting from menorrhagia and/or metrorrhagia.

Breast cancer

Clinical studies performed in premenopausal women with endocrine responsive early stage breast cancer have been conducted with triptorelin in order to suppress oestradiol ovarian secretion, the main source of oestrogens. Based on studies performed in healthy women and women with endometriosis, the effect of triptorelin is achieved 3-4 weeks after administration.

Two phase 3 studies (SOFT and TEXT) have explored the 5-year benefit of ovarian function suppression (OFS) in combination with tamoxifen (T) or an aromatase inhibitor (exemestane - E) in premenopausal women with endocrine responsive early stage breast cancer.

Triptorelin was the main treatment used to achieve OFS (91.0% of randomised subjects in the SOFT study, and 100% in the TEXT study). The remaining 9% of women in the SOFT study had bilateral oophorectomy or bilateral ovarian irradiation.

SOFT study results

The SOFT study was designed to answer the question of the added value of OFS to tamoxifen as adjuvant treatment of premenopausal women with endocrine responsive early stage breast cancer.

A total of 3047 women were analysed (1015 women in the T+OFS, 1018 women in the T alone and 1014 women in the E+OFS arm).

At a median follow-up of 67 months (5.6 years), treatment with T+OFS non significantly reduced the hazard of a Disease Free Survival (DFS) event versus T alone (HR=0.83; 95% CI, 0.66 to 1.04; p=0.10). The estimated 5-year DFS was 86.6% (95% CI, 84.2% to 88.7%) among women patients assigned to T+OFS compared with 84.7% (95% CI, 82.2% to 86.9%) for women assigned to T alone.

However, after adjustment for prespecified covariates in the multivariate Cox model, women assigned treatment with T+OFS had a significantly reduced hazard of a DFS event compared with women assigned T alone, with a reduction of 22% (HR=0.78; 95% CI, 0.62 to 0.98; p=0.03).

Women assigned treatment with T+OFS had a non-significantly reduced hazard of a breast cancer event compared with women assigned T alone (HR=0.81; 95% CI, 0.63 to 1.03; p=0.09). The estimated 5-year Breast Cancer Free Interval (BCFI) was 88.4% (95% CI, 86.1% to 90.3%) for women assigned treatment with T+OFS compared with 86.4% (95% CI, 84.0% to 88.5%) for women assigned T alone.

However, after adjusting for pre-specified covariates in the multivariable Cox model, women assigned T+OFS had a significantly reduced hazard of a BCFI event compared with women assigned T with a reduction of 25% (HR=0.75; 95% CI, 0.59 to 0.96; p=0.02).

The absolute benefit is higher in women who received adjuvant chemotherapy. The DFS rate at 5 years for women who received adjuvant chemotherapy was 80.7% in the T + OFS arm and 77.1% in the T arm only (HR=0.82; 95% CI, 0.64 to 1.07) with an absolute benefit of 3.6% for T+OFS.

In particular, the benefit of adding OFS was apparent for 5 year DFS in a post-hoc analysis for the subgroup of women less than 40 years old (HR=0.74; 95% CI, 0.53, 1.03) with an absolute benefit of 4.4% for T+OFS compared to T alone.

In the SOFT study, subjects assigned E+OFS had a statistically significantly reduced hazard of a DFS event, as compared with subjects assigned T alone (HR=0.68, 95% CI, 0.53 to 0.86). The estimated 5-year DFS rate was 89.0% (95% CI, 86.8% to 90.9%) among subjects assigned to E+OFS as compared with 84.7% (95% CI, 82.2% to 86.9%) among subjects assigned T alone.

