1 NAME OF THE MEDICINAL PRODUCT

Diphereline® P.R. Powder and Solvent for Suspension for Injection 3.75 mg/vial

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

- **Endometriosis**

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

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

- **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.

4.2 Posology and method of adminstration

Posology

- **Prostate cancer**

One intramuscular injection of Diphereline P.R. 3.75 mg every 4 weeks.

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 PR 3.75 mg every 4 weeks. The treatment must be initiated 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 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 intramuscular injection of Diphereline PR 3.75 mg every 4 weeks. The treatment must be initiated in the first five days of the menstrual cycle. Clinical studies were conducted for durations between 3 to 4 months.

- **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 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 to 14 years.

- **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.

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 sustained 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

Hypersensitivity to GnRH, its analogues or to any of the excipients (see section 4.8).
Pregnancy and breast feeding.
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 appropriate if symptoms occur. Patients with known depression should be monitored closely during therapy.

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

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

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

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 results in suppression of the pituitary gonadal system. Normal function is usually restored after treatment is discontinued. Diagnostic tests of pituitary gonadal function conducted during treatment and after discontinuation of therapy with GnRH analogues may therefore be misleading.

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 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 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 (especially 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 at recommended dose, Diphereline P.R. 3.75 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.

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 premenopausal 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 premenopausal 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, premenopausal status should be confirmed following chemotherapy and before commencement of triptorelin, by blood concentrations of oestradiol and 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 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 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 an aromatase inhibitor than in 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. 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.

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 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 fertility in patients treated with GnRH analogues during childhood is 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.

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 P.R. 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 is not recommended 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 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)

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 estimated for post marketing adverse events. Therefore, they are classified as "Frequency not known".

System Organ Class	Very common	Common	Uncommon	Rare	Frequency not known
Infections and infestations				Nasopharyngitis	
Blood and lymphatic		Anaemia	Thrombocytosis		

system disorders					
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	
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		Nausea, dry mouth	Abdominal pain, constipation, diarrhoea, vomiting	Abdominal distension, dysgeusia, flatulence	
Skin and subcutaneous tissue disorders	Hyperhidrosis		Acne, alopecia, erythema, pruritus, rash,	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, dysstasia, 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 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 changes, dyspareunia, dysmenorrhoea, genital haemorrhage, ovarian hyperstimulation syndrome, ovarian hypertrophy, pelvic pain, abdominal pain, vulvovaginal dryness, hyperhidrosis, hot flushes and asthenia.

The following adverse reactions, considered as at least possibly related to triptorelin treatment, were reported. Most of these are known to be related to biochemical or surgical castration.

The frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥ 1/100 to <1/10), uncommon (≥1/1000 to <1/100). No frequency can be estimated for post marketing adverse events. Therefore, they are classified as "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	
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, diarrhoea, dry mouth, flatulence, mouth ulceration, vomiting	
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.

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.

The prolonged use of GnRH analogues can induce bone loss, risk factor of potential 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000).

System Organ Class	Very common	Common	Uncommon	Rare
Cardiac disorders			Myocardial ischaemia	QT prolongation
Endocrine disorders		Diabetes mellitus (glucose intolerance), hyperglycaemia		
Gastrointestinal disorders	Nausea			
General disorders and administration site conditions	Fatigue	Injection site reaction		
Immune system disorders		Hypersensitivity		
Musculoskeletal and connective tissue disorders	Musculoskeletal Disorder, osteoporosis	Fracture		
Nervous system disorders			Cerebral ischaemia, central nervous system haemorrhage	
Psychiatric disorders	Insomnia, libido decreased, depression			
Renal and urinary disorders	Urinary incontinence			
Reproductive system and	Dyspareunia, vulvovaginal			

breast disorders	dryness			
Skin and subcutaneous tissue disorders	Hyperhidrosis			
Vascular disorders	Hot flushes, hypertension	Embolism		

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 (≥1/10); common (≥ 1/100 to <1/10), uncommon (≥1/1000 to <1/100). No frequency can be estimated for post marketing adverse events. Therefore, they are classified as “Frequency not known”.

