# Triptorelin
# Pamorelin

## 3.75 mg Powder for Injection (IM/SC)
## 11.25 mg and 22.5 mg Powder for Injection (IM)

### Antineoplastic / Gonadotropin-Releasing Hormone Analog

**FORMULATIONS**
Each vial contains:
Triptorelin (as embonate)……..3.75 mg, 11.25 mg, or 22.5 mg

**PRODUCT DESCRIPTIONS**
Triptorelin (Pamorelin) is a white to off-white powder for reconstitution prior to injection. The reconstituted suspension is a homogeneous, milky, prolonged-release suspension. An *in vitro* dissolution test showed the bimodal release characteristic of the triptorelin microgranules in the suspension an initial release involved leaching of triptorelin near the surface of the microgranules detected at 1 hour. Subsequently, triptorelin is gradually released from within the body of the microgranules as a result of microporosity generation in the degrading polymer and enhanced water uptake that is reflected in measurements made at 48 and 72 hours.

After reconstitution with 2 mL of solvent, 1 mL of reconstituted suspension contains 1.875 mg (for 3.75 mg), 5.625 mg (for 11.25 mg), or 11.25 mg (for 22.5 mg) of triptorelin. These products contain < 1 mmol (23 mg) sodium per vial.

**CLINICAL PHARMACOLOGY**
**Pharmacodynamics / Mechanism of Action**
Triptorelin is a synthetic decapeptide agonist analog of gonadotropin releasing hormone (GnRH). After the first administration, there is a transient surge in circulating levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone. After chronic and continuous administration, usually 2 to 4 weeks after initiation of therapy, a sustained decrease in LH and FSH secretion and marked reduction of testicular steroidogenesis are observed. A reduction of serum testosterone concentration to a level typically seen in surgically castrated men is obtained. Consequently, the result is that tissues and functions that depend on these hormones for maintenance become quiescent. These effects are usually reversible after cessation of therapy.

**Pharmacokinetics**
Following a single intramuscular (IM) injection of Triptorelin (Pamorelin) to patients with prostate cancer, mean peak triptorelin serum concentrations of 28.4 ng/mL, 38.5 ng/mL and 44.1 ng/mL occurred in 1 to 3 hours after the 3.75 mg, 11.25 mg and 22.5 mg doses, respectively. Triptorelin did not accumulate over 9 months (3.75 mg and 11.25 mg) and 12 months (22.5 mg) of treatment.

After IM injection of prolonged-release triptorelin 3 mg in patients with endometriosis, the maximum blood level of triptorelin is obtained between 2 to 6 hours after injection and the peak value reached is 11 ng/mL. There was no evidence of accumulation of triptorelin following monthly injections over 6 months. The minimum blood level oscillates between 0.1 and 0.2 ng/mL. The bioavailability of the prolonged-release product is approximately 50%.

Results of pharmacokinetic investigations conducted in healthy men and women indicate that after intravenous (IV) 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 in men and 3 minutes, 47 minutes, and 5 hours in women.

The volume of distribution following a single intravenous (IV) bolus dose of 0.5 mg of triptorelin peptide was 30 to 33 L in healthy male volunteers and women with endometriosis. It is not known whether triptorelin is distributed into milk and there is no evidence that it binds to plasma proteins.

No metabolites of triptorelin have been identified. Triptorelin is degraded by peptidases in the various tissues and plasma into inactive fragments, or cleared by the kidneys and liver. Cytochrome P450 (CYP) enzymes are unlikely to be involved in the metabolism or clearance of triptorelin. *In vitro* data showed that triptorelin was not a significant CYP inhibitor, CYP inducer, P-glycoprotein (P-gP) substrate or inhibitor.

Triptorelin is eliminated by both the liver (major) and the kidneys. Following IV administration of 0.5 mg triptorelin peptide to 6 healthy male volunteers with a creatinine clearance of 149.9 mL/min, 41.7% of the dose was excreted in urine as intact peptide with a total triptorelin clearance of 221.9 mL/min. In males with hepatic or moderate or severe renal impairment, the area under the plasma concentration-time curve (AUC) increased 2- to 4-fold compared with healthy males.