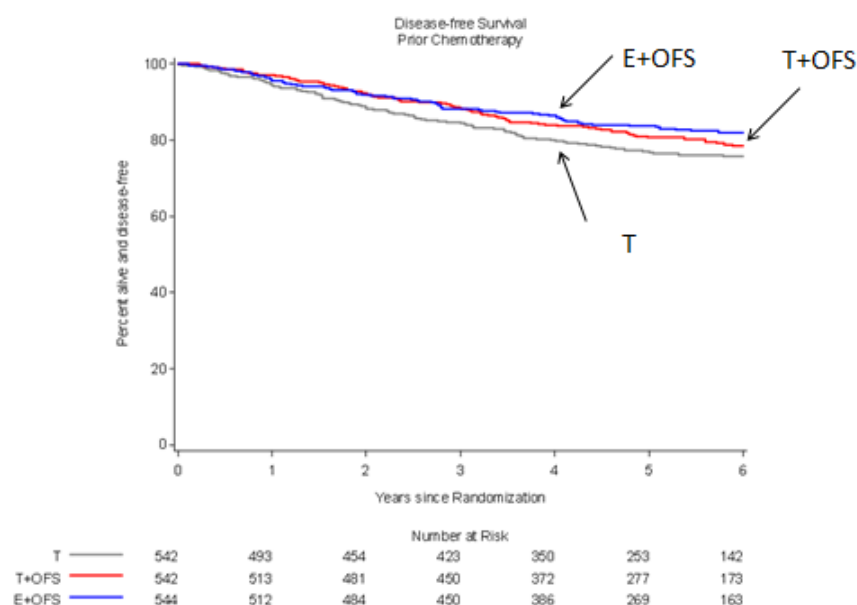
Subjects assigned E+OFS had a statistically significantly reduced hazard of a breast cancer event as compared with subjects assigned T alone (HR=0.64; 95% CI, 0.49 to 0.83). The estimated 5-year BCFI

was 90.9% (95% CI, 88.9% to 92.6%) among subjects assigned E+OFS compared with 86.4% (95% CI, 84.0% to 88.5%) among subjects assigned T alone.

Subjects assigned E+OFS had a statistically significantly reduced hazard of a distant recurrence as compared with subjects assigned T alone (HR=0.71; 95% CI, 0.52 to 0.96). The estimated 5-year Distant Recurrence Free Interval (DRFI) was 93.0% (95% CI, 91.2% to 94.5%) among subjects assigned E+OFS compared with 90.7% (95% CI, 88.6% to 92.4%).

The absolute benefit is higher in women who received adjuvant chemotherapy. The DFS rate at 5 years for women who received adjuvant chemotherapy was 83.8% in the E + OFS arm and 77.1% in the T arm only (HR=0.70, 95%CI, 0.53 to 0.92) with an absolute benefit of 6.7% for E+OFS.

Kaplan-Meier Estimates of DFS in women who received prior chemotherapy



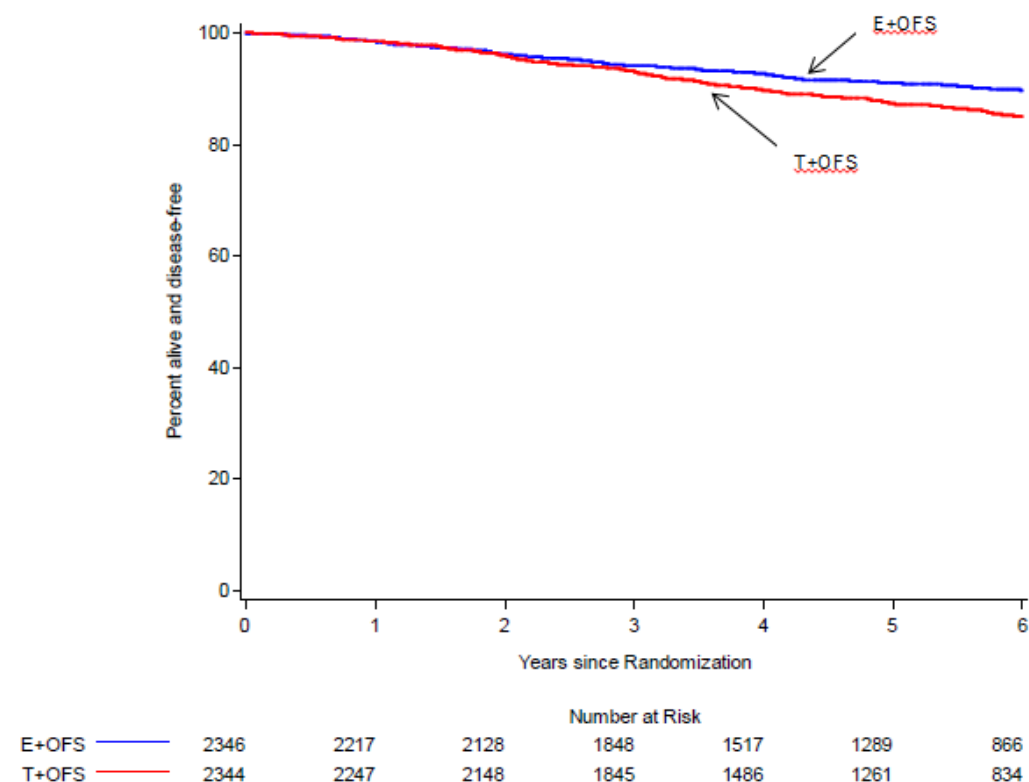
In the 3 arms SOFT study, women who received chemotherapy had a higher proportion of high risk clinical criteria of recurrence: 49.3% below age < 40, 56.9% with lymph nodes positive, 47.0% with breast tumour size > 2 cm and 33.7% with tumour grade 3.