System Organ Class	Very common	Common	Uncommon	Frequency not known
Immune system disorders		Hypersensitivity		Anaphylactic shock
Metabolism and nutrition disorders			Obesity	
Psychiatric disorders			Mood altered	Affect lability, depression, nervousness
Nervous system disorders		Headache		
Eye disorders			Visual impairment	Visual disturbance
Vascular disorders		Hot flushes		Hypertension
Respiratory, thoracic and mediastinal			Epistaxis	

disorders				
Gastrointestinal disorders		Abdominal pain	Vomiting, constipation, nausea	
Skin and subcutaneous tissue disorders		Acne	Pruritus, 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	
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 increased, blood pressure increased

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 effect on the gonads by decreasing the sensitivity of the 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 may consequently increase initial testosterone levels. Continuing the treatment decreases LH and FSH levels 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 (mainly T2c-T4 with some T1C to T2B patients with pathological regional nodale 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 (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).

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 analysed (EORTC22863, 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 castration-resistant prostate cancer, clinical studies have shown the benefit from the addition of abiraterone acetate, an androgen biosynthesis inhibitor, or of enzalutamide, an androgen receptor inhibitor, to GnRH analogues, such as triptorelin.

Central 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.

Endometriosis

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

Uterine fibromyomas

Studies have demonstrated a consistent and marked reduction in uterine and/or fibroid volume becoming maximal in a three to six month treatment period.

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 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.

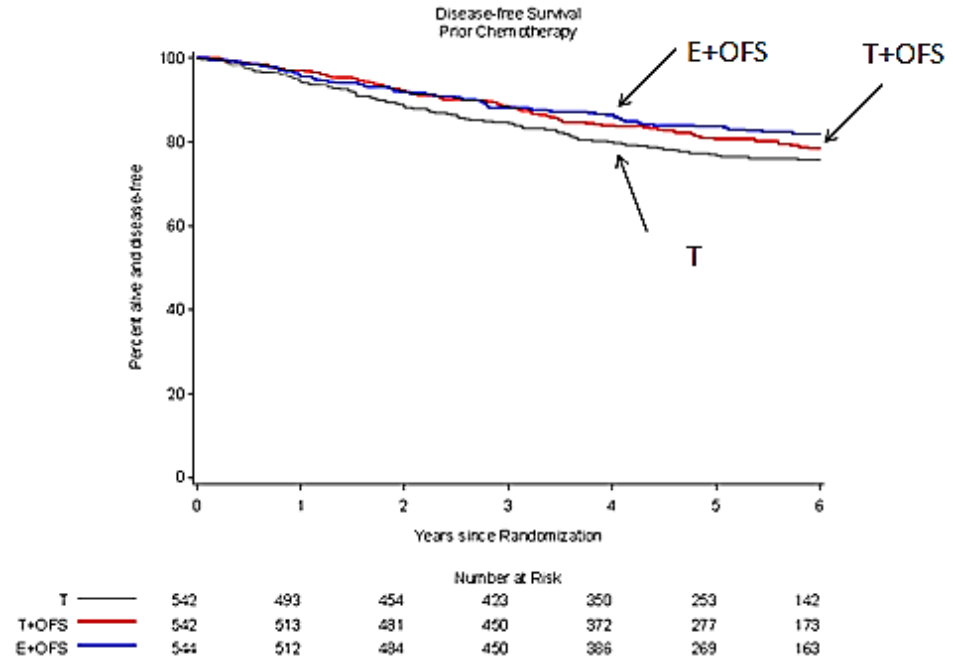
In the SOFT study, subjects assigned E+OFS had a statistically significantly reduced hazard of a DFS event, as compared with subjects assigned T alone (HR=0.68, 95% CI, 0.53 to 0.86). The estimated 5-year DFS rate was 89.0% (95% CI, 86.8% to 90.9%) among subjects assigned to E+OFS as compared with 84.7%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

