SUMMARY OF PRODUCT CHARCTERISTICS

PAMORELIN®

NAME OF THE MEDICINAL PRODUCT

Pamorelin Powder for Suspension for Injection.

Strengths: 3.75 mg, 11.25 mg, and 22.5 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Pamorelin 3.75mg contains triptorelin embonate equivalent to 3.75 mg of triptorelin. After reconstitution in 2 ml solvent, 1 ml of reconstituted suspension contains 1.875 mg of triptorelin.

Each vial of Pamorelin 11.25 mg contains triptorelin embonate equivalent to 11.25 mg of triptorelin. After reconstitution in 2 ml solvent, 1 ml of reconstituted suspension contains 5.625 mg of triptorelin.

Each vial Pamorelin 22.5 mg contains triptorelin embonate equivalent to 22.5 mg of triptorelin. After reconstitution in 2 ml solvent, 1 ml of reconstituted suspension contains 11.25 mg of triptorelin.

PHARMACEUTICAL FORM

Pamorelin is supplied as lyophilized powder for intramuscular (IM) injection.

CLINICAL PARTICULARS

Therapeutic indications

Pamorelin 3.75 mg, 11.25 mg, and 22.5 mg is indicated for the treatment of locally advanced or metastatic, hormone-dependent prostate cancer.

Pamorelin 3.75 mg, 11.25 mg, and 22.5 mg are indicated as concomitant to and following radiotherapy in patients with high-risk localized or locally advanced prostate cancer.

Pamorelin 3.75 mg is indicated for the treatment of endometriosis.

Pamorelin 3.75 mg is indicated for the pituitary down-regulation in the context of assisted reproduction technology.

Pamorelin 3.75 mg is indicated as adjuvant treatment, in combination with tamoxifen or an aromatase inhibitor, of hormone receptor positive early stage breast cancer in women at high risk of recurrence who are confirmed as premenopausal after completion of chemotherapy.

Pamorelin 22.5 mg is indicated for the treatment of central precocious puberty (CPP) in children of 2 years of age and older with an onset of CPP before 8 years in girls and 10 years in boys.

Posology and method of administration

Pamorelin is administered by a single intramuscular injection.

Dosing schedule depends on the product strength selected (see Table 1).

Table 1 Pamorelin Recommended Dosing

Dosage	**3.75 mg**	**11.25 mg**	**22.5 mg**
Recommended dose	1 injection every 4 weeks	1 injection every 12 weeks	1 injection every 24 weeks

No dosage adjustment is necessary for patients with renal or hepatic impairment.

Endometriosis:

In women the treatment of endometriosis with Pamorelin 3.75 mg begins during the early follicular phase and should not exceed 6 months.

Pituitary down-regulation in the context of medically assisted procreation (IVF, GIFT etc.):

One intramuscular injection of Pamorelin 3.75 mg administered either in the early follicular phase, usually on the 2nd day of the menstrual cycle, or in the mid-luteal phase, usually on the 21st day of the previous cycle. In general, the stimulation by gonadotrophins should be performed when the plasma levels of oestrogens are consistent with ovarian suppression, usually less than 50 pg/ml around the 15th day of the cycle.

Breast cancer:

One intramuscular injection of Pamorelin 3.75 mg every 4 weeks in combination with tamoxifen or an aromatase inhibitor (AI).
Pamorelin 3.75 mg should be commenced after completion of chemotherapy, once pre-menopausal status has been confirmed.
The treatment with Pamorelin 3.75 mg must be initiated at least 6-8 weeks before starting aromatase inhibitor treatment. A minimum of two injections of Pamorelin 3.75 mg (with an interval of 4 weeks between injections) should be administered before commencement of aromatase inhibitor treatment.
During treatment with an aromatase inhibitor, Pamorelin 3.75 mg must not be interrupted to avoid rebound increases in circulating oestrogens.
The recommended treatment duration for adjuvant treatment in combination with other hormonotherapy is up to 5 years.

Prostate cancer:

In high-risk localized 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 **Clinical efficacy in men with prostate cancer**]. The treatment duration of androgen deprivation therapy recommended by medical guidances is 2-3 years in these patient populations receiving radiotherapy.

In patients with metastatic castration resistant prostate cancer not surgically castrated receiving a GnRH agonist, such as triptorelin, and eligible for treatment with an inhibitor of androgen biosynthesis (e.g. abiraterone acetate), or an inhibitor of androgen receptor function (e.g. enzalutamide), treatment with the GnRH agonist should be continued.

Central Precocious Puberty:

The treatment of children with Pamorelin 22.5 mg should be under the overall supervision of a paediatric endocrinologist or of a paediatrician or an endocrinologist with expertise in the treatment of central precocious puberty.

Treatment should be stopped around the physiological age of puberty in boys and girls and should not be continued in girls with a bone maturation of more than 12-13 years. There are limited data available in boys relating to the optimum time to stop treatment based on bone age, however it is advised that treatment is stopped in boys with a bone maturation age of 13-14 years.

Method of Administration

The lyophilized microgranules are to be reconstituted using 2 mL of sterile water for injection (see **Special precautions for disposal and other handling**).