Following a 0.5 mg IV bolus dose in 19 women, the total clearance was estimated to be 110 mL/min. Twenty percent of the dose was eliminated in the urine.

**INDICATIONS**
- Palliative treatment of locally advanced, non-metastatic hormone-dependent prostate cancer, as an alternative to surgical castration
- Treatment of metastatic hormone-dependent prostate cancer
- As adjuvant treatment to radiotherapy in patients with high-risk localized or locally advanced prostate cancer
- Treatment of endometriosis (***additional indication for 3.75 mg only***)

**DOSAGE AND ADMINISTRATION**
Triptorelin (Pamorelin) should be prescribed by and administered under the supervision of a qualified physician experienced in the use of hormonal therapy in prostate cancer.
Triptorelin (Pamorelin) is administered as a single intramuscular (IM) injection; the 3.75 mg format may also be administered as a single subcutaneous (SC) injection.
No dosage adjustment is necessary for patients with renal or hepatic impairment.
Caution is required with IM administration in patients treated with anticoagulants due to the potential risk of hematomas at the site of injection.

**INTERACTIONS WITH OTHER MEDICAMENTS**
CYP enzymes are unlikely to be involved in the metabolism or clearance of triptorelin. *In vitro* data showed that triptorelin was not a significant CYP inhibitor, CYP inducer, P-gP substrate or inhibitor. Therefore, drug-drug interactions with triptorelin are unlikely.

***Drugs Affecting Pituitary Secretion of Gonadotropins:*** Exercise caution when used concomitantly with Triptorelin (Pamorelin). It is also recommended that the patient's hormonal status be monitored.
***Laboratory Test Alterations:*** Chronic or continuous administration of triptorelin in therapeutic doses results in suppression of pituitary-gonadal axis. Diagnostic tests of the pituitary-gonadal function conducted during treatment and within 4 to 12 weeks after cessation of therapy may therefore be misleading.
Decreased hemoglobin and red blood cell count and increased glucose, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase were reported. Majority of the changes were mild to moderate.

**STATEMENT ON USAGE FOR HIGH RISK GROUPS**
**Pregnancy and Lactation** (see ***Contraindications***)
**Pregnancy Category X**
Triptorelin (Pamorelin) is contraindicated in women who are or may become pregnant. Expected hormonal changes that occur with Triptorelin (Pamorelin) treatment increase the risk of pregnancy loss and fetal harm if the drug is administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving Triptorelin (Pamorelin), the patient should be apprised of the potential hazard to the fetus.
**Breastfeeding:** It is not known to what extent triptorelin is distributed into breast milk. Because there are no well-controlled studies on the effect of triptorelin in breastfeeding women and many drugs are excreted in human milk, it is recommended that Triptorelin (Pamorelin) should not be used in breastfeeding women.

***Geriatric (> 65 years old)***
Clinical studies with Triptorelin (Pamorelin) have been conducted primarily in patients ≥ 65 years old since prostate cancer occurs mainly in an older population.
***Pediatric (< 18 years old)***
Safety and efficacy in pediatric patients have not been established.
***Renal or Hepatic Impairment***
After a single IV bolus administration of triptorelin, subjects with renal or hepatic impairment had higher triptorelin exposure than young healthy males. However, since Triptorelin (Pamorelin) is a sustained-release formulation and taking into account the large safety margin of triptorelin, this is considered of no clinical relevance and no dose adjustment is recommended in patients with renal or hepatic impairment.