Combined SOFT and TEXT study results

The primary objective of TEXT study was to evaluate the role of aromatase inhibitors (exemestane) in women treated with OFS compared with T+OFS including all women from SOFT and TEXT studies. A total of 4690 women were analysed: 2346 women in the E+OFS arm and 2344 women in the T+OFS arm.

At a median follow-up of 68 months (5.7 years), treatment with E+OFS statistically significantly reduced the hazard of a DFS event versus T+OFS (HR=0.72; 95% CI, 0.60 to 0.86; p=0.0002). The estimated 5-year DFS was 91.1% (95% CI, 89.7% to 92.3%) for women assigned to E+OFS compared with 87.3% (95% CI, 85.7% to 88.7%) for women assigned T+OFS.

Kaplan-Meier Estimates of DFS OFS+E vs OFS +T



Women assigned E+OFS had a statistically significantly reduced hazard of a breast cancer event compared with women assigned T+OFS (HR=0.66; 95% CI, 0.55 to 0.80; $P<0.0001$). The estimated 5 year BCFI was improved at 92.8% (95% CI, 91.6% to 93.9%) for women assigned E+OFS compared with 88.8% (95% CI, 87.3% to 90.1%) for women assigned T+OFS.

5.2 Pharmacokinetic properties

Following intramuscular injection of the sustained release form, an initial phase of release of the active substance is observed, followed by a further phase of regular release during 28 days ($C_{\max} = 0.32 \pm 0.12$ ng/ml) providing a mean, steady-state triptorelin release of 46.6 ± 7.1 µg/day, with product bioavailability of approximately 53% over one month.

5.3 Preclinical safety data

The molecule did not demonstrate any specific toxicity in animal toxicological studies. The effects observed were related to the pharmacological properties of the substance on the endocrine system. The resorption of the powder is complete within 40 - 45 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.

To be read carefully before the injection.

INSTRUCTION FOR USE

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

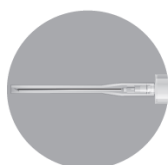
Prepare the patient by disinfecting the injection site. This operation needs to be performed first because once reconstituted, the drug should be injected immediately.

2 - PREPARATION OF THE INJECTION

Two needles are provided in the box:

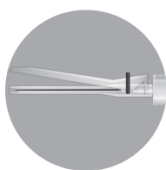
- **Needle 1:** a long needle (38 mm) without safety device to be used for reconstitution
- **Needle 2:** a long needle (38mm) with safety device to be used for injection

needle 1 - 38 mm



20 Gauge

needle 2 - 38 mm



20 Gauge

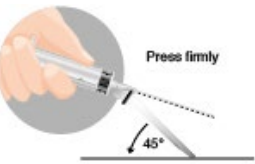
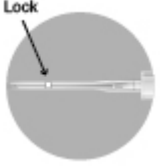
The presence of bubbles on top of the lyophilisate is a normal appearance of the product.
The following steps must be completed in a continuous sequence.

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 on to the syring 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 sedimentation, inject immediately into the disinfected area as quickly as possible (within 1 minute from reconstitution).	
4 – AFTER USE	

• 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. Used needles, any unused suspension or other waste material should be disposed of in accordance with local requirements.	 Method A or  Method B 
---	--

MANUFACTURER

IPSEN PHARMA BIOTECH
Chemin Departemental No. 402,
83870 Signes, France.

DATE OF REVISION

April 2025

PRODUCT REGISTRATION HOLDER

Zuellig Pharma Sdn Bhd
No. 15 Persiaran Pasak Bumi
Section U8, Perindustrian Bukit Jelutong
40150 Shah Alam, Selangor Darul Ehsan, Malaysia