The solvent for suspension should be drawn into the injection syringe and transferred to the vial containing the powder. The vial should be agitated to thoroughly disperse particles and obtain a uniform suspension. The agitation should be done by moving back and forth from bottom to top and back and forth from left to right alternately. The suspension will appear milky. The suspension obtained should be drawn back into the injection syringe. The injection needle has to be changed and the resulting suspension for injection should be administered immediately. The suspension should be discarded if not used immediately after reconstitution.

Once reconstituted, the suspension of Pamorelin should be injected relatively rapidly and in an uninterrupted manner in order to avoid any potential blockage of the needle.

Since Pamorelin is a suspension of microgranules for intramuscular (IM) injection only, inadvertent intravascular injection must be strictly avoided.

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

Pamorelin must be administered under the supervision of a physician.

Contraindications

Pamorelin is contraindicated in patients with known hypersensitivity to triptorelin, GnRH (Gonadotropin releasing hormone), other GnRH agonist analogues or to any of the excipients of Pamorelin.

Pamorelin is contraindicated in patients with spinal cord compression secondary to prostate cancer metastases.

Pamorelin is contraindicated during pregnancy and breast-feeding.

Pamorelin is contraindicated in patients with unexplained vaginal bleedings.

Initiation of aromatase inhibitor before adequate ovarian suppression with triptorelin has been achieved is contraindicated.

Special warnings and precautions for use

Caution is required in patients treated with anticoagulants, due to the potential risk of haematomas at the site of injection.

Pamorelin contains less than 1 mmol sodium per dose.

Pituitary apoplexy

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

Depression

Mood changes, including depression have been reported with androgen deprivation therapy. However, a hypothetical mechanism for suicide attempt in patients suffering from prostate cancer might be an aggravation of underlying depression in at psychiatric risk patients. Patients with known risk of depression should be monitored closely during therapy.

Prostate cancer

Reduction in bone density

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. This may also lead to an incorrect diagnosis of bone metastases.

The use of GnRH agonists may cause reduction in bone mineral density. In men, preliminary data suggest that the use of a bisphosphonate in combination with a GnRH agonist may reduce bone mineral loss. 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).

Transient Increase in Serum Testosterone

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.

Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, hematuria, or ureteral or bladder outlet obstruction.

A small number of patients may experience a temporary worsening of signs and symptoms of prostate cancer (tumour flare) and a temporary increase in cancer related pain (metastatic pain), which can be managed symptomatically.

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

Metastatic Vertebral Lesions and Urinary Tract Obstruction

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 surgical castration considered. Careful monitoring is indicated during the first weeks of treatment, particularly in patients suffering from vertebral metastases, at risk of spinal cord compression, and in patients with urinary tract obstruction.

Effect on QT/QTc Interval

Prolongation of the QT interval has been observed during long-term androgen deprivation therapy. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients who are at significant risk of developing prolongation of QT such as those with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure or in patients receiving class IA or class III antiarrhythmic medications.

Hyperglycemia and diabetes

Hyperglycaemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycaemia may represent development of diabetes mellitus or worsening of glycaemic control in patients with diabetes. Monitor blood glucose and/or glycosylated haemoglobin (HbAlc) periodically patients receiving a GnRH agonist and manage with current practice for the treatment of hyperglycaemia or diabetes.

Cardiovascular diseases

An increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratio, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and managed according to current clinical practice.
Adjustment of antihypertensive therapy may be required in patients receiving such medication.

Laboratory Test Interactions

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.

Women

It should be confirmed that the patient is not pregnant before prescription of Pamorelin.

Reduction in bone mineral density

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 abuse, 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; IVF

Used at the recommended dose, triptorelin causes 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.

Follicular recruitment, induced by the use of GnRH analogues and gonadotrophins, may be markedly increased in a minority of predisposed patients, particularly in case of Polycystic Ovarian Syndrome. As with other GnRH analogues there have been reports of ovarian hyperstimulation syndrome (OHSS) associated with the use of triptorelin in combination with gonadotrophins.

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.

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, 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, 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 premenopausal 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 assessments 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.
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.

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

Hyperglycaemia and diabetes were reported as 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.

Premenopausal women with breast cancer receiving triptorelin in combination with exemestane or tamoxifen should have regular monitoring of cardiovascular risk factors and blood pressure.

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.

Precocious puberty

Treatment of children with progressive brain tumours should follow a careful individual appraisal of the risks and benefits.

Pseudo-precocious puberty (gonadal or adrenal tumour or hyperplasia) and gonadotropin-independent precocious puberty (testicular toxicosis, familial Leydig cell hyperplasia) should be precluded.

In girls, initial ovarian stimulation at treatment initiation, followed by the treatment-induced oestrogen withdrawal, may lead, in the first month, to vaginal bleeding of mild or moderate intensity.

The therapy is a long-term treatment, adjusted individually. Pamorelin 22.5 mg should be administered as precisely as possible in regular 6 monthly (24 weekly) periods. An exceptional delay of the injection date for a few days (169 ± 3 days) does not influence the results of the therapy.

