Note:
Purple/double strikethrough: relocated text, current place
Purple: relocated text, proposed place
Red/strikethrough: deleted text
Blue: additional text and amended information

Changes related to procedure XXX :
Text highlighted in Yellow: Alignment to Swiss PI and the following changes: addition of warning and adverse reaction for anaemia, convulsions; revision of the warning for depression to include very rare case of suicidal ideation; correction of the SOC for adverse reactions fracture, diabetes and hyperglycaemia).

Changes related to procedure No. 201111302012A :
Text highlighted in Green: Addition of the new indication IVF.

SUMMARY OF PRODUCT CHARACTERISTICS

Justification

1. NAME OF THE MEDICINAL PRODUCT

Pamorelin 3.75 mg powder for suspension for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pamorelin 3.75 mg is supplied as lyophilized powder for Intramuscular (IM) injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pamorelin 3.75 mg is indicated for the treatment of locally advanced or metastatic prostate cancer.

Pamorelin 3.75 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 3.75 mg is indicated for the treatment of endometriosis. See section 5.1.

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

Addition of the indication for pituitary down-regulation in the context of assisted reproduction technology in procedure No. 201111302012A.

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

4.2 Posology and method of administration

Posology

The recommended dose of Pamorelin 3.75 mg is 3.75 mg of triptorelin (1 vial) administered once a month (4 weeks) as a single intramuscular injection.

Prostate cancer:

In high-risk localised or 'locally advanced hormone-dependent prostate cancer as concomitant to and following radiation therapy' clinical data have show 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.

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 assisted reproduction technology :

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.

Text revised according to NPRA's request received on 27.02.2026 during procedure No. 201111302012A. Alignment of the posology to the one approved in Singapore Package Insert.

Breast cancer:

An intramuscular injection administered 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 (see section 4.4).

The treatment with Pamorelin 3.75 mg should 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 should not be interrupted to avoid rebound increases in circulating estrogens in pre-menopausal women.

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

Patients with renal or hepatic impairment

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

Paediatric population

The safety and efficacy of Pamorelin 3.75 mg have not been established in neonates, infants, children and adolescents, therefore Pamorelin 3.75 mg is not indicated for the use in these populations.

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

Since Pamorelin 3.75 mg is a suspension of microgranules, inadvertent intravascular injection must be strictly avoided.

Pamorelin 3.75 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).

Breast cancer in premenopausal women.

Initiation of aromatase inhibitor therapy before achieving sufficient ovarian function suppression using triptorelin (see sections 4.2 and 4.4).

4.4 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.~~

Text moved to align to Swiss PI

~~*Pharmaceutical excipients of particular interest:*~~

~~Pamorelin 3.75 mg contains less than 1 mmol sodium per dose, i.e. essentially "sodium-free".~~

Text moved at the end of the section 4.4 to align with Swiss PI following NPRA's request received on 27.01.2026 during procedure 112701 Moreover, a subtitle is added for sake of clarity.

General Warnings	Subtitle added for sake of clarity
Hypersensitivity reactions: A few rare allergic reactions have been observed shortly after injection of Pamorelin 3.75 mg. Rare cases of anaphylactic shock and angioneurotic oedema have been described following triptorelin administration.	Alignment to Swiss PI
Pituitary apoplexy: Rare~~ly~~ cases of pituitary apoplexy (clinical syndrome resulting from pituitary infarction) have been described in patients treated ~~treatment~~ with GnRH agonists ~~may reveal the presence of a previously unknown gonadotroph cell pituitary adenoma~~. Most cases occurred within 2 weeks, and some within an hour of the first injection. ~~These patients may present with a~~ Pituitary apoplexy has manifested itself as ~~characterized by~~ sudden headache, vomiting, visual disturbances ~~impairment~~, ~~and~~ 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.	Alignment to Swiss PI
Mood disorders/depression: In patients undergoing treatment with GnRH agonists, ~~there is~~ 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) was reported. Patients should be informed accordingly and treated appropriately if symptoms occur. Patients with known depression should be monitored closely during therapy	Text moved to align to Swiss PI. Indeed, warning moved from prostate cancer subsection to general subsection as this warning is applicable to all populations. Moreover, wording is revised to include suicidal ideation, and suicide attempts as per Depression/Suicidal_ideation/ Suicide_attemps Module2.5 section 2.5.5.2
Convulsions: Convulsions have been reported during treatment with GnRH analogues, particularly in women and children. Some of these patients had risk factors for convulsions (such as a history of epilepsy, intracranial tumours or concomitant treatment with drugs known to pose a risk of reactions in the form of convulsions). But convulsions have also been reported in patients in the absence of such risk factors.	Added as per Convulsion Module2.5 section 2.5.5.2.
Patients on anticoagulants: Caution is required in patients treated with anticoagulants, due to the potential risk of haematomas at the site of injection.	Addition of subtitle for sake of clarity and text moved to align to Swiss PI. Wording of the warning revised for alignment with other strength

