SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pamorelin 22.5 mg powder for suspension for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Pamorelin 22.5 mg is indicated in the treatment of high-risk localised or locally advanced hormone-dependent prostate cancer in combination with radiotherapy. See section 5.1.

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

4.2 Posology and method of administration

Posology

The recommended dose of Pamorelin 22.5 mg is 22.5 mg of triptorelin (1 vial) administered every six months (twenty four weeks) as a single intramuscular injection.

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

Patients with renal or hepatic impairment

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

Paediatric population

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

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:

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

Precautions to be taken before handling or administrating the medicinal product

Pamorelin 22.5 mg is only intended for intramuscular use.

Since Pamorelin 22.5 mg is a suspension of microgranules, inadvertent intravascular injection must be strictly avoided.

Pamorelin 22.5 mg must be administered under the supervision of a physician.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

Triptorelin is contraindicated during pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

General Warnings

Hypersensitivity reactions:
A few rare allergic reactions have been observed shortly after injection of Pamorelin 22.5 mg. Rare cases of anaphylactic shock and angioneurotic oedema have been described following triptorelin administration.

Pituitary apoplexy:
Rare cases of pituitary apoplexy (clinical syndrome resulting from pituitary infarction) have been described in patients treated with GnRH agonists. Most cases occurred within 2 weeks, and some within an hour of the first injection. Pituitary apoplexy has manifested itself as sudden headache, vomiting, visual disturbances, ophthalmoplegia, an altered mental state and sometimes cardiovascular collapse. Immediate medical intervention is essential. GnRH agonists should therefore not be administered in cases of known pituitary adenoma.

Mood disorders/depression:
In patients undergoing treatment with GnRH agonists, an increased risk of incident depression (which may be severe and includes very rare cases of suicidal ideation or suicide attempts from post marketing experience). Patients should be informed accordingly and treated appropriate if symptoms occur. Patients with known depression should be monitored closely during therapy.

Convulsions:

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

Patients on anticoagulants:

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

Other precautions:

Paraesthesia and severe migraines are rare. In severe or recurrent cases, discontinue treatment.

An increase in the lymphocyte count has been described in patients treated with GnRH analogues.

Warning for the treatment of Prostate cancer

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. This is also possible if the interval between 2 injections is > 24 weeks. 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 tumour flare and a 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 metastases, at the risk of spinal cord compression, and in patients with urinary tract obstruction.

After surgical castration, triptorelin does not induce any further decrease in serum testosterone levels. Once 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 6 months (twenty four weeks). The effectiveness of treatment can be monitored by measuring serum levels of testosterone and prostate specific antigen.

Osteoporosis/bone density:

The use of GnRH agonists may cause reduction in bone mineral density and osteoporosis, thus increasing the risk of fractures. The consequence may be a false diagnosis of bone metastases. 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).

Risk of Diabetes/cardiovascular risk:

Epidemiological studies have revealed that patients may experience metabolic changes (e.g. glucose intolerance, fatty liver), and an increased risk of diabetes mellitus and/or cardiovascular disease during androgen deprivation therapy. Patients at high risk for

metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.

Effect on QT/QTc interval:
Androgen deprivation therapy may prolong the QT interval. In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5) physicians should assess the benefit risk ratio including the potential for Torsade de pointes prior to initiating Pamorelin 22.5 mg.

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

Warning on the treatment of Central precocious puberty:

Before treatment is started, the diagnosis of CPP must be confirmed based on suitable hormone assays (e.g. a GnRH stimulation test) and the proven presence of the corresponding clinical symptoms.

Treatment of children with progressive intracranial 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.

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

Epiphysiolis:
Slipped capital femoral epiphysis can be seen after withdrawal of GnRH agonist treatment. The suggested theory is that the low concentrations of oestrogen during treatment with GnRH agonists weaken the epiphysial plate. The increase in growth velocity after stopping the treatment subsequently results in a reduction of the shearing force needed for displacement of the epiphysis.

Bone density:
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.

Pharmaceutical excipients of particular interest:

Pamorelin 22.5 mg contains less than 1 mmol (23 mg) sodium per dose, i.e. essentially “sodium-free”.

4.5 Interaction with other medicaments and other forms of interaction

When triptorelin is co-administered with drugs affecting pituitary secretion of gonadotrophins caution should be taken and it is recommended that the patient's hormonal status should be supervised.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Pamorelin 22.5 mg 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 Pregnancy and lactation

Pregnancy

Pamorelin 22.5 mg is indicated for adult men and children. There are very limited data on the use of triptorelin in pregnant women. Pamorelin 22.5 mg is not indicated for use in females.

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 return.

Animal studies have shown effects on reproductive parameters (see section 5.3 Preclinical safety data).

Lactation

It is not known whether triptorelin passes into breast milk or whether it could affect breast milk production. Pamorelin 22.5 mg is not indicated in lactating women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, the ability to drive and use machines may be impaired should the patient experience dizziness, somnolence, and visual disturbances being possible undesirable effects of treatment, or resulting from the underlying disease.

4.8 Undesirable effects

General tolerance in men

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 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 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); unknown frequency (based on spontaneous reports for market surveillance for which the frequency cannot be specified)

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare***	***Additional post-marketing Unknown frequency***
Blood and lymphatic system disorders			Thrombocytosis		Anaemia
Cardiac disorders			Palpitations		QT prolongation* (see sections 4.4 and 4.5)
Ear and labyrinth disorders			Tinnitus Vertigo		
Endocrine disorders					Pituitary apoplexy**
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 alkaline phosphatase increased	

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare***	***Additional post-marketing Unknown frequency***
			Blood pressure increased Blood urea increased Gamma-glutamyl transferase increased Weight decreased		
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	Convulsions ***
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		Unrinary 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

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare***	***Additional post-marketing Unknown frequency***
Vascular disorders	Hot flush	Hypertension		Hypotension	

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

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

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

Triptorelin 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 Special warnings and precautions for use).