After discontinuation of treatment the development of puberty characteristics will occur.

Information with regards to future fertility is still limited but future reproductive function and fertility appears to be unaffected by GnRH treatment. In most girls, regular menses will start on average one year after ending the therapy.

Bone mineral density may decrease during GnRH agonist therapy for central precocious puberty due to the expected effects of oestrogen suppression. However, after cessation of treatment subsequent bone mass accrual is preserved and peak bone mass in late adolescence does not seem to be affected by treatment.

Slipped capital femoral epiphysis can be seen after withdrawal of GnRH agonist treatment. The suggested theory is that the low concentrations of oestrogen during treatment with GnRH agonists weaken the epiphyseal 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.

Interaction with other medicaments and other forms of interaction

No drug interaction studies involving triptorelin have been conducted.

Human pharmacokinetic data with triptorelin suggest that C-terminal fragments produced by tissue degradation are either degraded completely within tissues or are rapidly degraded further in plasma or cleared by the kidneys. Therefore, hepatic microsomal enzymes (Cytochromes P450, CYP) are unlikely to be involved in the metabolism of triptorelin. In addition, in vitro data showed that triptorelin was not a significant CYP inhibitor, CYP inducer, P-glycoprotein (P-gP) substrate or inhibitor. Therefore, drug-drug interactions with triptorelin are unlikely. However, in the absence of relevant data and as a precaution, hyperprolactinemic drugs should not be used concomitantly with triptorelin since hyperprolactinemia reduces the number of pituitary GnRH receptors.

Since prolongation of the QT interval has been observed during androgen deprivation, 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, procainamide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products should be carefully evaluated.

Fertility, Pregnancy and Breast-feeding

Pregnancy:

Triptorelin **must** 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:

Pamorelin is contraindicated during lactation period.

Fertility:

In the context of medically assisted procreation, triptorelin has often been used in controlled studies to suppress endogenous gonadotropins and oestrogens.

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 certain undesirable effects, such as dizziness, somnolence, epileptic seizures, and abnormal vision, could impair the ability to drive and use machines.

Undesirable effects

General tolerance in men

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: Initial increase in testosterone levels, followed by almost complete suppression of testosterone. These effects, observed in approximately 50 % of the patients, included hot flushes, impotence, 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 Pamorelin treatment were reported. Most of these events are known to be related to biochemical or surgical castration.

The frequency of the adverse reactions is classified as follows: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10000, <1/1000), very rare (<1/10000).

Table 2 Treatment-Related Adverse Reactions in men

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare***	***Additional post-marketing Frequency not known***
Blood and lymphatic system disorders			Thrombocytosis		
Cardiac disorders			Palpitations		QT prolongation*
Ear and labyrinth disorders			Tinnitus Vertigo		
Eye disorders			Visual impairment	Abnormal sensation in eye Visual disturbance	
Gastrointestinal disorders		Dry mouth Nausea	Abdominal pain Constipation Diarrhoea Vomiting	Abdominal distension Dysgeusia Flatulence	
General disorders and administration site conditions	Asthenia	Injection site reaction (including erythema inflammation and pain) Oedema	Lethargy Oedema peripheral Pain Rigors Somnolence	Chest pain Dysstasia Influenza like illness Pyrexia	Malaise
Immune system disorders		Hypersensitivity		Anaphylactic reaction	Anaphylactic shock
Infections and infestations				Nasopharyngitis	

Investigations		Weight increase	Alanine aminotransferase increased Aspartate aminotransferase increased, Blood creatinine increased Blood pressure increased Blood urea increased Gamma-glutamyl transferase increased Weight decreased	Blood alkaline phosphatase increased	
Metabolism and nutrition disorders			Anorexia Diabetes mellitus Gout Hyperlipidaemia Increased appetite		
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	
Nervous system disorders	Paraesthesia in lower limbs	Dizziness Headache	Paraesthesia	Memory impairment	
Psychiatric disorders	Libido decreased	Loss of libido Depression* Mood changes*	Insomnia Irritability	Confusional state Decreased activity Euphoric mood	Anxiety
Renal and urinary disorders			Nocturia Urinary retention		Urinary incontinence
Reproductive system and breast disorders	Erectile dysfunction (including ejaculation failure, ejaculation disorder)	Pelvic plain	Gynaecomastia Breast pain Testicular atrophy Testicular pain		
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis	Orthopnoea	
Skin and subcutaneous tissue disorders	Hyperhidrosis		Acne Alopecia Erythema Pruritus Rash Urticaria	Blister Purpura	Angioneurotic oedema
Vascular disorders	Hot flush	Hypertension		Hypotension	

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

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, usually manifested by an increase in urinary symptoms or cancer-related pain, which can be managed symptomatically (see Section Special warnings and special precautions for use). Isolated cases of exacerbation of disease symptoms, either urethral obstruction or spinal cord compression by metastasis have occurred. Therefore, patients with metastatic vertebral lesions and/or with upper or lower urinary tract obstruction should be closely observed during the first few weeks of therapy.