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.

Alignment to Swiss PI

Warning on the treatment of Prostate cancer

Revision of subtitle for sake of clarity and to align to Swiss PI

~~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).~~

~~There is an increased risk of incident depression (which may be severe) in patients undergoing treatment with GnRH agonists, such as Triptorelin. Patients should be informed accordingly and treated appropriate if symptoms occur. Patients with known depression should be monitored closely during therapy.~~

Text moved to align to Swiss PI

~~Initially, t~~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 > 4 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.

Text relocated according to NPRA's request received on 27.01.2026 during procedure 112701.

A small number of patients may experience a temporary worsening of signs and symptoms of their prostate cancer (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 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 monthly injection (4 weeks). The effectiveness of treatment can be monitored by measuring serum levels of testosterone and prostate specific antigen.

Osteoporosis/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.~~

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. ~~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).

Text moved to align to Swiss PI. Reorganisation of the information about risk of bone loss and osteoporosis. Addition of subtitle for sake of clarity. Addition of precisions and information as per Swiss PI.

Text deleted according to NPRA's request received on 27.01.2026 during procedure 112701.

Risk of diabetes/cardiovascular risk:

~~In addition, from~~ Epidemiological studies ~~data~~, ~~it has been observed~~ have revealed that patients may experience metabolic changes (e.g. glucose intolerance, fatty liver), or an increased risk of diabetes mellitus and/or cardiovascular disease during androgen deprivation therapy. ~~However, prospective data did not confirm the link between treatment with GnRH analogues and an increase in cardiovascular mortality~~. Patients at high risk for metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.

Text moved, revision of the information to align to Swiss PI and addition of subtitle for sake of clarity.

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 3.75 mg.

Addition of subtitle for sake of clarity

~~In addition, from epidemiological data, it has been observed that patients may experience metabolic changes (e.g. glucose intolerance, fatty liver), or an increased risk of cardiovascular disease during androgen deprivation therapy. However, prospective data did not confirm the link between~~

Text moved above to align to Swiss PI

~~treatment with GnRH analogues and an increase in cardiovascular mortality. Patients at high risk for metabolic or cardiovascular diseases should be carefully assessed before commencing treatment and adequately monitored during androgen deprivation therapy.~~	
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.	Added as per Anaemia Module 2.5 section 2.5.5.2
~~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.~~	It is proposed to remove this paragraph as redundant with information provided above under subsection for Prostate cancer warning.
~~*Women*:~~ ~~It should be confirmed that the patient is not pregnant before prescription of Pamorelin.~~	As per Swiss PI this information is removed as already presented in subsection 4.5 Pregnancy and Lactation.
Warnings on pituitary down-regulation in the context of assisted reproduction technology: The risk of ovarian hyperstimulation cannot be ruled out, even in the case of prior treatment with triptorelin. Extreme caution (clinical and ultrasound monitoring) is required at the first signs of hyperstimulation, especially if it has been induced by exogenous gonadotropins during or at the end of the luteal phase. The clinical and paraclinical signs of even moderate hyperstimulation are hypovolaemia, tachycardia, hypotension, oliguria, dehydration, ascites, pleural effusion, and disorders of renal function and coagulation, which may require hospitalisation depending on their severity. In the case of stimulation induced by exogenous gonadotropins (in the context of medically assisted reproduction), the risk of twins or ectopic pregnancy is increased. This is why ultrasound monitoring of the pregnancy is essential during the first 4 weeks.	Addition of the warning on medically assisted reproduction following the proposal of the new indication in procedure No. 201111302012A.
Warning on the treatment of Breast cancer	Revision of subtitle for sake of clarity and to align to Swiss PI
The treatment of pre-menopausal women with hormone receptor-positive early-stage breast cancer with triptorelin in combination with tamoxifen or an aromatase inhibitor should be subject to a careful individual risk-benefit assessment.	Text moved at the beginning of the section to align to Swiss PI
In pre-menopausal breast cancer patients, treatment with an aromatase inhibitor should only be initiated after sufficient	Addition of text for alignment to Swiss PI