Figure 1: Kaplan-Meier Estimates of DFS in women who received prior chemotherapy



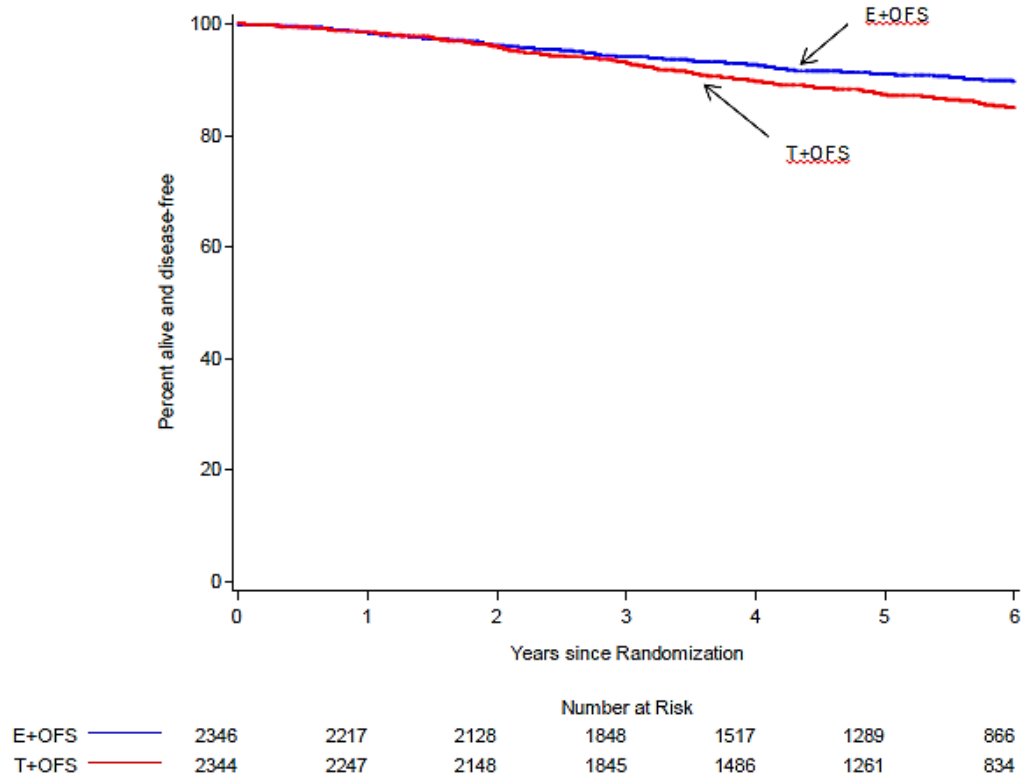
In the 3 arms SOFT study, women who received chemotherapy had a higher proportion of high risk clinical criteria of recurrence: 49.3% below age < 40, 56.9% with lymph nodes positive, 47.0% with breast tumour size > 2 cm and 33.7% with tumour grade 3.

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.

Figure 2: 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 phase of regular release during 28 days.

After intramuscular injection of Diphereline P.R. 3.75 mg in women with endometriosis and uterine fibroids the maximum blood level of triptorelin is obtained between 2 to 6 hours after injection, the peak value reached is 11 ng/mL. There was no evidence of accumulation of the product following monthly injections over six months.

Trough plasma concentrations are maintained between 0.1 and 0.2 ng/mL. The bioavailability of the sustained release product is approximately 50%.

These data observed in endometriosis and uterine fibroma patients can be extrapolated to breast cancer patients as it is not expected that the disease has an impact on the prolonged release properties of the product.

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 Incompatibilities

In absence of incompatibility study, this medicinal product should not be taken with other medicinal products.

6.2 Shelf life

3 years.
After reconstitution, an immediate use is recommended.

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 2 needles.