The use of synthetic GnRH analogues to treat prostate cancer may be associated with increased bone loss and may lead to osteoporosis and increases the risk of bone fracture. This may also lead to an incorrect diagnosis of bone metastases.

General tolerance in Women

As a consequence of decreased oestrogen levels, the most commonly reported adverse events (expected in 10% of women or more) were headache, libido decreased, sleep disorder, mood altered, dyspareunia, dysmenorrhoea, vaginal bleeding, ovarian hyperstimulation syndrome, ovarian hypertrophy, pelvic pain, abdominal pain, vulvovaginal dryness, hyperhidrosis, hot flushes and asthenia.

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

The frequency of the adverse reactions is classified as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (cannot be estimated from the available data).

Table 3 Treatment-related Adverse Reactions in Women

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Frequency not known***
Cardiac disorders			Palpitations	
Ear and labyrinth disorders			Vertigo	
Eye disorders			Dry eye Visual impairment	Visual disturbance
Gastrointestinal disorders		Nausea Abdominal pain Abdominal discomfort	Abdominal distension Dry mouth Flatulence Mouth ulceration Vomiting	Diarrhoea
General disorders and administration site conditions	Asthenia	Injection site reaction (including pain, swelling, erythema and inflammation) Oedema peripheral		Pyrexia Malaise
Immune system disorders		Hypersensitivity		Anaphylactic shock
Investigations		Weight increased	Weight decreased	Blood alkaline phosphatase increased Blood pressure increased
Metabolism and nutrition disorders			Decreased appetite Fluid retention	
Musculoskeletal and connective tissue disorders		Arthralgia Muscle spasms Pain in extremities	Back pain Myalgia	Muscular weakness
Nervous system disorders	Headache	Dizziness	Dysgeusia Hypoastesia Syncope Memory impairment Disturbance in attention Paraesthesia Tremor	
Psychiatric disorders	Sleep disorder (including insomnia) Mood disorder Libido decreased	Depression* Nervousness	Affect lability Anxiety Depression** Disorientation	Confusional state
Reproductive system and breast disorders	Breast disorder Dyspareunia Genital bleeding (including vaginal bleeding withdrawal bleed) 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

Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis	
Skin and subcutaneous tissue disorders	Acne Hyperhidrosis Seborrhea		Alopecia Dry skin Hirsutism Onychoclasis Pruritus Rash	Angioneurotic oedema Urticaria
Vascular disorders	Hot flush			Hypertension

* 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

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. Vaginal bleeding including menorrhagia, metrorrhagia may occur in the month following the first injection.

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

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 combined were hot flushes, musculoskeletal disorders, fatigue, insomnia, sweating, 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).

Table 4 Treatment-related Adverse Reactions in Women with Breast cancer

System Organ Classes	***Very Common ≥1/10***	***Common ≥1/100 to <1/10***	***Uncommon ≥1/1000 to <1/100***
Cardiac disorders			myocardial Ischaemia
Endocrine disorders		diabetes mellitus (glucose intolerance) hyperglycaemia	
Gastrointestinal disorders	nausea		
General disorders and administration site conditions	fatigue sweating	injection site reaction	
Immune system disorders		hypersensitivity	
Musculoskeletal and connective tissue disorders	musculoskeletal disorder osteoporosis	fracture	
Nervous system disorders		central nervous system haemorrhage	cerebral ischaemia

System Organ Classes	***Very Common*** ***≥1/10***	***Common*** ***≥1/100 to <1/10***	***Uncommon*** ***≥1/1000 to <1/100***
Psychiatric disorders	insomnia libido decreased depression		
Renal and urinary disorders	urinary incontinence		
Reproductive system and breast disorders	dyspareunia vulvovaginal dryness		
Vascular disorders	hot flush 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%).

Musculoskeletal disorder and fractures were also more commonly reported in combination with exemestane than in 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 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

Table 5 Treatment-related Adverse Reactions in Children

System Organ Class	*Very Common Treatment related AEs*	*Common Treatment related AEs*	*Uncommon Treatment related AEs*	*Additional Post-marketing Frequency unknown*
Eye disorders			Visual impairment	Visual disturbance
Gastrointestinal disorders		Abdominal pain	Vomiting Constipation Nausea	
General disorders and administration site conditions		Injection site reaction (including injection site pain, injection site erythema and injection site inflammation)	Malaise	
Immune system disorders		Hypersensitivity		Anaphylactic shock
Investigations		Weight increased		Blood pressure increased Blood prolactin increased
Metabolism and nutrition disorders			Obesity	
Musculoskeletal and connective tissue disorders			Neck pain	Myalgia
Nervous system disorders		Headache		
Psychiatric disorders			Mood altered	Affect lability Depression Nervousness
Reproductive system and breast disorders	Vaginal bleeding (including vaginal haemorrhage, withdrawal bleed, uterine haemorrhage, vaginal discharge, vaginal bleeding including spotting)		Breast pain	

Respiratory, thoracic and mediastinal disorders			Epistaxis	
Skin and subcutaneous tissue disorders		Acne	Pruritus Rash Urticaria	Angioneurotic oedema
Vascular disorders		Hot flush		Hypertension

Treatment with GnRH analogues may reveal the presence of a previously unknown gonadotroph cell pituitary adenoma. These patients may present with pituitary apoplexy which is characterized by sudden headache, vomiting, visual impairment and ophthalmoplegia.

Increased lymphocyte count has been reported with patients undergoing GnRH analogue treatment. This secondary lymphocytosis is apparently related to GnRH induced castration and seems to indicate that gonadal hormones are involved in thymic involution.

Hypersensitivity and anaphylactic reactions have been reported with triptorelin.

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

Overdose

The pharmaceutical properties of Pamorelin and its mode of administration make accidental or intentional overdose unlikely. There is no human experience of overdose. Animal tests suggest that no effect other than the intended therapeutic effects on sex hormone concentration and on the reproductive tract will be evident with higher doses of Pamorelin. If overdose occurs, this should be managed symptomatically.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group:

Hormones and related agents, gonadotrophin releasing hormone analogues.

ATC code: L02AE04

Mechanism of action and pharmacodynamic effects

Triptorelin, a GnRH agonist, acts as a potent inhibitor of gonadotrophin secretion when given continuously and in therapeutic doses. In males, animal and human studies show that after administration of triptorelin there is an initial and transient increase in circulating levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone.

However, chronic and continuous administration of triptorelin results in decreased LH and FSH secretion and suppression of testicular and ovarian steroidogenesis. A reduction of serum testosterone levels into the range normally seen in surgically castrated men occurs approximately 2 to 4 weeks after initiation of therapy.

Pamorelin 3.75 mg is designed to deliver 3.75 mg of triptorelin over a 1-month period. Once the castration levels of testosterone have been achieved by the end of the first month, serum testosterone levels are maintained for as long as the patients receive their injection every four weeks.

Pamorelin 11.25 mg is designed to deliver 11.25 mg of triptorelin over a 3-month period. Once the castration levels of testosterone have been achieved by the end of the first month, serum testosterone levels are maintained for as long as the patients receive their injection every twelve weeks.

Pamorelin 22.5 mg is designed to deliver 22.5 mg of triptorelin over a 6-month period. Once the castration levels of testosterone have been achieved by the end of the first month, serum testosterone levels are maintained for as long as the patients receive their injection every twenty-four weeks.

This results in accessory sexual organ atrophy. These effects are generally reversible upon discontinuation of the medicinal product. The effectiveness of treatment can be monitored by measuring serum levels of testosterone and prostate specific antigen. As shown during the clinical trial program, there was a 97%, 96%, and 97% median relative reduction in prostate specific antigen (PSA) at month 6 for Pamorelin 3.75 mg, 11.25 mg, and 22.5 mg, respectively.

In animals, administration of triptorelin resulted in the inhibition of growth of some hormone-sensitive prostate tumours in experimental models.

In treated women, menstruation returns approximatively 2 months after the last injection of Pamorelin.

Clinical efficacy in men with prostate cancer

Following a single intramuscular injection of Pamorelin 3.75 mg to healthy male volunteers, serum testosterone levels first increased by peaking on day 4 and thereafter declined to low levels by 4 weeks. By week 8, following this single injection, low levels of testosterone were no longer maintained. A similar serum testosterone profile was observed in patients with

advanced prostate cancer when injected intramuscularly with triptorelin embonate and following the second injection testosterone levels were maintained within the castrate range.

Administration of Pamorelin 3.75 mg (1-month) formulation and Pamorelin 11.25 mg (3-month) to patients with advanced prostate cancer as an intramuscular injection for a total of 9 and 3 doses, respectively, over 9 months resulted in both achievement of castration levels of testosterone in 92.7% and 97.7% of patients after four weeks and in maintenance of castrate levels of testosterone from month 2 through month 9 of treatment in 94.2 % and 94.4% of patients receiving 1-month and 3-month formulations, respectively.

Administration of Pamorelin 22.5 mg to patients with advanced prostate cancer as an intramuscular injection for a total of 2 doses (12 months) resulted in both achievement of castrate levels of testosterone in 97.5% of patients after four weeks and maintenance of castrate levels of testosterone in 93.0% of the patients from month 2 through month 12 of treatment.

Evidence for the indication of high-risk localized or locally advanced prostate cancer is based on published studies of radiotherapy combined with GnRH analogues. Clinical data from seven published studies were analyzed (EORTC 22961, EORTC 22991 and EORTC 22863, RTOG 85-31, RTOG 92-02, RTOG 86-10, D'Amico et al, 2008), which all demonstrate a benefit for the combination of GnRH analogue with radiotherapy.
The results of these studies show that radiotherapy followed by 3 year androgen deprivation therapy is preferable to radiotherapy followed by 6 months androgen deprivation therapy.

In patients with metastatic castration-resistant prostate cancer, clinical studies have shown the benefit from the addition of an androgen biosynthesis inhibitor (e.g. abiraterone acetate), or of an androgen receptor inhibitor (e.g. enzalutamide) to GnRH analogues, such as triptorelin.

Clinical efficacy in women

Following a single intramuscular injection of Pamorelin 3.75 mg to healthy premenopausal women, the mean time to oestradiol suppression was around 4 days and the mean duration of oestradiol suppression was around 27 days.

Endometriosis
Continued administration of triptorelin induces suppression of the oestrogen secretion and thus enables resting of ectopic endometrial tissue.
In a randomized, single-blind, clinical trial conducted in 137 women with clinically verified endometriosis comparing triptorelin (3.75 mg IM q4w x 6) with leuprolide (3.75 mg IM q4w x6), triptorelin was shown to be comparable to leuprolide in relieving or reducing the clinical symptoms associated with endometriosis.
Of the women who participated in the study, 80% showed reduction in pelvic pain, 100% showed reduction in dysmenorrhea, and 66% showed reduction in dyspareunia from baseline after 6 months of triptorelin therapy. Serum oestradiol levels were suppressed (<184 pmol/L) by 4 weeks, and were maintained at suppressed levels for the remainder of the 6 month treatment period. The range of oestradiol levels attained at 6 months (24 weeks) of therapy was 17 – 128 pmol/L. By 12 weeks, most women (90%) also became amenorrheic in response to the low levels of oestrogen. Once treatment ended, the mean time to return to menses was 81 days (range: 6 – 116). Oestrogen levels returned to baseline values by 3 months post treatment.

Down-regulation in the context of medically assisted procreation (IVF)
The administration of triptorelin induces an initial phase of gonadotrophin stimulation (FSH and LH) followed by an inhibition phase. The treatment ensures suppression of the intercurrent LH peak enabling enhanced folliculogenesis and increased follicular retrieval and in consequence a greater percentage of pregnancies per cycle.

Breast cancer:
Clinical studies performed in premenopausal women with hormone receptor positive early stage breast cancer have been conducted with triptorelin in order to suppress ovarian oestradiol secretion, the main source of oestrogens. Based on studies performed in healthy women and women with endometriosis**,** the effect of triptorelin in terms of oestradiol suppression is achieved 3-4 weeks after the treatment initiation.

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

Triptorelin was the main treatment used to achieve OFS (91.0% of randomized 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.

The SOFT study was designed to answer the question of the added value of OFS to tamoxifen as adjuvant treatment of pre-menopausal women with hormone receptor-positive early stage breast cancer.

The SOFT study included subjects following breast surgery who remained premenopausal after the completion of adjuvant or neoadjuvant chemotherapy and premenopausal women who had not received chemotherapy and for whom adjuvant T alone was considered suitable treatment. Subjects were randomized to receive E+OFS, T+OFS or T alone.

The TEXT study was designed to evaluate the role of aromatase inhibitors (AIs) (exemestane) in the adjuvant treatment of premenopausal women with hormone receptor positive early stage breast cancer who are treated with OFS.

In the TEXT study women were included following breast surgery and randomized to treatment with T+OFS or E+OFS; those receiving chemotherapy commenced it concurrently with the GnRH agonist triptorelin after randomization.
The primary efficacy endpoint in both studies was disease-free survival (DFS) and secondary endpoints included breast cancer-free interval (BCFI), and overall survival (OS).

<u>SOFT study results</u>
The OFS question analysis compared DFS between subjects randomly assigned to T+OFS versus T alone. At a median follow-up of 67 months (5.6 years), DFS events were reported for 160/1018 subjects (15.7%) receiving T alone and 139/1015 subjects (13.7%) receiving T+OFS (HR 0.78; 95% CI: 0.62 – 0.98).
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). OS was also improved in women receiving T+OFS as compared to women receiving T alone (HR=0.74; 95% CI: 0.51 – 1.09).

Overall, 53.3% of subjects received prior chemotherapy (i.e. subjects who tended to have a high risk of recurrence of breast cancer). The absolute difference at 5 years was more notable among subjects who received prior chemotherapy: DFS, 80.7% (T+OFS) versus 77.1% (T alone) (see Table 6).

Table 6 OFS Question: 67-month Efficacy Results for Subjects who Received Prior Chemotherapy (ITT Population)

Efficacy Endpoints	T Alone N=542		T+OFS N=542		T Alone vs T+OFS Hazard Ratio (95% CI)
	Events	Event-free rates (%)	Events	Event-free rates (%)	
DFS[a]	122	77.1	107	80.7	0.82 (0.64 to 1.07)
BCFI	116	78.0	97	82.5	0.78 (0.60 to 1.02)
OS[b]	57	90.9	39	94.5	0.64 (0.42 to 0.96)

BCFI=breast cancer-free interval, CI=confidence interval, DFS=disease-free survival, DRFI=distant recurrence-free interval, ITT=intention-to-treat, OFS=ovarian function suppression, OS=overall survival, T=tamoxifen

a Disease-free survival is defined as the first occurrence of local or distant recurrence, contralateral breast cancer, or death from any cause

b Overall survival data immature at 67-months.

An updated analysis after a median follow-up of 8 years of subjects with previous chemotherapy has confirmed the positive benefit/risk profile of the 8-year OFS with triptorelin treatment with DFS, 76.7% (T+OFS) versus 71.4% (T alone); BCFI, 78.9% (T+OFS) versus 73.6% (T alone) and OS, 89.4 (T+OFS) versus 85.1% (T alone).

Combined SOFT and TEXT study results

The AI Question analysis combined the data from TEXT and SOFT studies and compared DFS between subjects randomly assigned to E+OFS versus T+OFS.

At a median follow-up of 68 months (5.7 years), DFS events were reported for 514/4690 subjects (11.0%) in the ITT population. Overall, the estimated 5-year DFS was improved at 91.1% (95% CI, 89.7% to 92.3%) among subjects assigned to E+OFS versus 87.3% (95% CI, 85.7% to 88.7%) among subjects assigned to T+OFS (HR=0.717; 95% CI, 0.602 to 0.855; p=0.0002). 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). OS was similar in women receiving E+OFS as compared to women receiving T+OFS (HR=1.14; 95% CI: 0.86 – 1.51). Table 7 shows the efficacy results for subjects who received prior chemotherapy in the AI analysis.

Table 7 AI Question: 68-month Efficacy Results for Subjects who Received Prior Chemotherapy (ITT Population)

Efficacy Endpoints	E+OFS N=544		T+OFS N=543		Hazard Ratio E+OFS vs T+OFS (95% CI)
	Events	Event-free rates (%)	Events	Event-free rates (%)	
DFS[a]	81	84.3	98	80.6	0.84 (0.62 to 1.13)
BCFI	72	86.1	90	82.2	0.82 (0.60 to 1.12)

AI=aromatase inhibitor, BCFI=breast cancer-free interval, CI=confidence interval, DFS=disease-free survival, E=exemestane, DRFI=distant recurrence-free interval, ITT=intention-to-treat, OFS=ovarian function suppression, OS=overall survival, T=tamoxifen

a Disease-free survival is defined as the first occurrence of local or distant recurrence, contralateral breast cancer, or death from any cause.

An updated analysis after a median follow-up of 8 years of subjects with previous chemotherapy has confirmed the positive benefit/risk profile of the 8-year OFS with triptorelin treatment with DFS, 80.4% (E+OFS) versus 76.7% (T+OFS) and BCFI, 82.3% (E+OFS) versus 78.9% (T+OFS), and OS, 87.2% (E+OFS) versus 89.4% (T+OFS).

Clinical efficacy in children

Administration of Pamorelin 22.5 mg to children with precocious puberty as an intramuscular injection for a total of 2 doses (12 months) resulted in suppression of stimulated LH concentrations to prepubertal levels in 95.5% of subjects by month 3 and 9, and in 93.2 % and 97.7% of subjects at months 6 and 12, respectively.

The consequence is a regression or stabilization of secondary sex characteristics and slowing down of accelerated bone maturation and growth. In girls, initial ovarian stimulation at treatment initiation, followed by the treatment-induced oestrogen increase, may lead, in the first month, to uterine 'withdrawal' bleeding of mild or moderate intensity.

Pharmacokinetic properties

Absorption:

Pamorelin 3.75 mg: Following a single intramuscular injection in patients with prostate cancer, median (range) t_{max} was 2 (2-4) hours and geometric mean C_{max} after the first injection was 15.6 (9.1-25.2) ng/mL.

Pamorelin 11.25 mg: Following a single intramuscular injection in patients with prostate cancer, median (range) t_{max} was 2 (2-6) hours and geometric mean C_{max} after the first injection was 35.8 (16.5-57.4) ng/mL.

Pamorelin 22.5 mg: Following a single intramuscular injection in patients with prostate cancer, median (range) t_{max} was 3 (2-12) hours and geometric mean C_{max} after the first injection was 40.0 (22.2-76.8) ng/mL. In children with precocious puberty t_{max} was 4 (2-8) hours and C_{max} (0-169 days) was 39.9 (19.1-107.0) ng/ml.

Triptorelin did not accumulate over 9 months (Pamorelin 3.75 mg and 11.25 mg) or 12 months (Pamorelin 22.5 mg) of treatment.

After IM administration of triptorelin embonate 1-month formulation in healthy premenopausal women, triptorelin serum concentration peaked at 2 hours (range 1 to 4 hours) post-dose with a geometric mean C_{max} of 18.5 ng/mL (range 1.34 to 35.7 ng/mL).

The geometric mean AUC over 29 days was 211.6 ng•h/mL (range 39.1 to 349.5 ng•h/mL).

Distribution:

Results of pharmacokinetic investigations conducted in healthy men indicate that after intravenous bolus administration, triptorelin is distributed and eliminated according to a 3-compartment model and corresponding half-lives are approximately 6 minutes, 45 minutes, and 3 hours.

The volume of distribution at steady state of triptorelin following intravenous administration of 0.5 mg triptorelin acetate is approximately 30 l in healthy male volunteers. Since there is no evidence that triptorelin at clinically relevant concentrations binds to plasma proteins, medicinal product interactions involving binding-site displacement are unlikely.

Biotransformation:

Metabolites of triptorelin have not been determined in humans. However, human pharmacokinetic data suggest that C-terminal fragments produced by tissue degradation are either completely degraded within tissues or are rapidly further degraded in plasma, or cleared by the kidneys.

Elimination:

Triptorelin is eliminated by both the liver and the kidneys. Following intravenous administration of 0.5 mg triptorelin to healthy male volunteers, 42 % of the dose was excreted in urine as intact triptorelin, which increased to 62 % in subjects with hepatic impairment. Since creatinine clearance (Cl_{creat}) in healthy volunteers was 150 ml/min and only 90 ml/min in subjects with hepatic impairment, this indicates that the liver is a major site of triptorelin elimination. In these healthy volunteers, the true terminal half-life of triptorelin was 2.8 hours and total clearance of triptorelin 212 ml/min, the latter being dependent on a combination of hepatic and renal elimination.

Special populations:

Following intravenous administration of 0.5 mg triptorelin to subjects with moderate renal insufficiency (Cl_{creat} 40 ml/min), triptorelin had an elimination half-life of 6.7 hours, 7.81 hours in subjects with severe renal insufficiency (Cl_{creat} 8.9 ml/min) and 7.65 hours in patients with impaired hepatic function (Cl_{creat} 89.9 ml/min).

The effects of age and race on triptorelin pharmacokinetics have not been systematically studied. However, pharmacokinetic data obtained in young healthy male volunteers aged 20 to 22 years with an elevated creatinine clearance (approximately 150 ml/min) indicated that triptorelin was eliminated twice as fast in the young population. This is related to the fact that triptorelin clearance is correlated to total creatinine clearance, which is well known to decrease with age.

Because of the large safety margin of triptorelin and since Pamorelin is a sustained release formulation, no dose adjustment is recommended in patients with renal or hepatic impairment.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetics/pharmacodynamics relationship of triptorelin is not straightforward to assess, since it is non-linear and time-dependent. Thus, after acute administration in naive subjects, triptorelin induces a dose-dependent increase of LH and FSH responses.

When administered as a sustained release formulation, triptorelin stimulates LH and FSH secretion during the first days post dosing and, in consequence, testosterone secretion. As shown by the results of the different bioequivalence studies, the maximal increase in testosterone is reached after around 4 days with an equivalent C_{max} which is independent from the release rate of triptorelin. This initial response is not maintained despite continuous exposure to triptorelin and is followed by a progressive and equivalent decrease of testosterone levels. In this case too, the extent of triptorelin exposure can vary markedly without affecting the overall effect on testosterone serum levels.

Preclinical safety data

The toxicity of triptorelin towards extragenital organs is low.

The observed effects were mainly related to the exacerbation of the pharmacological effects of triptorelin.

In chronic toxicity studies at clinically relevant doses, triptorelin induced macro- and microscopic changes in the reproductive organs of male rats, dogs and monkeys. These were considered as a reaction to suppressed gonadal function caused by the pharmacological activity of the compound. The changes were partly reversed during recovery. After subcutaneous administration of 10 µg/kg to rats on days 6 to 15 of gestation, triptorelin did not elicit any embryotoxic, teratogenic, or any other effects on the development of the offspring (F1 generation) or their reproductive performance. At 100 µg/kg, a reduction in maternal weight gain and an increased number of resorptions were observed.

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.

At a dose equivalent to 8 times the recommended human therapeutic dose (based on body surface area), animal studies showed adverse effects on organogenesis in rats (maternal toxicity and embryotoxicity). Isolated cases of hydroureter have been observed in young rats exposed *in utero* to high doses of triptorelin.

In the context of medically assisted procreation, triptorelin has often been used in controlled studies to suppress endogenous gonadotropins and oestrogens.

PHARMACEUTICAL PARTICULARS

List of excipients

Powder:

Poly (d,l-lactide-co-glycolide)
Mannitol
Carmellose sodium (carboxymethylcellulose sodium)
Polysorbate 80

Incompatibilities

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

Shelf life

3 years.

Use immediately after reconstitution.

From a microbiological point of view, the ready-for-use suspension for injection should be used immediately.

Special precautions for storage

Do not store above 30°C.

For storage conditions of the reconstituted medicinal product see Section Shelf-life.

Pack size

Each box of Pamorelin contains vial(s) of the lyophilized triptorelin embonate powder.

Pamorelin 3.75 mg is available in boxes of 1 vial or 3 vials.

Pamorelin 11.25 mg is available in boxes of 1 vial or 2 vials.

Pamorelin 22.5 mg is available in boxes of 1 vial.

Not all presentations may be available locally

Special precautions for disposal and other handling

The powder should be suspended immediately before use. The powder is to be suspended in 2 ml Sterile water for injection.

The homogenous, milky suspension for injection is reconstituted by agitation. The agitation should be done by moving back and forth from bottom to top and back and forth from left to right alternately.

The suspension should be discarded if it is not administered immediately after reconstitution. See also Section Shelf-life.

For intramuscular use only. Do not administer intravenously.

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

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

Manufactured by:

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