**UNDESIRABLE EFFECTS**
The majority of adverse reactions related to Triptorelin (Pamorelin) are a result of its pharmacological action, i.e., induced variation in serum testosterone levels, either an increase in testosterone at the initiation of treatment, or a decrease in testosterone once castration is achieved in men; in women, hot flushes, vaginal dryness and amenorrhea
***Hypersensitivity Reactions:*** Allergic reactions may occur (see ***Warnings and Precautions***).
***Local Effects:*** Local reactions such as injection site erythema, inflammation or pain were commonly reported.
***Cardiovascular Effects:*** Hypertension was uncommon. Purpura and hypotension were rare. Thromboembolic events (including pulmonary emboli, cerebrovascular accident, myocardial infarction, deep venous thrombosis, transient ischemic attack and thrombophlebitis) have been reported during post-marketing experience. QT/QTc prolongation has been reported in patients receiving androgen deprivation therapy (see ***Warnings and Precautions***).
***Nervous System Effects:*** Paresthesia in the lower limbs was very common. Dizziness and headache were common. Memory impairment, depression, insomnia, irritability, mood swings, confusional state, decreased activity, euphoric mood, anxiety, and emotional lability were also reported.
***Endocrine / Metabolic Effects:*** Edema (peripheral, leg or ankle) was common. Anorexia, gout and increased appetite were uncommon. Increased alkaline phosphatase, diabetes mellitus and hyperglycemia may occur (see ***Warnings and Precautions***).
***Gastrointestinal and Hepatic Effects:*** Nausea was commonly reported. Abdominal pain, constipation, diarrhea, and vomiting were uncommon. Abdominal distension, dry mouth, dysgeusia, and flatulence were rare. Dyspepsia and abnormal hepatic function may occur.
***Musculoskeletal System Effects:*** Back pain was very common. Musculoskeletal pain and pain in the extremity are common. Arthralgia, muscle cramp, muscular weakness, and myalgia were uncommon. Joint stiffness or swelling, musculoskeletal stiffness, osteoarthritis, bone pain, generalized pain, leg or extremity pain, and chest pain may occur.
***Respiratory Effects:*** Nasopharyngitis was rare. Dyspnea was uncommon. Orthopnea and epistaxis were rare. Coughing and bronchitis may occur.
***Dermatologic Effects:*** Hyperhidrosis was very common. Seborrhea, acne, alopecia, pruritus, and rash were uncommon. Blister, angioneurotic edema and urticaria have been reported.
***Genitourinary Effects:*** Erectile dysfunction and decreased libido were common. Testicular atrophy, gynecomastia and testicular pain were uncommon. Ejaculation failure has been rarely reported. Hot flushes, breast pain, impotence, urinary tract infection, dysuria, and urinary retention may occur. Dyspareunia, dysmenorrhea, genital hemorrhage (including menorrhagia, metrorrhagia), ovarian hyperstimulation syndrome, ovarian hypertrophy, pelvic pain, vulvovaginal dryness, and amenorrhea were very common in women.
***Sensory Effects:*** Tinnitus was uncommon. Vertigo, abnormal sensation in the eye, visual disturbance, and blurred vision were rare. Eye pain and conjunctivitis may occur.
***Others:*** Asthenia was very common. Fatigue and bruising were commonly reported. Lethargy, pain, rigors, and somnolence were uncommon. Dysstasia, influenza-like illness, pyrexia, malaise, and anemia have also been reported.

**OVERDOSE AND TREATMENT**
There is no experience of overdosage in clinical trials. Animal data do not predict any effects other than those on sex hormone concentration and consequent effect on the reproductive tract. If overdosage occurs, therapy should be discontinued immediately and the appropriate supportive and symptomatic treatment administered.

**AVAILABILITY**
Pamorelin 3.75 mg Powder for Injection (IM/SC) - Type1 glass vial (Box of 1)
Pamorelin 11.25 mg Powder for Injection (IM) - Type1 glass vial (Box of 1)
Pamorelin 22.5 mg Powder for Injection (IM) - Type1 glass vial (Box of 1)

**STORAGE CONDITIONS**
Store at temperatures not exceeding 30°C. Keep out of sight and reach of children.

**CAUTION**
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by Debio Recherche Pharmaceutique SA
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Date of Revision: _____

**Hypogonadism:** Long-term administration of triptorelin in therapeutic doses will cause suppression of pituitary gonadotropins and gonadal hormone production with clinical symptoms of hypogonadism. Normal function is usually restored after treatment is discontinued. However, whether the clinical symptoms of induced hypogonadism will reverse in all patients has not yet been established.

***Hypersensitivity Reactions***
Anaphylactic shock, hypersensitivity and angioedema have been reported. If a hypersensitivity reaction develops, Triptorelin (Pamorelin) should be discontinued; appropriate supportive and symptomatic care should be provided.