6.5 Instructions for use and handling

The suspension for injection must be reconstituted using an aseptic technique and only using the ampoule of solvent for injection.

The instructions for reconstitution hereafter and in the leaflet must be strictly followed.

The solvent should be drawn into the syringe provided using the reconstitution needle (20 G, without safety system) and transferred to the vial containing the powder. The suspension should be reconstituted by swirling the vial gently from side to side for long enough until a homogenous, milky suspension is formed. Do not invert the vial.

It is important to check there is no unsuspended powder in the vial. The suspension obtained should then be drawn back into the syringe, without inverting the vial. The reconstitution needle should then be changed and the injection needle (20 G, with safety device) used to administer the product.

As the product is a suspension, the injection should be administered immediately after reconstitution to prevent precipitation.

For single use only.

Used needles, any 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

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

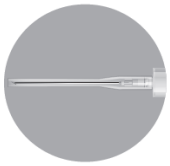
Prepare the patient by disinfecting the injection site. This operation needs to be performed first because once reconstituted, the drug should be injected immediately.

2 – PREPARATION OF THE INJECTION

Two needles are provided in the box:

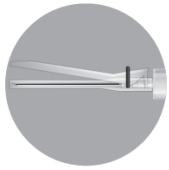
- **Needle 1**: a long needle (38 mm) without safety device to be used for reconstitution
- **Needle 2**: a long needle (38 mm) with safety device to be used for injection

needle 1 - 38 mm



20 Gauge

needle 2 - 38 mm

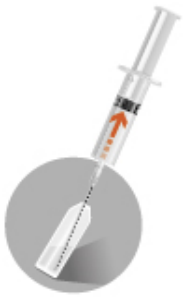


20 Gauge

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

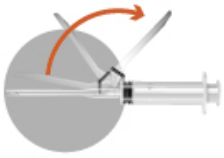
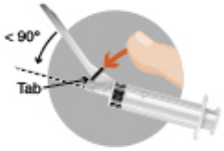
2a

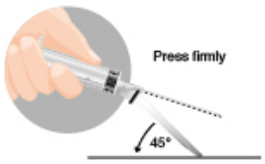
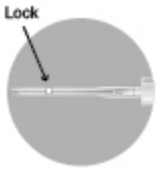
- Take out the ampoule containing the solvent. Tap any solution within the tip of the ampoule back to the main body of the ampoule.
- Screw Needle 1 (without safety device) on to the syringe. Do not remove the needle protection yet.
- Break open the ampoule with dot face up.
- Remove the needle protection from Needle 1. Insert the needle in the ampoule and draw up all the solvent into the syringe.
- Put aside the syringe containing the solvent.



2b

- Take out the vial containing the powder; Tap any powder which has accumulated at the top of the vial back to the bottom of the vial.

• Remove the plastic tap on the top of vial. • Take back the syringe containing the solvent and insert the needle through the rubber stopper vertically into the vial. Inject the solvent slowly, so that, if possible, it washes down the entire upper part of the vial.	
2c • Pull up Needle 1 above the liquid level. Do not remove the needle from the vial. Reconstitute the suspension by swirling gently from side to side. Do not invert the vial. • Make sure that the agitation is long enough to obtain an homogeneous and milky suspension. • Important: Check there is no unsuspended powder in the vial (if any powder clumps are present, continue swirling until they disappear).	
2d • When the suspension is homogeneous, pull down the needle without inverting the vial, draw up all of the suspension. A small amount will remain in the vial and should be discarded. An overfill is included to allow for this loss. • Grasp the coloured hub to disconnect the needle. Remove Needle 1 used for the reconstitution from the syringe. Screw on to the syringe Needle 2. • Move the safety sheath away from the needle and towards the syringe barrel. The safety sheath remains in the position you set. • Remove the needle protection from the needle. • Prime the needle to remove air from the syringe and inject immediately.	 
3 – INTRAMUSCULAR INJECTION	
• To avoid precipitation, inject immediately intramuscularly.	
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 engage 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 

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