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

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

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, < 1/10); uncommon (≥ 1/1000, < 1/100); unknown frequency (based on spontaneous reports for market surveillance for which the frequency cannot be specified.

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Additional Post-marketing Unknown frequency***
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	

System Organ Class	*Very Common*	*Common*	*Uncommon*	*Additional Post-marketing Unknown frequency*
Musculoskeletal and connective tissue disorders			Neck pain	Myalgia
Nervous system disorders		Headache		Idiopathic intracranial hypertension (pseudotumor cerebri) (see section 4.4) Convulsions *
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

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

General

Increased lymphocytes 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.

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

4.9 Overdose

The pharmaceutical properties of Pamorelin 22.5 mg 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 22.5 mg. If overdose occurs, this should be managed symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 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. 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), testosterone in males and oestradiol in females.

However, chronic and continuous administration of triptorelin results in decreased LH and FSH secretion and suppression of testicular and ovarian steroidogenesis.

In men with prostate cancer:

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 22.5 mg is designed to deliver 22.5 mg of triptorelin over a 6-month (24 weeks) period. Once the castration levels of testosterone have been achieved by the end of the first month (4 weeks), 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 programme, there was a 97% median relative reduction in prostate specific antigen (PSA) at month 6 for Pamorelin 22.5 mg.

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

Clinical efficacy and safety in prostate cancer

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 castration levels of testosterone in 97.5% of patients after four weeks and maintenance of castration levels of testosterone in 93.0% of the patients from Month 2 through Month 12 of treatment.

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

In a phase III randomized clinical trial (EORTC 22961) including 970 patients with locally advanced prostate cancer (mainly T2c-T4 with some T1C to T2B patients with pathological regional nodal disease) of whom 483 were assigned to short-term androgen suppression (6 months) in combination with radiation therapy and 487 to long-term therapy (3 years), a non-inferiority analysis compared the short term to long term concomitant to and following hormonal treatment with LHRH agonists , mainly triptorelin (62.2%) or goserelin (30.1%).

Overall, total mortality at 5 years in the "short-term hormonal treatment" and "long-term hormonal treatment" groups was 19.0% and 15.2% respectively, with a relative risk of 1.42 (an upper one sided 95.71% CI = 1.79; or two sided 95.71% CI = [1.09; 1.85], p = 0.65 for non-inferiority and p = 0.0082 for post-hoc test of difference between groups of treatment). The 5-year mortality specifically related to the prostate cancer in the " short-term hormonal treatment "and" long-term hormonal treatment" groups was 4.78% and 3.2% respectively, with a relative risk of 1.71 (95% CI = [1.14 to 2.57], p = 0.002).

Overall quality of life using QLQ-C30 did not differ significantly between the two groups (P= 0.37).

Evidence for the indication of high-risk localized prostate cancer is based on published studies of radiotherapy combined with GnRH analogues. Clinical data from five published studies were analysed (EORTC 22863, RTOG 85-31, RTOG 92-02, RTOG 86-10, and D'Amico et al., JAMA, 2008), which all demonstrate a benefit for the combination of GnRH analogue with radiotherapy. Clear differentiation of the respective study populations for the indications locally advanced prostate cancer and high-risk localized 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 androgren receptor inhibitor, to GnRH analogues, such as triptorelin.

Clinical efficacy and safety in children with precocious puberty

In a non-comparative clinical study, 44 children with central precocious puberty (39 girls and 5 boys) were treated with a total of two intramuscular injections of Pamorelin 22.5 mg over 12 months (48 weeks). Suppression of stimulated LH concentrations to prepubertal levels was achieved 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 stabilisation 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.

5.2 Pharmacokinetic properties

Absorption:

Following a single intramuscular injection of Pamorelin 22.5 mg in patients with prostate cancer, t_{max} was 3 (2-12) hours and C_{max} (0-169 days) 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 12 months of treatment.

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.

Other 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 22.5 mg 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.

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

poly (d,l-lactide-co-glycolide)
mannitol
carmellose sodium (carboxymethylcellulose sodium)
polysorbate 80

6.2 Incompatibilities

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

6.3 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.

6.4 Special precautions for storage

Do not store above 30ºC.

For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Pack size

Each box of Pamorelin contains vial(s) of the drug product.

Pamorelin 22.5 mg is available in boxes of 1 vial.

6.6 Special precautions for disposal and other handling

The powder should be suspended immediately before use. The powder is to be suspended in 2ml Sterile water for injection. The homogenous, milky suspension for injection is reconstituted by vigorous agitation by up and down movements for 30 seconds.

After reconstitution in the vial, the injection should be done with 2 minutes.

Withdraw the suspension into the syringe.

Do not prime the needle before injection.

The suspension of Pamorelin 22.5 mg should be intramuscularly injected within 10 seconds relatively rapidly and uninterrupted manner in order to avoid any potential blockage of the needle.

For single use only.

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

The suspension should be discarded if it is not administered immediately after reconstitution. See also section 6.3.

7. PRODUCT REGISTRATION HOLDER

Orient Europharma (M) Sdn Bhd
E-08 Garden Shoppe, One City
Jalan USJ 25/1C, 47650 Subang Jaya
Selangor, Malaysia

8. MARKETING AUTHORISATION NUMBER(S)

MAL18116083ARZ

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15.11.2018

DATE OF REVISION OF THE TEXT

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