suppression of ovarian function has been achieved with triptorelin (see also "Posology and method of administration"). To ensure that ovarian function is sufficiently suppressed in premenopausal women, triptorelin therapy should be administered for at least 6-8 weeks prior to starting aromatase inhibitor, and triptorelin injections should be administered as stated every four weeks and without any interruption during the aromatase inhibitor therapy.

Patients who have stopped triptorelin treatment must also stop aromatase inhibitors within one month of the last triptorelin administration (28-day formulation).

Text moved at the beginning of the section to align to Swiss PI

Women who are premenopausal at the time of the diagnosis and who become amenorrhoeic following chemotherapy may or may not have continued estrogenic production from the ovaries. Following chemotherapy and prior to starting triptorelin therapy, regardless of the menstrual status, pre menopause must be confirmed by determining whether blood levels of oestradiol and follicle-stimulating hormone (FSH) are consistent with those of premenopausal women so as to avoid unnecessary triptorelin treatment in the case that menopause has been induced by the chemotherapy.

After starting triptorelin therapy, it is important to confirm that ovarian function has been adequately suppressed (menopause induced by GnRH analogue) by regularly assessing circulating FSH and oestradiol levels if aromatase inhibitor therapy is planned in this subpopulation of women, in line with clinical practice guidelines in force. As a result, ovarian function suppression must be confirmed by low blood levels of FSH and oestradiol prior to starting aromatase inhibitor treatment, and the doses must be repeated every three months for as long as triptorelin is associated with an aromatase inhibitor.

The objective of this is to avoid rebound increases in circulating estrogen levels induced by the aromatase inhibitor, with consequential implications for breast cancer. It should be noted that circulating levels of FSH are reduced in response to the ovarian function suppression induced by the inhibition of the gonadotrope function by the GnRH analogue (induced menopause), unlike natural menopause where FSH levels are elevated.

~~Triptorelin, when used as adjuvant therapy in association with tamoxifen or an aromatase inhibitor, is associated with an increased risk of osteoporosis. Osteoporosis has been reported more frequently in patients using triptorelin in association with an aromatase inhibitor than in those using triptorelin in association with tamoxifen (39% versus 25%).~~

Text removed to align to Swiss PI. Indeed, Swiss Health Authorities', requested us to remove these paragraphs and to replace them by "*The treatment of pre-menopausal women with hormone*

~~Bone mineral density should be assessed prior to triptorelin therapy, in particular among women with multiple risk factors for osteoporosis. These patients must be closely monitored and treatment for, or prophylaxis of, osteoporosis should be initiated when appropriate.~~	*receptor-positive early-stage breast cancer with triptorelin in combination with tamoxifen or an aromatase inhibitor should be subject to a careful individual risk-benefit assessment."*
~~Treatment of premenopausal women with endocrine responsive early-stage breast cancer with triptorelin in association with tamoxifen or an aromatase inhibitor should follow a careful individual appraisal of the risks and benefits~~	Text moved to align to Swiss PI
~~Patients who have discontinued triptorelin therapy must also discontinue aromatase inhibitors in the month following the last administration of triptorelin (28-day formulation).~~	Text moved to align to Swiss PI
~~The risk of musculoskeletal disorders (including joint or musculoskeletal pain) when triptorelin is used in association with either an aromatase inhibitor or tamoxifen is around 89% and 76%, respectively.~~	Text moved to align to Swiss PI
Hypertension has been very frequently reported as an adverse event subject to special supervision when triptorelin is associated with either exemestane or tamoxifen (see section 4.8). Premenopausal women with breast cancer receiving triptorelin in association with either exemestane or tamoxifen should have regular monitoring of cardiovascular risk factors and blood pressure.	
Hyperglycemia and diabetes have been frequently reported as adverse events subject to special supervision when triptorelin is associated with either exemestane or tamoxifen (see section 4.8). Premenopausal women with breast cancer receiving triptorelin in association with either exemestane or tamoxifen should have regular monitoring of risk factors for diabetes with blood glucose monitoring on a regular basis, and anti-diabetic treatment initiated, if necessary, according to national guidelines.	
Depression was reported in approximately 50% of patients treated with triptorelin in association 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.	
The risk of musculoskeletal disorders (including joint or musculoskeletal pain) when triptorelin is used in association with either an aromatase inhibitor or tamoxifen is around 89% and 76%, respectively.	Text moved to align to Swiss PI

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

~~Chemotherapy can induce temporary amenorrhea 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.~~

Alignment to Swiss PI, information removed as already available within the 5th paragraph.

Warning on the treatment of Endometriosis

Revision of subtitle for sake of clarity and to align to Swiss PI

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.~~

The aetiology of any potential vaginal haemorrhages should be determined before triptorelin is administered.

Alignment to Swiss PI

Before beginning treatment for endometriosis with Pamorelin 3.75 mg, any possibility of pregnancy must be ruled out. During treatment and afterwards, non-hormonal contraceptive methods should be used until normal menstrual cycles have returned. Pamorelin 3.75 mg normally causes amenorrhoea; if this persists, patients should inform their doctor.

Alignment to Swiss PI

After the menopause, medicinal treatment of endometriosis is only indicated in rare cases (e.g. in oestrogen-producing tumours triggering a reactivation of endometriosis and if surgical treatment is contraindicated).

In patients treated with GnRH analogues for endometriosis, the addition of HRT (an oestrogen and a progestin) has been shown to reduce mineral density loss and vasomotor symptoms.

The use of GnRH agonists is not recommended in patients aged under 18 years. Particular attention should be paid to adolescent girls and young women (especially those aged under 16), who may not have reached their maximum bone mineral density.

No data are available on the clinical effects of therapy lasting longer than 6 months. If a longer duration of use is planned, bone mineral density should be measured before starting treatment and checked at regular intervals during treatment. To avoid loss of bone density due to treatment, an adequate intake of calcium and vitamin D (through the diet)

is recommended. If necessary, patients should be advised to modify their lifestyle by, for example, taking regular physical exercise that places a load on the skeleton, stopping smoking and consuming alcohol in moderation.

~~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.~~

Alignment to Swiss PI

~~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.~~

Pharmaceutical excipients of particular interest:
Pamorelin 3.75 mg contains less than 1 mmol (23 mg) sodium per dose, i.e. essentially "sodium-free".

Subtitle added for sake of clarity, text moved and additional of information (1mmol = 23mg) to align to Swiss PI.

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 given 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 3.75 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).

~~*Paediatric Population*~~

Alignment to Swiss PI.

~~Interaction studies have only been performed in adults.~~

4.6 Pregnancy and Lactation

<u>Pregnancy:</u>

Revision of the section 4.6 to align information between

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.

different strengths, i.e. Pamorelin 3.75 mg and Pamorelin 22.5 mg.

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

Lactation:

Revision of the section 4.6 to align information between different strengths, i.e. Pamorelin 3.75 mg and Pamorelin 22.5 mg.

It is not known whether triptorelin passes into breast milk or whether it could affect breast milk production. Pamorelin is contraindicated during lactation period.

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), ~~not known~~ unknown frequency (based on spontaneous reports for market surveillance for which the frequency

Revision of post marketing adverse reaction wording for alignment between Table 1, Table 2 and Table 3.

cannot be specified). ~~(cannot be estimated from the available data).~~

Table 1. Pamorelin 3.75 mg: Treatment-Related Adverse Reactions in men

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Rare***	***Additional post-marketing Unknown frequency ~~not known~~***
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 increased	Alanine aminotransferase increased Aspartate aminotransferase increased Blood creatinine increased Blood pressure increased Blood urea increased Gamma-glutamyl transferase increased	Blood alkaline phosphatase increased	

System Organ Class	*Very Common*	*Common*	*Uncommon*	*Rare*	*Additional post-marketing Unknown frequency ~~not known~~*
			Weight decreased		
Metabolism and nutrition disorders			Anorexia Diabetes mellitus Gout Hyperlipidemia 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	Depression* Mood changes* Loss of libido	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 pain	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

**Reported following initial administration in patients with pituitary adenoma

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

Footnote added as per Convulsion Module2.5 section 2.5.5.2.

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.

General tolerance in Women:

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

As a consequence of decreased estrogen 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)~~; unknown frequency (based on spontaneous reports for market surveillance for which the frequency cannot be specified)~~not known (cannot be estimated from the available data).~~

Revision of post marketing adverse reaction wording for alignment between Table 1, Table 2 and Table 3. Moreover, rare frequency is deleted as not described in below Table 2

Table 2 Treatment-related Adverse Reactions in women

System Organ Class	***Very Common***	***Common***	***Uncommon***	***Additional post-marketing Unknown frequency ~~not known~~***
Cardiac disorders			palpitations	

System Organ Class	*Very Common*	*Common*	*Uncommon*	*Additional post-marketing Unknown frequency ~~not known~~*
Ear and labyrinth disorders			vertigo	
Endocrine disorders				pituitary apoplexy***
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, ~~tiredness~~		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 extremities	back pain, myalgia	muscular weakness
Nervous system disorders	headache	dizziness	dysgeusia, hypoesthesia, syncope, memory impairment, disturbance in attention, paraesthesia, tremor	Convulsions ****
Psychiatric disorders	sleep disorder (including insomnia), mood altered, 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 bleeding), ovarian hyperstimulation syndrome,	breast pain	coital bleeding, cystocele, menstrual disorder (including dysmenorrhoea, metrorrhagia and menorrhagia), ovarian cyst, vaginal discharge	amenorrhoea

System Organ Class	*Very Common*	*Common*	*Uncommon*	*Additional post-marketing Unknown frequency ~~not known~~*
	ovarian hypertrophy, pelvic pain, vulvovaginal dryness			
Respiratory, thoracic and mediastinal disorders			Dyspnoea, epistaxis	
Skin and subcutaneous tissue disorders	acne, hyperhidrosis, seborrhoea		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

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

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

Asthenia adverse event added to align with above text in the frame of the new indication in procedure No. 201111302012A.

Footnote added as per Convulsion Module2.5 section 2.5.5.2.

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 metrorrhagia may occur in the month following the first injection.

Breast Cancer

In TEXT and SOFT studies, the most frequently adverse events during triptorelin therapy lasting for up to 5 years in association with tamoxifen or an aromatase inhibitor were hot flushes, musculoskeletal disorders, fatigue, insomnia, hyperhidrosis vaginal dryness and depression. The frequencies of the adverse events during triptorelin therapy in combination with tamoxifen (N = 2325) or exemestane (N = 2318) are shown below.

Depending on their incidence, adverse events are classified as follows: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10000, <1/1,0000); very rare (<1/10,000), unknown frequency

Revision of the frequency wording for alignment with Swiss PI.

(based ~~mainly~~ on spontaneous reports for market surveillance for which the frequency cannot be specified).

Table 3 Treatment-related Adverse Reactions in women with Breast cancer

System Organ Classes	***Very Common***	***Common***	***Uncommon***	***Rare***	***Very rare***	***Additional post-marketing Unknown frequency***
Cardiac disorders			myocardial Ischemia			
~~Endocrine disorders~~ Metabolism and nutrition disorders		diabetes mellitus (glucose intolerance) hyperglycemia (adjuvant therapy for breast cancer)				
Gastrointestinal disorders	nausea					
General disorders and administration site conditions	hot flushes (almost 100%) fatigue (62.3%) sweating	injection site reaction				Reactions at the injection site (redness, inflammation and pain)
Hepatobiliary disorders						Abnormal liver function
Immune system disorders		Hypersensitivity reactions			Allergic reactions	
Musculoskeletal and connective tissue disorders	musculoskeletal disorder (82%) osteoporosis (32%)	~~fracture~~				
Nervous system disorders	headaches (17%)		cerebral ischemia central nervous system bleeding	migraine, paresthesia		
Psychiatric disorders	Insomnia (58%) libido decreased (18-45%) emotional disturbances (15%) depression (50% during adjuvant therapy for breast cancer)					

System Organ Classes	*Very Common*	*Common*	*Uncommon*	*Rare*	*Very rare*	*Additional post-marketing* ***Unknown frequency***
Renal and urinary disorders	urinary incontinence (15%)					
Reproductive system and breast disorders	Spotting (56%) dyspareunia (30.5%) vulvo-vaginal dryness (25-50%)					
Skin and subcutaneous tissue disorders						exanthema (including bullous eruption)
Vascular disorders	hot flushes hypertension	embolism other vasomotor disorders				
Injury, poisoning and procedural complication		Fracture				

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

Alignment to Swiss PI

The ADRs identified in Table 3 should be used in addition to the triptorelin ADRs identified in Table 2 to fully describe the ADR profile for the use of triptorelin in combination with either exemestane or tamoxifen

Osteoporosis was reported more frequently when triptorelin was administered in association with exemestane than in the association with tamoxifen (39% vs 25%) (see section 4).

Musculoskeletal disorder and fractures were also more reported more frequently when triptorelin therapy was associated with exemestane than in combination with tamoxifen (for musculoskeletal disorders: 89% vs 76%; for fractures: 7% vs 5% respectively).

Hypertension has been reported as a very frequent adverse event when triptorelin was administered in association with either exemestane or tamoxifen (23% and 22%, respectively).

Hyperglycemia and diabetes have been reported as frequent adverse events when triptorelin was administrated in association with either exemestane or tamoxifen (hyperglycaemia: 2.6% and 3.4%; diabetes: 2.3% and 2.3% respectively).

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 3.75 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 3.75 mg. If overdose occurs, this should be managed symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Hormones and related agents, gonadotropin 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.

This results in accessory sexual organ atrophy. These effects are generally reversible upon discontinuation of the medicinal product.

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 and safety 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.

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

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 analyzed (EORTC 22863, RTOG 85-31, RTOG 92-02, RTOG 86-10, and D'Amico *et al.*, JAMA, 2008), which all demonstrate a benefit for the combination of GnRH analogue with radiotherapy. Clear differentiation of the respective study populations for the indications locally advanced prostate cancer and high-risk 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 androgen receptor inhibitor, to GnRH analogues, such as triptorelin.

Clinical efficacy and safety in women

Endometriosis

Continued administration of triptorelin induces suppression of the estrogen 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 estradiol 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 estradiol 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 estrogen. Once treatment ended, the mean time to return to menses was 81 days (range: 6 – 116). Estrogen levels returned to baseline values by 3 months post treatment

Pituitary Down-regulation in the context of assisted reproduction technology:

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.

Addition information related to the proposal of the new indication, “pituitary down-regulation in the context of assisted reproduction technology” as per procedure No. 201111302012A.

Breast cancer:

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

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

Triptorelin was the main therapy used to obtain 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 underwent bilateral oophorectomy or bilateral ovarian irradiation.

SOFT Study results

The SOFT study consisted of patients who undergone breast surgery and remained premenopausal after completing adjuvant or neoadjuvant chemotherapy and premenopausal women who had not received chemotherapy and for whom therapy with adjuvant T alone was deemed appropriate. The subjects received E + OFS , T + OFS or T alone on a randomised basis. In the TEXT study, women were included following breast surgery and randomised to treatment with T + OFS or E + OFS; patients undergoing chemotherapy started it concurrently with the GnRH analogue after randomisation. The efficacy of the two studies was evaluated using the primary endpoint, 5-year disease-free survival (DFS), and secondary endpoints, including the breast cancer-free interval (BCFI), the distant recurrence-free interval (DRFI) and the overall survival (OS).

To analyze this question about OFS, the study compared DFS between subjects allocated to T+OFS versus T alone on a randomised basis. At a median follow-up of 67 months (5.6 years), DFS events were reported for 299/2033 subjects (14.7%) in the intention-to-treat population (ITT).

Overall, 53.3% of subjects who 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 3)

Table 4 OFS Question: Efficacy results at 67-months 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)
DRFI	90	83.6	82	84.8	0.87 (0.64 to 1.17)
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.

Combined SOFT and TEXT study results:

The primary objective of TEXT study was to assess 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.

The analysis of the AI question combined the TEXT and SOFT studies and compared OFS between subjects allocated to E+OFS versus T+OFS on a randomised basis.

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. 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). Table 4 shows the efficacy results for subjects who received prior chemotherapy beforehand in the analysis of the AI.

Table 5 AI Question: Efficacy results at 68-months 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)
DRFI	61	88.0	77	84.6	0.81 (0.58 to 1.12)
OS[b]	46	91.8	35	94.1	1.39 (0.89 to 2.15)

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.

b Immature overall survival data at 68 months

An updated analysis following a median follow-up of 8 years confirmed the results of the five years analysis.

5.2 Pharmacokinetic properties

Absorption:

Following a single intramuscular injection of Pamorelin 3.75 mg in healthy male volunteers, mean peak triptorelin serum concentration was 30 ng/ml at 1-3 hours. The concentrations decline rapidly and stabilise at plasma levels of about 0.1 ng/l, which are maintained for at least 1 month.

Absolute bioavailability of intramuscular triptorelin relative to intravenous triptorelin was approximately 80%. After

repeated monthly intramuscular administration of Pamorelin 3.75 mg, no significant accumulation has been observed.

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 to half-lives of 6 minutes, 45 minutes, and 3 hours.

The steady-state volume of distribution is approximately 30 litres. Triptorelin does not bind to plasma proteins at clinically relevant concentrations.

Metabolism:

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. Total clearance of triptorelin is about 200 ml/min and its terminal half-life is 2.8 hours.

In women

Following an intramuscular injection of Pamorelin 3.75 mg in healthy premenopausal women, maximum concentrations of triptorelin were usually observed around two hours after the injection, with a geometric mean C_{max} of 18.5 ng/ml.

The time until the suppression of oestradiol was around 4.2 days (geomean) and the duration of oestradiol suppression was around 26.7 days (geomean). Despite a high intersubject variability, overall, five days after the IM injection of Pamorelin 3.75 mg, oestradiol suppression was observed for a duration of around 30 days.

Hepatic impairment

The portion of intact triptorelin excreted in urine, increased to 62 % in subjects with hepatic impairment indicating that the liver plays an important role in triptorelin elimination

Renal impairment

Impaired renal function leads to a delay in triptorelin elimination.

The half-life was 6.7 hours in patients with moderate renal insufficiency (mean creatinine clearance of 40 ml/min) and 7.8 hours in patients with severe renal insufficiency (mean creatinine clearance of 8.9 ml/min).

Other special populations:

Elderly patients

The influence of age on triptorelin pharmacokinetics has 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.

Genetic polymorphisms

Ethnicity: The effects of age and race on triptorelin pharmacokinetics have not been systematically studied.

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 30°C.

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

6.6 Special precautions for disposal and other handling

The powder should be suspended immediately before use. The powder is to be suspended in 2 ml 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 within 2 minutes.

Withdraw the suspension into the syringe.

Do not prime the needle before injection.

The suspension of Pamorelin 3.75 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)

MAL16025032ARZ

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25.02.2016/06.10.2020

10. DATE OF REVISION OF THE TEXT

12.06.2026