***Metastatic Vertebral Lesions and Urinary Tract Obstruction***
Patients with prostate cancer and metastatic vertebral lesions and/or with upper or lower urinary tract obstruction may experience increased neurologic and/or genitourinary complication during initial Triptorelin (Pamorelin) therapy; such patients should be closely observed during the first few weeks of therapy.

Cases of spinal cord compression, which may contribute to weakness or paralysis with or without fatal complications, have been reported with GnRH agonists. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted, and in extreme cases an immediate orchiectomy considered.

***Cardiovascular Effects***
Thromboembolic events, including pulmonary embolism, cerebrovascular accident, myocardial infarction, deep-vein thrombosis, transient ischemic attack, and thrombophlebitis, have been reported in patients receiving triptorelin. GnRH agonists, including triptorelin, may increase the risk of certain cardiovascular diseases (e.g., myocardial infarction, sudden cardiac death and stroke) in men with prostate cancer. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with other cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

**Effect on QT/QTc Interval:** Androgen deprivation therapy has the potential to prolong QT/QTc interval on ECG. QT prolongation is a physiologic consequence of hormonal therapies that induces androgen ablation in males with prostate cancer and should be considered in assessing the risk-benefit of treatment with hormonal therapy. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risk in patients with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure and in patients taking Class IA (e.g., quinidine, procainamide), Class III (e.g., amiodarone, sotalol, dofetilide, ibutilide), or Class IC (e.g., flecainide, propafenone) antiarrhythmic medications.

***Hematologic Effects***
Anemia is a known physiologic consequence of testosterone suppression. Assessment of anemia risk and management according to local clinical practice and guidelines should be considered.

***Pituitary Apoplexy***
Pituitary apoplexy, a clinical syndrome resulting from infarction of the pituitary gland, has been reported rarely in patients receiving GnRH agonists, such as triptorelin. In most cases, a previously unknown gonadotroph cell pituitary adenoma was diagnosed in patients experiencing pituitary apoplexy. Pituitary apoplexy typically occurred within 2 weeks following the first dose of triptorelin, but occurred within the first hour in some patients. In these cases, pituitary apoplexy was characterized by sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention is required.

***Depression***
Mood changes, including depression, have been reported. Patients with known depression should be monitored closely during therapy.

***Serum Testosterone Levels***
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 injection as scheduled. The effectiveness of treatment can be monitored by measuring serum levels of testosterone and prostate specific antigen periodically or as indicated.

***Vaginal Bleeding***
Since menses should stop during Triptorelin (Pamorelin) treatment, the patient should notify her physician if regular menstruation persists. Patients missing successive doses of Triptorelin (Pamorelin) may experience breakthrough bleeding.

***Ovarian Cysts***
As with other drugs that stimulate the release of gonadotropin or that induce ovulation, ovarian cysts have been reported to occur, usually within the first 2 months of treatment. In most cases, these enlargements resolve spontaneously in 4 to 6 weeks. However, in some cases they may require discontinuation of drug and/or surgical intervention.

***Carcinogenicity, Mutagenicity, Impairment of Fertility***
Triptorelin is not mutagenic *in vitro* or *in vivo*. In mice, no oncogenic effect has been shown with triptorelin at doses up to 6000 mcg/kg after 18 months of treatment. A 23-month carcinogenicity study in rats has shown an almost 100 % incidence of benign pituitary tumors at each dose level, leading to premature death. The increased incidence in pituitary tumors in rats is a common effect associated with GnRH agonist treatment. The clinical relevance of this is not known.

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 mcg/kg, a reduction in maternal weight gain and an increased number of resorptions were observed.

No studies have been conducted to specifically assess the effect of triptorelin on male fertility.

***Effects on Ability to Drive or Use Machines***
No studies 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.

As with other drugs administered by injection, the injection site should be varied periodically.
Since Triptorelin (Pamorelin) is a suspension of microgranules, inadvertent intravascular injection must be strictly avoided.

**Recommended Dosing for Triptorelin (Pamorelin):**
**Prostate Cancer**

| 3.75 mg | 11.25 mg | 22.5 mg |
|---|---|---|
| 1 **intramuscular (IM)** injection<br>or<br>1 **subcutaneous (SC)** injection<br>every month (4 weeks) | 1 **IM** injection<br>every 3 months (12 weeks) | 1 **IM** injection<br>every 6 months (24 weeks) |

Due to different release characteristics, the different dosage strengths of Triptorelin (Pamorelin) are not additive and must be selected based on the desired dosing schedule.

**Endometriosis (for 3.75 mg only)**
- Single IM or SC injection every 28 days, to be initiated in the first 5 days of the menstrual cycle. The maximum duration of treatment should be 6 months.
- Treatment duration depends on the initial severity of the disease and the changes observed in the clinical features (functional and anatomical) during treatment.
- Experience in women has been limited to women ≥ 18 years old treated for 6 months.
- Maintaining estradiol suppression is important in the management and relief of chronic pain associated with endometriosis. Missing an appointment by a few days should not disrupt the benefits of treatment, but keeping a consistent schedule of Triptorelin (Pamorelin) injections is an important part of treatment.

***Directions for Reconstitution***
The powder should be reconstituted immediately before use. The lyophilized microgranules are to be reconstituted in 2 mL of **Sterile Water for Injection only. No other diluents should be used.**
- Using a syringe fitted with a sterile 21-gauge needle, withdraw 2 mL of Sterile Water for Injection and inject into the vial
- Shake the vial **gently** and thoroughly to completely disperse the powder to obtain a homogeneous milky suspension.
- Slowly withdraw the entire contents of the reconstituted suspension into the syringe.
- Inspect the solution for particulate matter and discoloration before administration.

The suspension should be administered immediately after reconstitution since the product does not contain any preservative. For single use only. Discard any unused suspension.

***Incompatibilities***
In the absence of compatibility studies, Triptorelin (Pamorelin) should not be mixed with other medicinal products.

***Handling Precautions***
- Wash hands with soap and water and put on gloves immediately prior to preparing the injection.
- Used injection needles should be disposed of in a designated container.

**CONTRAINDICATIONS**
- Hypersensitivity to triptorelin, GnRH, GnRH agonist analogs, or any component in the product
- Pregnant or breastfeeding women
- Women with undiagnosed abnormal vaginal bleeding

**WARNINGS AND PRECAUTIONS**
**General**
Initially, Triptorelin (Pamorelin), like other GnRH agonists, causes a transient increase in serum testosterone levels. As a result, worsening (flare) of signs and/or symptoms of prostate cancer and/or development of new symptoms may occasionally occur during the initial weeks of Triptorelin (Pamorelin) therapy. Cancer-related pain (metastatic pain), bone pain, neuropathy, or hematuria have been reported. These will subside with continued treatment and can be managed symptomatically.

Worsening of the clinical condition may occasionally require discontinuation of therapy.
Before initiating treatment with Triptorelin (Pamorelin), pregnancy must be ruled out (see ***Statement on Usage for High Risk Groups***).

Retreatment for endometriosis cannot be recommended since safety data beyond 6 months are not available.

**Fetal or Neonatal Morbidity and Mortality** (see ***Statement on Usage for High Risk Groups***)

***Endocrine / Metabolic Effects***
**Bone Mineral Density Loss:** The use of GnRH agonists may cause a reduction in bone mineral density. Some of the bone density loss over the course of Triptorelin (Pamorelin) therapy may not be reversible. For a period of up to 6 months, this bone loss should not be important.

In men, preliminary data suggest that the use of a bisphosphonate in combination with a GnRH agonist may reduce bone mineral loss. No specific data is available for patients with established osteoporosis or with risk factors for osteoporosis (e.g., chronic alcohol abuse, smokers, long-term therapy with drugs that reduce bone mineral density, family history of osteoporosis, malnutrition). Particular caution is necessary since reduction in bone mineral density is likely to be more detrimental in these patients. Treatment with Triptorelin (Pamorelin) should be considered on an individual basis and should only be initiated if the benefits of treatment outweigh the risk following very careful appraisal. Consideration should be given to additional measures in order to counteract loss of bone mineral density.

For the treatment of endometriosis, patients with major risk factors for loss of bone mineral density are advised not to receive repeated courses of therapy with GnRH analogs beyond 6 months.

**Hyperglycemia and Diabetes:** Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes.