PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]TRELSTAR®

Triptorelin for injectable suspension

Powder for injectable suspension,

3.75 mg triptorelin (as pamoate) per vial (1 month sustained-release formulation),

11.25 mg triptorelin (as pamoate) per vial (3 month sustained-release formulation),

22.5 mg triptorelin (as pamoate) per vial (6 month sustained-release formulation),

intramuscular injection

Luteinizing Hormone-Releasing Hormone (LHRH) Analog

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RECENT MAJOR LABEL CHANGES

3 SERIOUS WARNINGS AND PRECAUTIONS BOX	[09/2022]
4 DOSAGE AND ADMINISTRATION, 4.3 Reconstitution	[09/2022]
7 WARNINGS AND PRECAUTIONS, Endometriosis, Musculoskeletal	[09/2022]
7 WARNING AND PRECAUTIONS, 7.1.3 Pediatrics	[09/2022]

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TRELSTAR (triptorelin for injectable suspension) is indicated for:

- The management and relief of chronic pain associated with endometriosis.
- The palliative treatment of hormone dependent advanced carcinoma of the prostate gland (stage D2).

For the management and relief of chronic pain in endometriosis, experience in women has been limited to women 18 years of age or older treated for 6 months.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (> 65 years of age): No data are available to Health Canada for the management and relief of chronic pain associated with endometriosis in geriatric patients. The majority of the patients studied in the clinical trials for the palliative treatment of prostate cancer with TRELSTAR were 65 years and older (see 14 CLINICAL TRIALS).

2 CONTRAINDICATIONS

TRELSTAR is contraindicated in:

- Patients with hypersensitivity to luteinizing hormone-releasing hormone [LHRH; also known as gonadotropin-releasing hormone (GnRH)] or LHRH agonist analogs, or any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. Anaphylactic reactions to synthetic LHRH or LHRH agonist analogs have been reported (see 7 WARNINGS AND PRECAUTIONS and 8.5 Post-Market Adverse Reactions). For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Women who are or may become pregnant while receiving the drug. TRELSTAR may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus (see 7 WARNINGS AND PRECAUTIONS).
- Nursing women (see 7 WARNINGS AND PRECAUTIONS).
- Women with undiagnosed abnormal vaginal bleeding.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

TRELSTAR should be prescribed by a qualified health professional experienced in the use of hormonal therapy in prostate cancer or endometriosis. TRELSTAR should be administered by a health professional.

The following is a clinically significant adverse event **observed in men with prostate cancer**:

- Clinical testosterone flare reaction (see 7 WARNINGS AND PRECAUTIONS, Prostate Cancer, General)

The following is a clinically significant adverse event **observed in patients taking LHRH agonist drugs:**

- Osteoporosis (see 7 WARNINGS AND PRECAUTIONS, Endometriosis, Musculoskeletal and 7 WARNINGS AND PRECAUTIONS, Prostate Cancer, Musculoskeletal)

The following is a rare clinically significant adverse event **observed in patients taking LHRH agonist drugs**:

- Pituitary apoplexy (see 7 WARNINGS AND PRECAUTIONS, All Indications, Endocrine and Metabolism)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Due to different release characteristics, the dosage strengths are not additive and must be selected based upon the desired dosing schedule.

Pregnancy should be excluded in females of reproductive potential before treatment.

4.2 Recommended Dose and Dosage Adjustment

Health Canada has not authorized an indication for pediatric use.

Endometriosis

The recommended dose of TRELSTAR for the management and relief of chronic pain associated with endometriosis is an intramuscular injection of 3.75 mg (as peptide base) incorporated in a depot formulation, every 28 days (1 month). Total treatment duration should be no longer than 6 months.

Prostate Cancer

TRELSTAR is intended for long-term administration unless clinically inappropriate.

TRELSTAR (1 month sustained-release formulation) 3.75 mg triptorelin/vial: The recommended dose of TRELSTAR 3.75 mg is 3.75 mg (as peptide base) incorporated in a depot formulation, every month.

TRELSTAR (3 month sustained-release formulation) 11.25 mg triptorelin/vial: The recommended dose of TRELSTAR 11.25 mg is 11.25 mg (as peptide base), incorporated in a depot formulation, every 3 months.

TRELSTAR (6 month sustained-release formulation) 22.5 mg triptorelin/vial: The recommended dose of TRELSTAR 22.5 mg is 22.5 mg (as peptide base), incorporated in a depot formulation, every 6 months.

4.3 Reconstitution

TRELSTAR is supplied in single-dose vials containing lyophilized powder. This powder is to be reconstituted with 2 mL of sterile water for injection according to Table 1. Instructions are provided (see below) for reconstitution using the TRELSTAR dose delivery system MIXJECT (with Pre-Filled Syringe Containing Sterile Water for Injection), and reconstitution of the TRELSTAR vial without MIXJECT (without Pre-Filled Syringe Containing Sterile Water for Injection).

Table 1 - Reconstitution

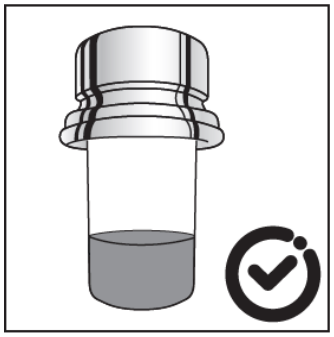
Strength	Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
3.75 mg	6 mL	2 mL	2 mL	1.875 mg
11.25 mg	6 mL	2 mL	2 mL	5.625 mg
22.5 mg	6 mL	2 mL	2 mL	11.250 mg

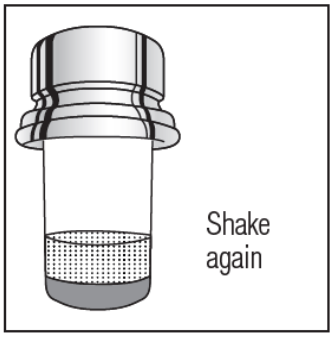
Single use only. Inject immediately after reconstitution and discard unused portion. The suspension should be discarded if not used immediately after reconstitution.

As with all parenteral admixtures, the reconstituted product should be examined for the presence of foreign particulate matter, agglomeration or discoloration. Any defective units should be discarded.

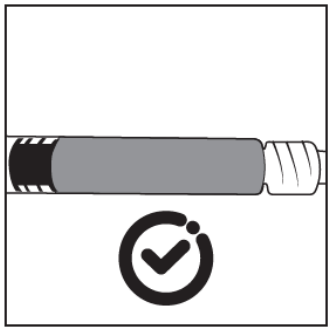
General Instructions and Recommendations

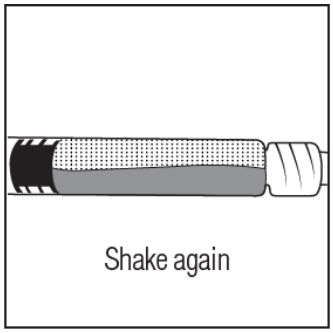
- The product is a suspension of microparticles that can sediment in the diluent. The product should appear homogenous, thick, and milky before administration. If the product sediments in the vial, shake again.





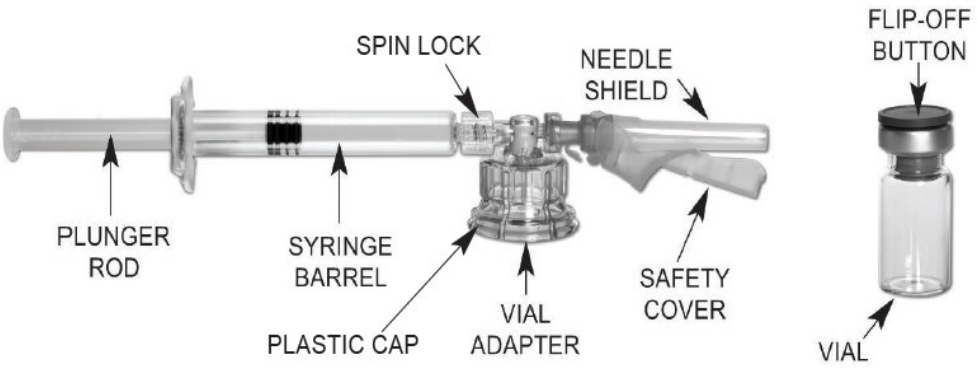
- If the particles settle it will lead to a needle blockage. It is very important to inject within 2 minutes after reconstitution. If the product sediments in the syringe, shake again before injection.





Instructions for Use – TRELSTAR Dose Delivery System (with Pre-Filled Syringe Containing Sterile Water for Injection), MIXJECT

Please read the instructions completely before you begin.

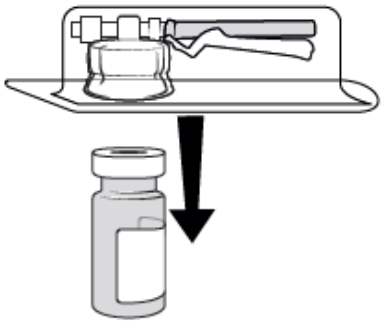


MIXJECT Preparation

Wash your hands with soap and hot water and put on gloves immediately prior to preparing the injection. Place the sealed tray on a clean, flat surface that is covered with a sterile pad or cloth. Peel the cover away from the tray and remove the MIXJECT components and the TRELSTAR vial. Remove the Flip-Off button from the top of the vial, revealing the rubber stopper. Place the vial in a standing upright position on the prepared surface. Disinfect the rubber stopper with an alcohol wipe. Discard the alcohol wipe and allow the stopper to dry. Proceed to *MIXJECT Activation*.

MIXJECT Activation

1.



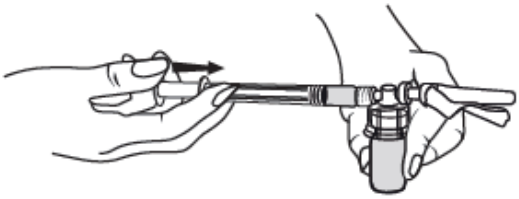
Remove the paper backing from the MIXJECT device. Do not remove the MIXJECT device from the blister pack. Place the vial on a hard surface. Center the MIXJECT device on the stopper and push straight down onto the vial top until it snaps securely into place.
Remove the blister pack from the MIXJECT device.

2.

Screw the plunger rod into the barrel end of the syringe. Hold the syringe by the spin lock. Remove the cap from the syringe barrel.

While holding the syringe by the spin lock, connect the syringe to the vial adapter by screwing it half a turn clockwise (only until it feels snug) into the opening on the side of the vial adapter.
Do not over tighten the spin lock.

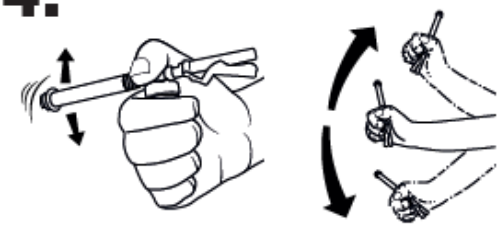
3.



While holding the vial, place your thumb on the plunger rod and inject the entire amount of diluent from the syringe into the vial.

At this stage prepare the patient for injection. **The following steps should be completed without interruption.**

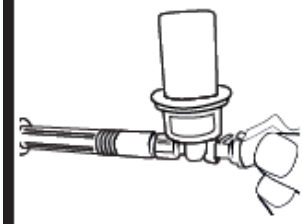
4.



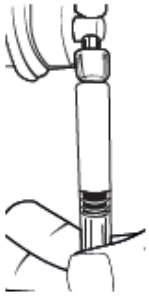
Mix the vial thoroughly by shaking and ensure that the diluent rinses the sides of the vial. Keep the plunger depressed while shaking. Check the appearance of the suspension through the bottom of the vial. The suspension should appear **homogeneous, thick, and milky.**

Shake the vial again if there is sedimentation. The product must be injected within **less than 2 minutes from now.**

5.



Invert the MIXJECT system and slowly pull back plunger rod to withdraw entire content from the vial into the syringe.



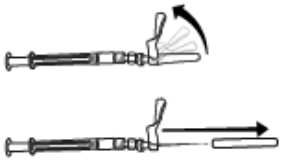
Hold the syringe upright to remove air bubbles.

6.

Return the vial to its upright position and disconnect the syringe from the MIXJECT vial adapter by turning the plastic cap of the vial adapter clockwise. Grasp only the plastic cap when removing.

Ensure that the product is homogenous, thick, milky and that there is no sedimentation before injection. If there is sedimentation, shake the syringe again before injection.

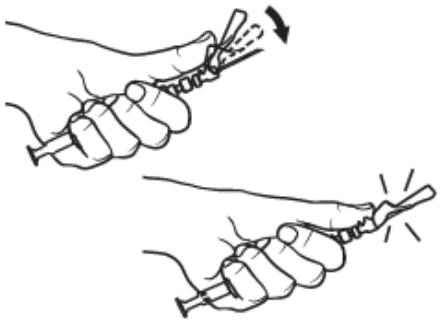
7.



Lift up the needle safety cover, remove the clear plastic shield then **immediately** inject entire content of syringe.

Do not prime the needle.
The injection of the suspension should be performed relatively rapidly and in a steady and uninterrupted manner to avoid any potential blockage of the needle.

8.



MIXJECT Disposal
After administering the injection, immediately activate the safety mechanism by centering your thumb or forefinger on the textured finger pad area of the safety cover and pushing it forward over the needle until you hear or feel it lock. Use the one-handed technique and activate the mechanism away from yourself and others. Activation of the safety cover causes virtually no splatter. Immediately discard the syringe assembly after a single use into a suitable sharps container.

Instructions for Use – TRELSTAR vial (without Pre-Filled Syringe Containing Sterile Water for Injection)

The lyophilized powder is to be reconstituted **in sterile water for injection**. **No other diluent should be used**. It is necessary for an aseptic technique to be maintained throughout preparation.

Preparation

1) Using a syringe fitted with a sterile 21-gauge needle, withdraw 2 mL **sterile water for injection**, USP, and after removing the flip-off seal from the vial, inject through the rubber stopper into the vial. Ensure the plunger rod remains pushed down.
2) Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear **homogenous, thick, and milky**. The product **must be injected within 2 minutes** after shaking is completed.
3) Withdraw the entire content of the reconstituted suspension into the syringe and **inject it immediately** in a steady and uninterrupted manner. **Do not prime the needle**. Ensure that the product is homogeneous, thick, and milky and that there is no sedimentation before injection. If there is sedimentation, shake the syringe again before injection.

Disposal

Dispose of the syringe and vial into a suitable sharps container.

4.4 Administration

TRELSTAR should be administered by a health professional.

TRELSTAR is administered as a single intramuscular injection. Since TRELSTAR is a suspension of microgranules, inadvertent intravascular injection must be strictly avoided.

As with other drugs administered by intramuscular injection, the injection site should be varied periodically.

4.5 Missed Dose

Maintaining suppression of sex hormones is important in the management and relief of chronic pain associated with endometriosis, and in treating the symptoms of hormone-dependent prostate cancer. Missing an appointment by a few days should not disrupt the benefits of treatment, but keeping a consistent schedule of TRELSTAR injections is an important part of treatment.

5 OVERDOSAGE

The pharmacologic properties of TRELSTAR and its mode of administration make accidental or intentional overdosage unlikely. There is no experience of overdosage from clinical trials. Acute animal toxicity of the drug is low and high multiples of clinical dose did not cause any adverse effects. If overdosage occurs, it should be managed symptomatically.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/Strength/Composition	Non-medicinal Ingredients
Intramuscular injection	Sterile vial of powder for injectable suspension, 3.75 mg (as triptorelin base), triptorelin pamoate	Carboxymethylcellulose sodium, mannitol, poly-*d*,*l*-lactide-co-glycolide, and polysorbate 80
Intramuscular injection	Sterile vial of powder for injectable suspension, 11.25 mg (as triptorelin base), triptorelin pamoate	Carboxymethylcellulose sodium, mannitol, poly-*d*,*l*-lactide-co-glycolide, and polysorbate 80
Intramuscular injection	Sterile vial of powder for injectable suspension, 22.5 mg (as triptorelin base), triptorelin pamoate	Carboxymethylcellulose sodium, mannitol, poly-*d*,*l*-lactide-co-glycolide, and polysorbate 80

TRELSTAR is available for use as:

1. TRELSTAR one single dose vial with a delivery system that contains:

   - One MIXJECT single dose delivery system with a 21-Gauge needle
   - One single use pre-filled syringe containing 2 mL Sterile Water for Injection

2. TRELSTAR one single dose vial without a delivery system

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

All Indications

Carcinogenesis and Mutagenesis

In a 23-month carcinogenicity study in rats, pituitary adenomas which resulted in premature deaths were observed in rats treated with triptorelin pamoate. No oncogenic effects were observed in mice given triptorelin pamoate for 18 months (see 16 NON-CLINICAL TOXICOLOGY).

Driving and Operating Machinery

No studies on the effects of TRELSTAR on the ability to drive and use machines have been performed. However, as fatigue and dizziness are common adverse reactions that might influence the ability to drive and use machines, due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Hypogonadism

Long-term administration of TRELSTAR will cause suppression of pituitary gonadotropins and gonadal hormone production with clinical symptoms of hypogonadism. These changes have been observed to reverse on discontinuation of therapy. However, whether the clinical symptoms of induced hypogonadism will reverse in all patients has not yet been established.

Pituitary apoplexy

During post-marketing experience, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of LHRH agonists (see 8.5 Post-Market Adverse Reactions). In a majority of these cases, a pituitary adenoma was diagnosed with the majority of pituitary apoplexy cases occurring within 2 weeks of the first dose of TRELSTAR, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

Hepatic/Biliary/Pancreatic

TRELSTAR exposure was higher in patients with hepatic insufficiency than in healthy volunteers. Clinical consequences of the increase and potential need for dose adjustment are unknown.

Immune

Hypersensitivity and anaphylactic reactions have been reported with triptorelin as with other LHRH agonists. TRELSTAR should not be administered to individuals who are hypersensitive to triptorelin, other LHRH agonists, or LHRH (see 8.5 Post-Market Adverse Reactions). In the event of a hypersensitivity reaction, TRELSTAR therapy should be discontinued immediately and the appropriate supportive and symptomatic care should be administered.

Psychiatric

There is an increased risk of depression (which may be severe) in patients undergoing treatment with LHRH agonists, including TRELSTAR. Patients should be informed accordingly and treated appropriately if symptoms occur.

Patients with known history of depression should be monitored closely during therapy.

Renal

TRELSTAR exposure was higher in patients with renal insufficiency than in healthy volunteers. Clinical consequences of the increase and potential need for dose adjustment are unknown.

Reproductive Health: Female and Male Potential

- **Fertility**

  Based on mechanism of action and findings in animals, TRELSTAR may impair fertility in males and females of reproductive potential (see 10.1 Mechanism of Action, 16 NON-CLINICAL TOXICOLOGY).

- **Function**

  Treatment with TRELSTAR may result in erectile dysfunction in males and decreased libido in females and males (see 8 ADVERSE REACTIONS).

- **Teratogenic Risk**

  Based on findings in animals, TRELSTAR may cause fetal harm if administered to pregnant women (see 16 NON-CLINICAL TOXICOLOGY). TRELSTAR is contraindicated in women who are or may become pregnant (see 2 CONTRAINDICATIONS, 7.1.1 Pregnant Women).

Endometriosis

General

During the early phase of therapy, sex hormones usually rise above baseline levels because of the physiologic effect of the drug. An increase in clinical signs and symptoms of endometriosis is often observed during the initial days of therapy. These will subside with continued treatment.

Worsening of the clinical condition may occasionally require discontinuation of therapy.

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

Genitourinary

Vaginal bleeding

Since menstruation should stop with effective doses of TRELSTAR, the patient should notify her health professional if regular menstruation persists. Patients missing successive doses of TRELSTAR 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.

Musculoskeletal

Changes in bone density

Bone loss can be expected as part of natural aging and can also be anticipated during the hypoestrogenic state caused by long-term use of TRELSTAR. Treatment with triptorelin for a period up to 6 months can lead to a reduction in bone mineral density, but this is generally reversible after the end of treatment. Some of the bone density loss over the course of TRELSTAR therapy may not be reversible.

It has been shown in patients treated with LHRH analogues for endometriosis that the addition of estrogen and progestogen therapy reduces bone mineral density loss and vasomotor symptoms. Therefore, if appropriate, consider co-administering estrogen and progestogen therapy with LHRH analogues while taking into account the risks and benefits of each treatment.

In patients with significant risk factors for decreased bone mineral content and/or bone mass such as family history of osteoporosis, chronic use of corticosteroids or anticonvulsants or chronic use of alcohol or tobacco, TRELSTAR may pose additional risk. In these patients, risk versus benefit must be weighted carefully before initiation of TRELSTAR therapy. Repeated courses of therapy with LHRH analogs beyond 6 months are not advisable for patients with major risk factors for loss of bone mineral content.

Prostate Cancer

General

TRELSTAR, like other LHRH agonists, causes a transient increase in serum concentration of testosterone during the first weeks of treatment. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, hematuria, or ureteral or bladder outlet obstruction. Cases of spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with LHRH agonists. If spinal cord compression or renal impairment due to ureteral obstruction develops, standard treatment of these complications should be instituted.

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should begin TRELSTAR therapy under close supervision.

Cardiovascular

There may be a relationship between androgen deprivation therapy and cardiovascular risk in men with prostate cancer on the basis of the demonstrated adverse impact of androgen deprivation on traditional cardiovascular risk factors, including serum lipoproteins, insulin sensitivity, and obesity. Reports of events related to cardiovascular ischemia including myocardial infarction, stroke and cardiovascular-related deaths have been received in patients treated with LHRH agonists. Health professionals should consider whether the benefits of androgen deprivation therapy outweigh the potential cardiovascular risk. Assessment of cardiovascular risk and management according to local clinical practice and guidelines should be considered (see Monitoring and Laboratory Tests).

Effect on QT/QTc interval

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with TRELSTAR therapy.

Androgen deprivation therapy has the potential to prolong QT/QTc interval on ECG (see 10.2 Pharmacodynamics). QT prolongation is a physiologic consequence of hormonal therapies that induce androgen ablation in males with prostate cancer and should be considered in assessing the risk-benefit of treatment with hormonal therapy. Health professionals 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 medications that might prolong the QT interval (see 9 DRUG INTERACTIONS).

Endocrine and Metabolism

Reduction in glucose tolerance

A reduction in glucose tolerance and an increased risk in developing diabetes have been reported in men treated with androgen deprivation therapy. Patients treated with TRELSTAR should undergo periodic monitoring of blood glucose. Diabetic patients may require more frequent monitoring when receiving TRELSTAR.

Hematologic

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.

Monitoring and Laboratory Tests

During therapy with TRELSTAR, patients should be routinely monitored by physical examinations and appropriate laboratory tests.

In prostate cancer patients, an assessment of bone lesions may require the use of bone scans. Prostatic lesions may be monitored by ultrasonography and/or CT scan in addition to digital rectal examination. The status of obstructive uropathy may be assessed and/or diagnosed using intravenous pyelography, ultrasonography or CT scan.

Response to TRELSTAR may be monitored by periodically measuring serum concentrations of testosterone and prostate specific antigen (PSA). Results of testosterone determinations are dependent on assay methodology. Some methods may either over- or underestimate the testosterone values in the hypogonadal testosterone range. The LC-MS/MS method is the reference method for

testosterone assessments when castrate levels are expected and was the assay method used in the clinical study supporting authorization of TRELSTAR 22.5 mg (6 month sustained-release formulation). It is advisable to be aware of the type and precision of the assay methodology in order to make appropriate clinical and therapeutic decisions.

Baseline risk factors of cardiovascular diseases should be assessed. Patients receiving TRELSTAR should be monitored periodically for risk factors, signs and symptoms of cardiovascular diseases. In addition, baseline ECG recording and serum potassium, calcium, and magnesium levels are recommended. Monitoring of ECG and serum electrolyte levels during treatment should also be considered for those at risk for electrolyte abnormality and QT prolongation (see Cardiovascular).

Blood glucose levels and/or glycosylated haemoglobin (HbA1c) should be checked periodically in patients treated with TRELSTAR and more frequently in diabetic patients (see Endocrine and Metabolism).

Musculoskeletal

Changes in bone density

Decreased bone mineral density can be anticipated with long term use of an LHRH agonist. Androgen deprivation therapy is associated with increased risks of osteoporosis and skeletal bone fractures. The risk of skeletal fracture increases with the duration of androgen deprivation therapy. Assessment of osteoporosis risk and management according to clinical practice and guidelines should be considered.

In patients with significant risk factors for decreased bone mineral content and/or bone mass such as chronic alcohol and/or tobacco use, presumed or strong family history of osteoporosis, chronic use of drug that can reduce bone mass such as anticonvulsants or corticosteroids, TRELSTAR may pose additional risk. In these patients, risk versus benefit must be weighed carefully before therapy with TRELSTAR is instituted.

7.1 Special Populations

7.1.1 Pregnant Women

TRELSTAR is contraindicated in women who are or may become pregnant (see 2 CONTRAINDICATIONS). The safe use of TRELSTAR during pregnancy has not been established clinically (see 8 ADVERSE REACTIONS). While no teratogenic effects were observed from animal studies, an embryotoxic effect of increased uterine resorption has been observed in pregnant rats administered triptorelin (see 16 NON-CLINICAL TOXICOLOGY). Before starting therapy with TRELSTAR, pregnancy must be excluded. When used regularly and at therapeutic doses, TRELSTAR inhibits ovulation and subsequently menstruation. However, contraception cannot be ensured. Females of childbearing potential should use nonhormonal methods of contraception while on therapy and should be advised to see their health professional if they think they may be pregnant. If a woman becomes pregnant while receiving TRELSTAR, therapy should be discontinued and the patient advised of the potential risk to the fetus. The possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy.

A small number of women have been inadvertently exposed to triptorelin during pregnancy. Of 28 pregnant women in France exposed to triptorelin in fertility trials, one case of trisomy 13 was reported in a woman who received triptorelin 15 days after conception. One case of trisomy 18 has been reported in Italy. In both cases, a causal relationship could not be established. In another study, very

long fetal exposure to triptorelin in a woman who became pregnant during a clinically induced pseudo menopause resulted in the term delivery of a healthy newborn.

7.1.2 Breast-feeding

It is not known to what extent TRELSTAR is excreted into human milk. Because there are no well-controlled studies on the effect of TRELSTAR in nursing women and because many drugs are excreted into human milk, TRELSTAR is contraindicated in nursing women (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Treatment with LHRH agonists may reduce bone mineral density (BMD). Given that adolescents may not have reached maximum bone mass (especially those under the age of 16 years), LHRH agonists are not recommended for the management and relief of chronic pain associated with endometriosis in patients under the age of 18 years.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): No data are available to Health Canada for the management and relief of chronic pain associated with endometriosis in geriatric patients.

The majority of the patients studied in the clinical trials for the palliative treatment of prostate cancer with TRELSTAR were 65 years and older (see 14 CLINICAL TRIALS).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Endometriosis

Adverse reactions reported in clinical trials of TRELSTAR were rarely severe enough to result in patient withdrawal from TRELSTAR treatment. In a controlled study with 137 endometriosis patients comparing triptorelin [3.75 mg] and leuprolide [3.75 mg] administered monthly for 6 months, one case of severe acute abdominal pain was judged probably related to therapy. No discontinuation of treatment was required for this patient.

Most adverse reactions resolved spontaneously without further medical intervention. As seen with other LHRH agonist therapies, the most commonly observed adverse events during TRELSTAR treatment were due to the expected physiological effects related to hypoestrogenism. These effects included hot flushes (91%), vaginal dryness (49%), and amenorrhea. During the first 1-2 weeks following the initial injection, the transient increase in estradiol levels may be associated with temporary worsening of signs and symptoms of endometriosis (see 7 WARNINGS AND PRECAUTIONS).

Prostate Cancer

Adverse reactions reported in clinical trials of TRELSTAR were rarely severe enough to result in patient withdrawal from TRELSTAR treatment. Postmarketing reports of anaphylactic shock and angioedema have been reported following TRELSTAR administration (see 7 WARNINGS AND PRECAUTIONS). In

clinical trials, no serious adverse events that were considered to be related to study drug administration were reported.

As seen with other LHRH agonist therapies, the most commonly observed adverse events during TRELSTAR treatment were due to the expected physiological effects related to decreased testosterone levels. These effects included hot flushes (45% for TRELSTAR 3.75mg), erectile dysfunction (50% for TRELSTAR 3.75mg), and decreased libido (45% for TRELSTAR 3.75mg). TRELSTAR, like other LHRH analogs, caused an initial transient increase in serum testosterone concentrations during the first few weeks of treatment. Potential exacerbations of signs and symptoms of the disease during the first few weeks of treatment may occur, including neurological problems such as weakness and/or paresthesia of the lower limbs in patients with vertebral metastases, and worsening of urinary obstruction or hematuria (see 7 WARNINGS AND PRECAUTIONS).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Endometriosis

In a controlled study comparing triptorelin [3.75 mg] and leuprolide [3.75 mg] administered via intramuscular (IM) injection monthly for 6 months to endometriosis patients, the following adverse events were reported by 5% or more of patients in the triptorelin study group regardless of relationship or association to treatment:

Table 3 – Adverse events reported by ≥ 5% patients during treatment with triptorelin and the related adverse events frequencies during treatment with leuprolide

Adverse Event	Triptorelin (n = 67) n (% of patients)	Leuprolide (n = 70) n (% of patients)
Gastrointestinal Disorders		
Nausea	9 (13)	6 (9)
Abdominal pain	7 (10)	8 (11)
General Disorders and Administration Site Conditions		
Ankle edema	16 (24)	11 (16)
Pain NOS*	8 (12)	6 (9)
Infections and Infestations		
Viral infection	9 (13)	8 (11)
Injury, Poisoning and Procedural Complications		
Accidental injury	5 (8)	1 (1)
Bruising	4 (6)	2 (3)

Adverse Event	Triptorelin (n = 67) n (% of patients)	Leuprolide (n = 70) n (% of patients)
Musculoskeletal and Connective Tissue Disorders		
Back pain	6 (9)	7 (10)
Arthralgia	5 (8)	5 (7)
Nervous System Disorders		
Headache	40 (60)	45 (64)
Dizziness	4 (6)	6 (9)
Psychiatric Disorders		
Insomnia	46 (69)	43 (61)
Depression	38 (57)	39 (56)
Libido decreased	36 (54)	37 (53)
Irritability	30 (45)	35 (50)
Renal and Urinary Disorders		
Urinary tract infection	4 (6)	0 (0)
Reproductive System and Breast Disorders		
Vaginal dryness	33 (49)	41 (59)
Breast disorder	21 (31)	22 (31)
Skin and Subcutaneous Tissue Disorders		
Sweating increased	57 (85)	61 (87)
Seborrhea	29 (43)	16 (23)
Acne	20 (30)	24 (34)
Vascular Disorders		
Hot flushes	61 (91)	65 (93)

* NOS = not otherwise specified. Medical Dictionary for Regulatory Activities (MedDRA) version 25.0.

Frequently reported adverse events (≥ 5%) for both the triptorelin and leuprolide groups included hot flushes, depression, irritability, headache, breast disorder, arthralgia, insomnia, decreased libido, acne, seborrhea, increased sweating, and vaginal dryness.

Prostate Cancer

Clinical Studies with Triptorelin Acetate

Triptorelin 3.75 mg (1 month sustained-release acetate formulation)

Three controlled clinical studies were conducted on 265 patients to compare a controlled release formulation of triptorelin acetate (N = 160) with orchiectomy (N = 105).

In the first study, all patients received an IM injection of 3.75 mg triptorelin and every month thereafter for 24 months, with the exception of 3 patients who received 100 µg triptorelin subcutaneously (SC) for the first month. In the second study, all patients received 100 µg triptorelin SC for the first 7 days, and 3.75 mg IM on Days 8, 28, and every month thereafter for up to 18 months. In the third study, all patients received an IM injection of 3.75 mg triptorelin on Days 0 and 28, and every month thereafter for 24 months.

In these studies, the most commonly observed adverse events reported in 5% or more of patients were: erectile dysfunction (50% in the triptorelin group and 41% in the orchiectomy group), decreased libido (45% of patients in the triptorelin group and 39% in the orchiectomy group), hot flushes (45% in the triptorelin group and 43% in the orchiectomy group), and reduced size of genitalia (12% in the triptorelin group). These events are known to be related to biochemical or surgical castration (see 14 CLINICAL TRIALS).

Adverse events reported by 1% or more of patients and considered possibly or probably related to the study drug are listed in Table 4.

Table 4 – Possibly or probably related systemic adverse events reported by ≥ 1% of patients treated with TRELSTAR (triptorelin acetate 3.75 mg formulation) and orchiectomy

Adverse Event	Triptorelin Acetate (3.75 mg) N = 156 n (%)	Orchiectomy N = 97 n (%)
Cardiac Disorders		
Heart disorder	5 (3.2)	1 (1.0)
Angina pectoris	1 (0.6)	3 (3.1)
Palpitation	1 (0.6)	1 (1.0)
Gastrointestinal Disorders		
Vomiting	4 (2.6)	4 (4.1)
Constipation	3 (1.9)	1 (1.0)
Diarrhea	3 (1.9)	1 (1.0)
Defecation disorder	0 (0.0)	1 (1.0)
General Disorders and Administration Site Conditions		
Edema	6 (3.8)	2 (2.1)
Asthenia	6 (3.8)	3 (3.1)
Injection site pain	6 (3.8)	NA
Back pain	3 (1.9)	0 (0.0)
Fatigue	2 (1.3)	0 (0.0)
Pain	2 (1.3)	2 (2.1)
Adverse event NOS**	3 (1.9)	0 (0.0)
Infections and Infestations		
Infection	0 (0.0)	1 (1.0)
Investigation		
Weight increase	8 (5.1)	4 (4.1)
Weight decrease	2 (1.3)	2 (2.1)

Adverse Event	Triptorelin Acetate (3.75 mg) N = 156 n (%)	Orchiectomy N = 97 n (%)
Metabolism and Nutrition Disorders		
Cachexia	2 (1.3)	0 (0.0)
Anorexia	2 (1.3)	1 (1.0)
Neoplasms Benign, Malignant and Unspecified		
Tumor flare	4 (2.6)	0 (0.0)
Nervous System Disorders		
Vertigo	0 (0.0)	1 (1.0)
Psychiatric Disorders		
Libido decreased*	70 (44.9)	38 (39.2)
Nervousness	4 (2.6)	1 (1.0)
Depression*	3 (1.9)	2 (2.1)
Aggressive reaction	0 (0.0)	1 (1.0)
Reproductive system and breast disorders		
Erectile dysfunction* (including failure to ejaculate, disorder of ejaculation)	78 (50.0)	40 (41.2)
Genital atrophy*	19 (12.2)	NA
Gynecomastia	2 (1.3)	0 (0.0)
Renal and Urinary Disorders		
Micturition frequency	3 (1.9)	2 (1.3)
Urinary incontinence	2 (1.3)	1 (1.0)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	6 (3.8)	0 (0.0)
Respiratory disorder	1 (0.6)	1 (1.0)
Hemoptysis	0 (0.0)	1 (1.0)
Skin and Subcutaneous Tissue Disorders		
Pruritus	2 (1.3)	0 (0.0)
Rash	0 (0.0)	1 (1.0)
Sweating increased	1 (0.6)	1 (1.0)
Vascular Disorders		
Hot flushes*	70 (44.9)	42 (43.3)
Flushing	0 (0.0)	2 (2.1)
Hypertension	2 (1.3)	0 (0.0)
Hypotension	0 (0.0)	1 (1.0)

NA = not applicable; * Expected pharmacological consequence of testosterone suppression; ** Data were insufficiently clear to be coded in three patients, NOS = not otherwise specified. MedDRA version 25.0.

Clinical Studies with Triptorelin Pamoate

TRELSTAR 3.75 mg (1 month sustained-release formulation) and TRELSTAR 11.25 mg (3 month sustained-release formulation)

The safety of TRELSTAR was also evaluated in a study that compared TRELSTAR 3.75 mg (1 month sustained-release formulation) and TRELSTAR 11.25 mg (3 month sustained-release formulation). The patients in this study were randomized to receive either three injections of TRELSTAR 11.25 mg, administered IM every 84 days for 9 months, or nine injections of TRELSTAR 3.75 mg, administered IM every 28 days for 9 months.

TRELSTAR 22.5 mg (6 month sustained-release formulation)

The safety of TRELSTAR was evaluated in a non-comparative study of TRELSTAR 22.5 mg (6 month sustained-release formulation). Each patient in this study received two injections of TRELSTAR 22.5 mg, with the first injection administered IM on Day 1 and the second injection administered IM on Day 169.

The safety profile was similar to the TRELSTAR 3.75 mg and TRELSTAR 11.25 mg strengths.

The following possibly or probably related systemic adverse events were reported by 1% or more of patients in the studies mentioned above for either TRELSTAR 3.75 mg, TRELSTAR 11.25 mg or TRELSTAR 22.5 mg:

Table 5 – Possibly or probably related systemic adverse events reported by ≥ 1% of patients in either treatment group treated with TRELSTAR 3.75 mg, TRELSTAR 11.25 mg, or TRELSTAR 22.5 mg

Adverse Event	TRELSTAR (3.75 mg)[1] N = 172 n (%)	TRELSTAR (11.25 mg)[1] N=174 n (%)	TRELSTAR (22.5 mg)[2] N = 120 n (%)
Cardiac Disorders			
Edema dependent	0 (0.0)	4 (2.3)	0 (0.0)
Palpitation	3 (1.7)	0 (0.0)	0 (0.0)
Eye Disorders			
Eye pain	1 (0.6)	2 (1.1)	0 (0.0)
Conjunctivitis	0 (0.0)	2 (1.1)	0 (0.0)
Gastrointestinal Disorders			
Constipation	4 (2.3)	3 (1.7)	0 (0.0)
Nausea	7 (4.1)	5 (2.9)	0 (0.0)
Diarrhea	4 (2.3)	2 (1.1)	0 (0.0)
Abdominal pain	1 (0.6)	2 (1.1)	0 (0.0)
Dyspepsia	2 (1.2)	3 (1.7)	0 (0.0)
General Disorders and Administration Site Conditions			
Back pain	6 (3.5)	5 (2.9)	0 (0.0)
Pain	10 (5.8)	6 (3.4)	0 (0.0)
Fatigue	5 (2.9)	4 (2.3)	5 (4.2)
Chest pain	0 (0.0)	3 (1.7)	0 (0.0)
Lethargy	0 (0.0)	0 (0.0)	2 (1.7)
Asthenia	2 (1.2)	2 (1.1)	0 (0.0)
Edema peripheral	3 (1.7)	2 (1.1)	0 (0.0)

Injection site bruising	0 (0.0)	0 (0.0)	2 (1.7)
Injection site induration	0 (0.0)	0 (0.0)	2 (1.7)
Injection site pain	2 (1.2)	7 (4.0)	2 (1.7)
Hepatobiliary Disorders			
Hepatic function abnormal	0 (0.0)	2 (1.1)	0 (0.0)
Immune System Disorders			
Allergic reaction	2 (1.2)	0 (0.0)	0 (0.0)
Metabolism and Nutrition Disorders			
Edema legs	14 (8.1)	11 (6.3)	0 (0.0)
Diabetes mellitus	2 (1.2)	1 (0.6)	0 (0.0)
Cramps legs	1 (0.6)	3 (1.7)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders			
Skeletal pain	20 (11.6)	23 (13.2)	0 (0.0)
Leg pain	5 (2.9)	9 (5.2)	0 (0.0)
Arthralgia	4 (2.3)	4 (2.3)	0 (0.0)
Myalgia	1 (0.6)	2 (1.1)	0 (0.0)
Nervous System Disorders			
Headache	7 (4.1)	12 (6.9)	2 (1.7)
Dizziness	5 (2.9)	5 (2.9)	2 (1.7)
Psychiatric Disorders			
Insomnia	2 (1.2)	3 (1.7)	0 (0.0)
Depression*	3 (1.7)	1 (0.6)	2 (1.7)
Anorexia	1 (0.6)	3 (1.7)	0 (0.0)
Libido decreased*	1 (0.6)	4 (2.3)	2 (1.7)
Renal and Urinary Disorders			
Urinary tract infection	3 (1.7)	0 (0.0)	0 (0.0)
Dysuria	3 (1.7)	8 (4.6)	0 (0.0)
Urinary retention	0 (0.0)	2 (1.1)	0 (0.0)
Reproductive System and Breast Disorders			
Testicular atrophy*	0 (0.0)	0 (0.0)	9 (7.5)
Breast pain male	5 (2.9)	4 (2.3)	0 (0.0)
Erectile dysfunction* (including failure to ejaculate, disorder of ejaculation)	7 (4.1)	4 (2.3)	12 (10.0)
Gynecomastia	0 (0.0)	3 (1.7)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders			
Coughing	1 (0.6)	3 (1.7)	0 (0.0)
Dyspnea	3 (1.7)	2 (1.1)	0 (0.0)
Pharyngitis	0 (0.0)	2 (1.1)	0 (0.0)
Skin and Subcutaneous Tissue Disorders			
Rash	1 (0.6)		0 (0.0)

Pruritus	2 (1.2)	3 (1.7) 0 (0.0)	0 (0.0)
Vascular Disorders Hypertension Hot flushes*	 8 (4.7) 114 (66.3)	 7 (4.0) 127 (73.0)	 0 (0.0) 86 (71.7)

* Expected pharmacological consequence of testosterone suppression
[1]Adverse reactions for TRELSTAR 3.75 mg and TRELSTAR 11.25 mg are coded using the WHO Adverse Reactions Terminology (WHOART)
[2]Adverse reactions for TRELSTAR 22.5 mg are coded using MedDRA (version 25.0)

8.3 Less Common Clinical Trial Adverse Reactions

Endometriosis

Less frequently reported adverse events (< 5% of women) included, but were not limited to:

Gastrointestinal Disorders: Diarrhea, irritable bowel, vomiting

General Disorders and Administration Site Conditions: Chest pain, fatigue, peripheral edema, injection site reaction

Musculoskeletal and Connective Tissue Disorders: Leg cramps, arthritis, arthrosis, myalgia

Nervous System Disorders: Amnesia

Psychiatric Disorders: Apathy

Reproductive System and Breast Disorders: Pelvic pain, leukorrhea, vaginal hemorrhage

Skin and Subcutaneous Tissue Disorders: Rash

Changes in Bone Mineral Density: After 6 months of treatment with triptorelin in 32 women, the average decrease in bone mineral density, as measured by dual energy x-ray absorptiometry, was 5.3% and 2.3% in lumbar spine and hip, respectively, compared to pre-treatment values. Lumbar spine and hip bone mineral density were still slightly decreased by 12 months follow-up (1.7% and 1.3%, respectively).

Prostate Cancer

Adverse drug reactions that were reported by less than 1% of subjects in TRELSTAR 3.75 mg, TRELSTAR 11.25 mg and TRELSTAR 22.5 mg treatment groups, and were considered to be possibly or probably related to study drug, included the following:

Gastrointestinal Disorders: Abdominal discomfort, abdominal pain, nausea

General Disorders and Administration Site Conditions: Malaise, injection site erythema, injection site pruritus, injection site reaction, injection site swelling

Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, prostatic antigen increased, weight increased

Musculoskeletal and Connective Tissue Disorders: Muscle weakness, musculoskeletal stiffness, pain in extremity

Neoplasms Benign, Malignant and Unspecified: Metastatic pain

Nervous System Disorders: Paresthesia

Psychiatric Disorders: Loss of libido

Renal and Urinary Disorders: Hematuria

Reproductive System and Breast disorders: Orchitis noninfective

Respiratory, Thoracic and Mediastinal Disorders: Rhinitis

Skin and Subcutaneous Tissue Disorders: Skin disorder

Vascular Disorders: Syncope vasovagal

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Endometriosis

In clinical trials, there were no clinically meaningful changes in laboratory values during or following triptorelin therapy. With the exception of serum and urine creatinine, which were relatively low throughout the study, chemistry results were generally within normal limits for most patients throughout the study. Triptorelin therapy had no significant effect on liver enzymes (ALT/AST), alkaline phosphatase, LDH, total bilirubin, urea or inorganic phosphorous during the study. Likewise, there was no significant treatment effect on hematology parameters (WBC, RBC, hemoglobin, hematocrit, platelet count, or WBC differential). For the most part, hematology test results were within normal limits throughout the study for patients in each treatment group with available data. Minor fluctuations in values were observed at various time points in each of the treatment groups, none of which were considered clinically meaningful.

Prostate Cancer

Table 6 – Abnormal laboratory findings for clinical trials in patients with prostate cancer

Laboratory measurement	TRELSTAR 3.75 mg % of patients	TRELSTAR 11.25 mg % of patients	TRELSTAR 22.5 mg % of patients
Increased in prothrombin time	4.9	10.5	13.6

The incidence rates greater than 15% for low abnormal laboratory values (hemoglobin and erythrocyte count) and high abnormal laboratory values (fasting glucose, BUN, and alkaline phosphatase) were comparable for both TRELSTAR 3.75 mg and TRELSTAR 11.25 mg. The following abnormalities in laboratory values not present at baseline, which were similar with the 3.75 mg and 11.25 mg formulation, were observed in 10% or more of patients for TRELSTAR 22.5 mg: decreased hemoglobin and RBC count and increased glucose (change from baseline to worst-case on-treatment). The relationship of these changes to drug treatment is difficult to assess in this population.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of TRELSTAR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

All Indications

Cases of anaphylactic shock and angioedema related to TRELSTAR have been reported during post-marketing surveillance (see 7 WARNINGS AND PRECAUTIONS).

During post-marketing experience, rare cases of pituitary apoplexy have been reported (see 7 WARNINGS AND PRECAUTIONS). Most cases of pituitary apoplexy were reported following the initial administration of LHRH agonist in patients with pituitary adenoma.

Prostate Cancer

During post-marketing experience, convulsions and thrombosis-related events including, but not limited to, pulmonary emboli, cerebrovascular accident, myocardial infarction, deep venous thrombosis, transient ischemic attack, and thrombophlebitis have been reported.

During post-marketing experience, worsening of pre-existing depression, including suicide attempts, has been reported in patients taking LHRH agonists, including TRELSTAR.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been conducted with TRELSTAR.

The concomitant use of medicinal products known to prolong the QTc interval with LHRH agonist drugs such as TRELSTAR should be carefully evaluated.

Avoid concomitant use of hyperprolactinemic drugs with LHRH agonist drugs such as TRELSTAR.

9.3 Drug-Behavioural Interactions

No data are available on the interaction of TRELSTAR with alcohol.

9.4 Drug-Drug Interactions

All Indications

Interactions with other drugs have not been established.

In the absence of relevant data and as a precaution, hyperprolactinemic drugs should not be prescribed concomitantly with TRELSTAR since hyperprolactinemia reduces the number of pituitary LHRH receptors.

Prostate Cancer

Since androgen deprivation treatment may prolong the QTc interval (see 10.2 Pharmacodynamics), the concomitant use of TRELSTAR with medicinal products known to prolong the QTc interval or medicinal products able to induce torsades de pointes should be carefully evaluated. Such medicinal products include but are not limited to, the examples that follow: Class IA (e.g., quinidine, disopyramide), Class III (e.g., amiodarone, sotalol, dofetilide, ibutilide, dronedarone), or Class IC (e.g., flecainide, propafenone) antiarrhythmic medicinal products, antipsychotics (e.g., chlorpromazine), antibiotics and analogues (e.g., erythromycin, clarithromycin, azithromycin), quinolone antibiotics (e.g., moxifloxacin), antimalarials (e.g., quinine), azole antifungals, 5-hydroxytryptamine (5-HT3) receptor antagonists (e.g., ondansetron), and beta-2 adrenoceptor agonists (e.g., salbutamol).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Administration of LHRH analogs, including triptorelin, in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within 4 to 12 weeks after treatment is discontinued. Diagnostic tests of pituitary-gonadal function conducted during treatment and within 4 to 12 weeks after discontinuation of therapy with a LHRH agonist may therefore be misleading.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Triptorelin is an LHRH agonist analog that possesses greater potency than the natural hormone. The potency relative to native LHRH has been demonstrated both in vitro and in vivo. Triptorelin was more active in stimulating luteinizing hormone (LH) release and in displacing ^{125}I-LHRH from pituitary receptor sites compared to native LHRH in animal models. The increased potency was correlated with an increased resistance to degradation on exposure to enzyme preparations derived from the animal models.

Triptorelin acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses. On administration of triptorelin there is an initial and transient increase in circulating levels of LH, follicle-stimulating hormone (FSH), and gonadal steroids (estradiol in women and testosterone in men). However, chronic and continuous administration of triptorelin results in decreased LH and FSH secretion and suppression of ovarian and testicular steroidogenesis. In premenopausal women, circulating estrogen is decreased to postmenopausal levels. In men, serum testosterone is reduced to levels into the range normally seen in surgically castrated men. This results in accessory sexual organ atrophy which is generally reversible upon discontinuation of drug therapy.

Prostate Cancer

LHRH agonists have demonstrated direct antiproliferative effects in prostate cancer cell lines. Long-term administration of triptorelin inhibited tumor growth in animal models of prostate cancer.

10.2 Pharmacodynamics

Triptorelin had higher ovulation-inducing capacity and LH- and FSH-releasing activity compared to native LHRH in animal models.

Endometriosis

A single intramuscular (IM) dose of 1.9, 3.75, or 7.5 mg to women with endometriosis, uterine myoma or dysfunctional bleeding resulted in transient dose-dependent increase in LH and estradiol following injection. By day 14, serum LH and estradiol concentrations decreased to levels typically seen in postmenopausal women. On day 28 and up to day 42 after injection, estradiol levels were still suppressed (<184 pmol/L) in the mid- and high-dose groups. Following LHRH challenge (100 mg) on day 28, 7/10 patients in the 1.9 mg group, 3/10 patients in the 3.75 mg group, and 0/10 patients in the 7.5

mg group responded to stimulation with increased LH levels. By day 56, estradiol concentrations returned to pre-treatment levels in the mid-dose group but were still suppressed in the high dose group (7/8 patients).

Chronic and continuous administration of triptorelin maintains suppression of estrogen levels (Table 7).

Table 7 – Estradiol level (pmol/L) profile over 24 weeks of treatment with 3.75mg of triptorelin (N=66)

	Week 0 Pretreatment	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Mean	124	48	48	52	51	52	46
SD	77	42	36	37	35	36	25

Prostate Cancer

Following a single IM injection of TRELSTAR 3.75 mg (1 month sustained-release formulation) to healthy male volunteers, serum testosterone levels first increased, 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 after IM injection.

Following IM injection of TRELSTAR 11.25 mg (3 month sustained-release formulation) in patients with advanced prostate cancer, serum testosterone levels first increased, peaking around day 2, and thereafter declined to low levels by 4 weeks. This suppression of testosterone, similar to castrate levels (<50 ng/dL), was maintained for 3 months after the first injection and on repeat administration. IM injection of TRELSTAR 11.25 mg every 3 months ensures that exposure to triptorelin is maintained with no clinically significant accumulation.

Following IM injection of TRELSTAR 22.5 mg (6 month sustained-release formulation) in patients with advanced prostate cancer, serum testosterone levels first increased, peaking on Day 3, and declined thereafter to low levels by Weeks 3 – 4. This suppression of testosterone, similar to castrate levels (<50 ng/dL), was maintained for 6 months after the first injection and on repeat administration. IM injection of TRELSTAR (22.5 mg) every 6 months ensures that exposure to triptorelin is maintained with no clinically significant accumulation.

Electrocardiography

Androgen deprivation therapy may prolong the QT interval. QT prolongation is a physiologic consequence of hormonal therapies that induce androgen ablation in males with prostate cancer. Information on the dose and duration of triptorelin treatment and magnitude of effects on ECG are not available.

10.3 Pharmacokinetics

Results of pharmacokinetic investigations conducted in both women and men indicate that after IV bolus administration, triptorelin is distributed and eliminated according to a 3-compartment model with elimination from the central compartment and corresponding distribution half-lives of approximately 3 minutes, 47 minutes, and 5 hours in women and 6 minutes, 45 minutes, and 3 hours in men.

Table 8 – Pharmacokinetic parameters of triptorelin following single intramuscular administration of TRELSTAR in males

Dose No. of Subjects	C_{max} (ng/mL)	T_{max} (h)	AUC (h·ng/mL)
3.75 mg 20 healthy male volunteers	28.43 ± 7.31	1.0 (1.0 - 3.0)	223.15 ± 46.96[a]
11.25 mg 13 prostate cancer patients	38.5 ± 10.5	2.0 (2.0 - 4.0)	2268.0 ± 444.63[b]
22.5 mg 15 prostate cancer patients	44.1 ± 20.2	3.0 (2.0 - 12.0)	2674.88 ± 1040.03[c]

Values presented are mean ±SD or median (range) for T_{max}
[a] AUC (0-28 d), [b] AUC (0-85 d), [c] AUC (0-169 d)
* Computed as the mean AUC of the study divided by the mean AUC of healthy volunteers corrected for dose (AUC = 36.1 h·ng/mL; 500 μg IV bolus of triptorelin).

Table 9 – Pharmacokinetic parameters following single IV administration of triptorelin to women with endometriosis or uterine myoma

Dose (No. of subjects)	C_{max} (ng/mL)	T_{max} (h)	AUC (h·ng/mL)	$t_{1/2}$* (h)	Cl_p (mL/min)	V_{ss} (L)	% elimin. Urine
0.5 mg IV Bolus (n=19)	115.8 ± 59.0	0.03 (0.03-0.17)	81.9 ± 32.9	5.37 ± 2.29	110 ± 40	32.9 ± 16.8	20 ± 10

Values presented are mean ±SD or median (range) for T_{max}
* Elimination half-life

Absorption

Triptorelin is not active when given orally. The pharmacokinetic parameters following single intramuscular injections of triptorelin 3.75 mg, 11.25 mg and 22.5 mg sustained release formulations are listed in Table 8. The plasma concentrations for the 3.75 mg formulation declined to 0.084 ng/mL at 4 weeks.

Distribution

The volume of distribution of triptorelin following IV administration of 0.5 mg triptorelin was approximately 30-33 L in healthy male volunteers and women with endometriosis. Since there is no evidence that triptorelin at clinically relevant concentrations binds to plasma proteins, drug interactions involving binding-site displacement are unlikely (see 9 DRUG INTERACTIONS).

Metabolism

Metabolites of triptorelin have not been determined in humans. However, human pharmacokinetic data suggest that C-terminal fragments produced by 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 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 211.9 mL/min. This percentage increased to 62.3% in patients with liver disease who have a lower creatinine clearance (89.9 mL/min). It has also been observed that the non-renal clearance of triptorelin (patient anuric, $Cl_{creat} = 0$) was 76.2 mL/min, thus indicating that the nonrenal elimination of triptorelin is mainly dependent on the liver (see Special Populations and Conditions

Following a 0.5 mg IV bolus dose to 19 women with endometriosis or uterine myoma, the total clearance was estimated to be 110 mL/min. Twenty percent of the dose was eliminated in the urine (Table 9).

Special Populations and Conditions

- **Geriatrics:** The effects of age 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 250 mL/min) indicates that triptorelin was eliminated twice as fast in this young population (see Hepatic Insufficiency) as compared to patients with moderate renal insufficiency. This is related to the fact that triptorelin clearance is partly correlated to total creatinine clearance, which is well known to decrease with age.
- **Hepatic Insufficiency:** After an IV injection of 0.5 mg triptorelin peptide, the two distribution half-lives were unaffected by hepatic impairment (Table). Clearance in patients with hepatic impairment was reduced compared to healthy volunteers and subjects with renal impairment. Compared to healthy volunteers, the half-life was prolonged in subjects with hepatic impairment.
- **Renal Insufficiency:** After an IV injection of 0.5 mg triptorelin peptide, the two distribution half-lives were unaffected by renal impairment, but renal insufficiency led to a decrease in total triptorelin clearance proportional to the decrease in creatinine clearance as well as an increase in volume of distribution and consequently an increase in elimination half-life (Table). Compared to healthy volunteers, the half-life was prolonged and clearance was reduced in subjects with renal impairment.

Table 10 – Pharmacokinetic parameters (mean ± SD) in healthy volunteers and special populations

Group	C_{max} (ng/mL)	AUC_{inf} (h·ng/mL)	Cl_p (mL/min)	Cl_{renal} (mL/min)	$T_{1/2}$ (h)	Cl_{creat} (mL/min)
6 healthy male volunteers	48.2 ±11.8	36.1 ±5.8	211.9 ±31.6	90.6 ±35.3	2.81 ±1.21	149.9 ±7.3
6 males with moderate renal impairment	45.6 ±20.5	69.9 ±24.6	120.0 ±45.0	23.3 ±17.6	6.56 ±1.25	39.7 ±22.5
6 males with severe renal impairment	46.5 ±14.0	88.0 ±18.4	88.6 ±19.7	4.3 ±2.9	7.65 ±1.25	8.9 ±6.0

6 males with liver disease	54.1 ±5.3	131.9 ±18.1	57.8 ±8.0	35.9 ±5.0	7.58 ±1.17	89.9 ±15.1

11 STORAGE, STABILITY AND DISPOSAL

Store TRELSTAR 3.75 mg, TRELSTAR 11.25 mg and TRELSTAR 22.5 mg vials supplied with MIXJECT Dose Delivery System (with Pre-Filled Syringe Containing Sterile Water for Injection) at 15-30°C.

Store TRELSTAR 3.75 mg, TRELSTAR 11.25 mg and TRELSTAR 22.5 mg vials (without Pre-Filled Syringe Containing Sterile Water for Injection) at 15-30°C.

Protect from light. Do not freeze.

Unused portion of reconstituted TRELSTAR 3.75 mg, TRELSTAR 11.25 mg and TRELSTAR 22.5 mg should be discarded immediately.

Dispose of the syringe and vial into a suitable sharps container.

Keep out of sight and reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

The use of gloves is recommended.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Triptorelin pamoate

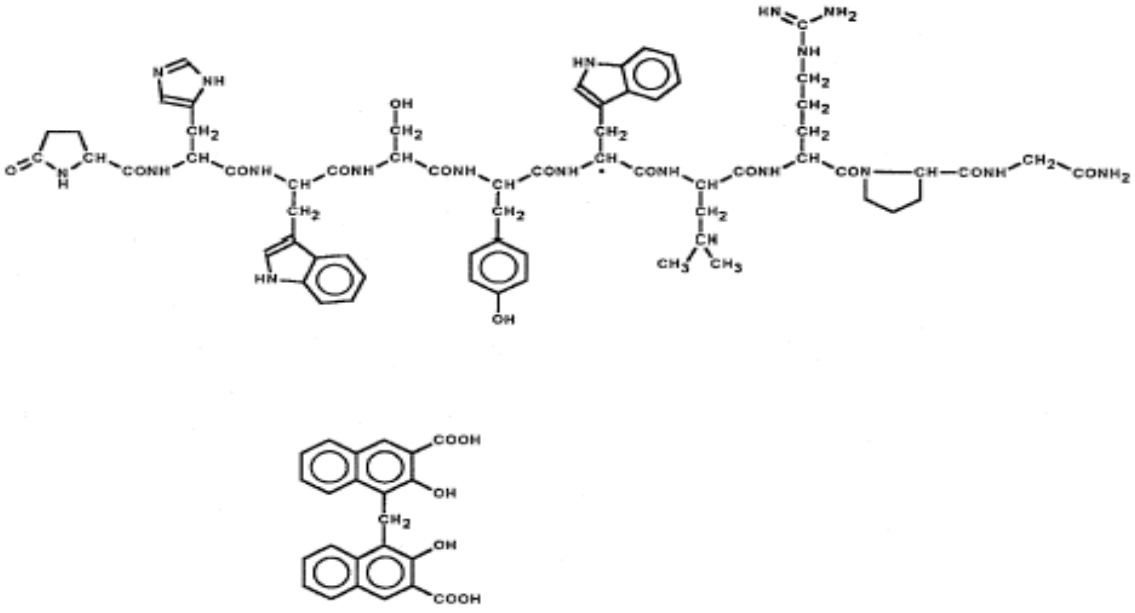
Chemical name: 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycine amide, pamoate salt

Molecular formula and molecular mass: $C_{64}H_{82}N_{18}O_{13} \bullet C_{23}H_{16}O_6$, 1699.9

Structural formula: Upper formula (D-Trp^6)-LHRH

Lower formula Pamoic acid (embonic acid)

All optically active amino acids are in L-configuration except where marked (*) for D-configuration.



Physicochemical properties: Yellowish powder, specific optical rotation $[\alpha]_D^{25} = -23.0^o \pm 2.5^o$,
Soluble in DMSO (660 mg/mL), pyridine (440 mg/mL) and water (60 µg/mL)

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Endometriosis

Table 10 – Summary of patient demographics for clinical trials in endometriosis

Study #	Study Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
UK DCP 94-097	Randomized, single-blind, comparative, parallel-group, multicenter	Triptorelin acetate microspheres 3.75 mg or leuprolide 3.75 mg, IM injection 24 weeks treatment, 12 months follow-up period after last dose	66 Triptorelin 70 Leuprolide acetate	32 (21-48 for Triptorelin; 20-49 for Leuprolide)	Female

A randomized, single-blind, clinical trial was conducted in 136 women with clinically verified endometriosis comparing triptorelin (3.75 mg IM q4w x6) with leuprolide (3.75 mg IM q4w x6).

The majority of patients were Caucasian (97%) in both treatment groups. Cycle length and duration of bleeding at baseline, and age at menarche, were similar between treatment arms. The mean duration of endometriosis was the same (1.2 years, range 0-11) in both groups, and a similar percentage of patients in both groups had minimal, mild, and moderate disease at pre-treatment laparoscopy (Table 11). Fifty-five (82%) patients in the triptorelin group and 57 (81%) in the leuprolide group completed the six-month treatment phase of the study.

Table 11 – Additional baseline characteristics for Study UK DCP 94-907

Baseline Characteristic	Triptorelin (n=66) 3.75 mg IM q4w x6	Leuprolide (n=70) 3.75 mg IM q4w x6
Pelvic Pain at entry:		
None	0 (0%)	1 (1.4%)
Mild	3 (4.5%)	1 (1.4%)
Discomforting	11 (16.7%)	18 (25.7%)
Distressing	20 (30.3%)	22 (31.4%)
Horrible	22 (33.3%)	17 (24.3%)
Excruciating	10 (15.2%)	11 (15.7%)

Stage of Disease:		
Minimal (r-AFS score 1-5)	31 (47%)	29 (41%)
Mild (r-AFS score 6-15)	19 (29%)	22 (31%)
Moderate (r-AFS score 16-40)	13 (20%)	11 (16%)
Severe (r-AFS score > 40)	3 (5%)	7 (10%)
Pelvic Examination at Visit 0:		
Normal	15 (23%)	16 (23%)
Localized tenderness	29 (44%)	34 (49%)
Moderate tenderness	15 (23%)	17 (24%)
Severe tenderness	7 (11%)	2 (3%)

The primary objective of the study was to demonstrate the equivalence of triptorelin and leuprolide, both as 1- month formulations, in terms of reduction in the pelvic pain associated with endometriosis. Reduction of pelvic pain was based on end-of-treatment versus baseline physician ratios for pelvic pain severity (six categories ranging from 0=absent to 5=excruciating). Other efficacy evaluations included endocrine blood levels (FSH, LH, E_2), breakthrough bleeding assessment, and pelvic examinations. Safety evaluations included collection of adverse events, hematology and blood chemistry laboratory testing, and bone mineral density testing in a subset of the population (approximately 60 patients).

Study Results

Table 12 – Results of study UK DCP 94-097 in patients with endometriosis

Pain Symptom	**Proportion of patients free of pain symptoms**			
	Triptorelin (n=66) 3.75 mg IM q4w x6		**Leuprolide (n=70) 3.75 mg IM q4w x6**	
	6 months of therapy	**12 months follow-up**	**6 months of therapy**	**12 months follow-up**
Pelvic Pain	42% (23/55)[1]	27% (9/33)	46% (27/59)	27% (9/33)
Dysmenorrhea	96% (53/55)	16% (5/32)	98% (58/59)	22% (7/32)
Dyspareunia	82% (45/55)	70% (23/33)	81% (48/59)	64% (21/33)

[1] Numbers in parenthesis reflect the proportion of patients without pain symptoms over the total number of patients still in the study at that assessment visit.

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.

At both timepoints of 6 months of therapy and after 12 months of follow-up, similar percentages of women in each treatment group were free of the pain symptoms associated with endometriosis. Triptorelin was shown to be comparable to leuprolide in relieving or reducing the clinical symptoms associated with endometriosis.

Prostate Cancer

Clinical Studies with Triptorelin Acetate

TRELSTAR 3.75 mg (1 month sustained-release formulation)

Table 13 - Summary of patient demographics for clinical trials in prostate cancer

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex
914CL14P	Multicenter, controlled, comparative, open, parallel	Triptorelin acetate 3.75 mg, IM injection, 24 months	76	73.5 (51.5-92.2)	Male
		Bilateral orchiectomy	49	73.3 (57.7-88.6)	
914CL7P	Multicenter, randomized, comparative, open, parallel	Triptorelin acetate 3.75 mg, IM injection, 24 months	44	74.7 (52.5-89.5)	Male
		Bilateral orchiectomy	16	75.3 (61.0-88.3)	
914CL17E	Multicenter, controlled, comparative, open, parallel	Triptorelin acetate 100 µg, SC injection, on days 1-7. Triptorelin acetate 3.75 mg, IM injection, on days 8 & 28, and thereafter every 4 weeks, for up to 18 months	40	70.5 (51.6-85.3)	Male
		Bilateral orchiectomy	40	72.5 (55.8-90.0)	

Three European, multicenter, long-term controlled studies, involving a total of 265 patients (160 triptorelin acetate, 105 orchiectomy) were conducted to assess the efficacy and safety of a triptorelin acetate 3.75 mg formulation for the treatment of advanced prostate cancer. A pharmacodynamic equivalence study in 24 healthy volunteers showed the equivalence of the triptorelin acetate formulation with the pamoate formulation currently marketed, in the terms of serum testosterone pharmacodynamics.

The primary efficacy criteria in all three studies were the reduction of serum testosterone to castration level (≤ 1.735 nmol/L) and relief of clinical symptoms (bone pain and urinary symptoms). Across the three studies, the mean age was 73 years in both the triptorelin and orchiectomy treatment groups. The mean weights were 71 kg and 70 kg in the triptorelin and orchiectomy treatment groups,

respectively. Of those evaluated, a similar proportion of patients in each group had Stage C (20% and 21%) or Stage D (80% and 79%) prostate cancer for triptorelin and orchiectomy patients, respectively.

Clinical Studies with Triptorelin Pamoate

TRELSTAR 3.75 mg (1 month sustained-release formulation) and TRELSTAR 11.25 mg (3 month sustained-release formulation)

Table 14 - Summary of patient demographics for clinical trials in prostate cancer

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex
DEB-96-TRI-01	Parallel group, randomized, controlled multicenter study	Triptorelin pamoate microgranules 11.25 mg, IM injection, 9 months treatment with injections every 84 days Triptorelin pamoate microgranules 3.75 mg IM injection, 9-month duration with injections every	Triptorelin pamoate 11.25 mg: 175 patients Triptorelin pamoate 3.75 mg: 173 patients	70.5 years (range: 45 to 96 years)	Male

A study involving 348 patients enrolled was conducted to compare TRELSTAR 3.75 mg and TRELSTAR 11.25 mg in subjects with advanced prostate cancer.

The primary objectives of this study were to demonstrate that TRELSTAR 11.25 mg is at least as effective as TRELSTAR 3.75 mg in terms of the percentage of patients achieving castration levels of serum testosterone (≤ 1.735 nmol/L) on Day 29 following initial intramuscular injection and the percentage of patients maintaining castration levels of serum testosterone from Months 2 to 9 of treatment.

Of the 348 patients, 165 were Caucasian, 130 were Black, and 51 were Other. Mean height was 172 cm (range: 153 to 195 cm), and mean weight was 72.9 kg (range: 38 to 129 kg). There was no clinically significant difference in age, race, height or weight between the two treatment groups. The mean age at onset of prostate cancer was 69.8 years (range: 44 to 96 years), and the mean disease duration was 6.9 months (range: 0 – 155 months). All patients, except one in the safety population had histologically proven prostate cancer. Of the 348 patients, 183 had prostate cancer at stage C and 162 had prostate cancer at stage D.

TRELSTAR 22.5 mg (6 month sustained-release formulation)

Table 15 - Summary of patient demographics for clinical trials in prostate cancer

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (range)	Sex
DEB-TRI6M-301	Multicentre, repeated dose, open, non	22.5 mg triptorelin embonate, IM injection, 48 weeks treatment	120 patients	71 years (range: 51	Male

	comparative study.			to 93 years)	

TRELSTAR 22.5 mg, was studied in a non-comparative trial in 120 men with advanced prostate cancer in South Africa. Patients received TRELSTAR 22.5 mg every 168 days for a total of up to 2 doses (maximum treatment period of 337 days). The primary efficacy endpoints were both achievement of castration by Day 29 and maintenance of castration from Day 57 through Day 337. The clinical trial population consisted of 64% Caucasian, 23% Black, and 13% Other patients.

Study Results

Clinical Studies with Triptorelin Acetate

TRELSTAR 3.75 mg (1 month sustained-release formulation)

Table 16 – Results of studies 914CL14, 914CL7P and 914CL17E in patients with prostate cancer

Primary Endpoints	Proportion of patients (n=160) for TRELSTAR 3.75 mg	Proportion of patients (n=105) for Bilateral orchiectomy
Serum testosterone levels at the castration level (≤ 1.735 nmol/L) at Month 1	73% (94/128)	74% (63/85)
Serum testosterone levels at the castration level (≤ 1.735 nmol/L) at Month 24	75% (24/32)	80% (12/15)

The efficacy results of the studies showed that monthly IM administration of triptorelin (3.75 mg) reduced serum testosterone levels in patients with advanced prostate cancer to an extent similar to that achieved after surgical orchiectomy. The effectiveness of this reduction in testosterone was confirmed by a relief of clinical symptoms which were comparable for triptorelin treatment and orchiectomy.

Clinical Studies with Triptorelin Pamoate

TRELSTAR 3.75 mg (1 month sustained-release formulation) and TRELSTAR 11.25 mg (3 month sustained-release formulation)

Table 17 – Results of study DEB-96-TRI-01 in patients with prostate cancer

Primary Endpoints	Proportion of patients (n=166) for TRELSTAR 11.25 mg	Proportion of patients (n=159) for TRELSTAR 3.75 mg
Chemical castration (≤ 1.735 nmol/L) 28 days after the first injection	97.6% (162/166)	92.5% (147/159)

The efficacy results showed that TRELSTAR 11.25 mg is at least as effective as TRELSTAR 3.75 mg in achieving castration on Day 29.

TRELSTAR 22.5 mg (6 month sustained-release formulation)

Table 18 – Results of study DEB-TRI6M-301 in patients with prostate cancer

Primary Endpoints	Proportion of patients (n=120) for TRELSTAR 22.5 mg
Chemical castration (≤ 1.735 nmol/L) at Day 29	97.5% (117/120)
Maintenance of chemical castration (≤ 1.735 nmol/L) from Day 57 through Day 337	93.0% (107/115)

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: In acute toxicity studies, no clinical symptoms were observed in either mice or rats with single doses up to 10 mg/kg triptorelin.

In subchronic and chronic toxicity studies of triptorelin, triptorelin acetate microspheres, and triptorelin pamoate microgranules in rats, beagle dogs, and monkeys, the only effects observed were expected consequences of the physiologic action of the drug. Serum levels of testosterone (in males), estradiol and progesterone (in females), and LH were suppressed in animals (rats, dogs, monkeys) administered 2 µg/kg/day and higher doses of triptorelin by daily injection or administered the equivalent average daily dose by once monthly intramuscular injection of a sustained release formulation (triptorelin acetate microspheres or triptorelin pamoate microgranules). At the same dose levels, spermatogenic arrest and atrophy of the testes and accessory sex organs were observed in male animals (rats, dogs, monkeys) and inhibition of estrus and atrophy of the ovary and accessory sex organs were observed in female animals (rats, dogs, monkeys). In both males and females, triptorelin caused decreases in weights of reproductive organs. Changes in the anterior pituitary (focal hyperplasia and benign microadenoma) were detected in male rats administered once monthly injections of triptorelin acetate microspheres or daily injection of triptorelin peptide for 6 months; these changes are commonly observed in rats in response to an altered hormonal environment. No changes were observed in the pituitary in dogs or monkeys after 6 months of drug administration.

On withdrawal of the drug, changes in serum hormones, reproductive organ weights, and microscopic atrophic changes in the gonads and accessory sex organs were reversible. Pituitary hyperplasia and benign microadenoma were not reversible.

Carcinogenicity: Carcinogenicity studies of triptorelin were performed in mice and rats. No oncogenic effects were observed in mice given from 120 to 6000 µg/kg triptorelin pamoate microgranules every 28 days for 18 months. An oncogenic effect in the pituitary gland (adenoma of the pars distalis) which resulted in premature deaths was observed in rats given from 120 to 3000 µg/kg triptorelin pamoate depot formulation every 28 days for 23 months. Changes in the anterior pituitary (focal hyperplasia and microadenoma) were judged to be related to the intrinsic pharmacologic activity of the drug. Similar changes in the anterior pituitary of male rats given triptorelin over a 6 month period had been observed in a chronic toxicity study in male rats.

Genotoxicity: The mutagenicity of triptorelin was assessed *in vitro* and *in vivo*. Triptorelin showed no mutagenic or clastogenic activity against Salmonella strains, Chinese Hamster Ovary (CHO) cells, and mouse lymphoma cells, under either metabolic activation or non-activation conditions. In the *in vivo* mouse micronucleus assay, triptorelin -treated animals showed no significant increase in micronucleus frequency compared to negative control, whereas the known clastogenic agent cyclophosphamide induced large and statistically significant increases in micronucleus frequency.

Reproductive and Developmental Toxicology: Developmental toxicity studies of triptorelin were performed in mice and rats. No maternal toxicity, fetal toxicity, or embryotoxic or teratogenic effects were observed when pregnant female mice were given daily subcutaneous injections of 2 to 200 µg/kg triptorelin on days 6 through 15 of gestation. No maternal toxicity, fetal toxicity, or embryogenic or teratogenic effects were observed when pregnant female rats were given daily subcutaneous injections of 10 µg/kg triptorelin on days 6 through 15 of gestation. However, maternal toxicity, demonstrated by reduced weight gain during the treatment period, and an embryotoxic effect, demonstrated by an increase in uterine resorption, were observed when pregnant female rats were given daily subcutaneous injections of 100 µg/kg triptorelin on days 6 through 15 of gestation.

Impairment of Fertility: After about 6 months of treatment with triptorelin, atrophy of the genital organs, consistent with reduced fertility, was observed in rats and monkeys at doses ranging from 2 to 2,100 µg/kg. These changes were considered to be a reflection of the suppressed gonadal function caused by the pharmacologic activity of the drug. These effects were largely reversed during a 2 or 4 month recovery period. Testicular changes have also been reported after prolonged administration of triptorelin in patients with prostate cancer.

PATIENT MEDICATION INFORMATION FOR ENDOMETRIOSIS PATIENTS

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr TRELSTAR®

Triptorelin for Injectable Suspension

Read this carefully before you start taking **TRELSTAR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TRELSTAR**.

Serious Warnings and Precautions

TRELSTAR should be prescribed by a qualified healthcare professional experienced in its use for the treatment of endometriosis. TRELSTAR should be administered by a healthcare professional.

TRELSTAR may cause the following serious side effects:

- **Bone mineral density changes:** osteoporosis (thin, fragile bones) and bone fractures
- **Pituitary apoplexy:** bleeding into the pituitary gland or lack of blood flow to the pituitary gland

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

What is TRELSTAR used for?

TRELSTAR is used in adult women to treat the pain associated with endometriosis. Endometriosis is a condition where the lining of the uterus (womb) grows outside of the uterus.

How does TRELSTAR work?

TRELSTAR belongs to a class of drugs called luteinizing hormone-releasing hormone (LHRH) analogs. It works by lowering the level of the hormone estrogen in your body. This may help reduce the pain and other symptoms of endometriosis.

What are the ingredients in TRELSTAR?

Medicinal ingredients: triptorelin pamoate

Non-medicinal ingredients: carboxymethylcellulose sodium, mannitol, poly-d,l-lactide-co-glycolide and polysorbate 80.

TRELSTAR comes in the following dosage forms:

Powder for injectable suspension: 3.75 mg (1 month sustained-release formulation).

Do not use TRELSTAR if you:

- are allergic (hypersensitive) to triptorelin, or to drugs called LHRH agonists or gonadotropin releasing hormone (GnRH) agonists, LHRH agonist analogs or GnRH agonist analogs, or to any other ingredient in TRELSTAR (see **What are the ingredients in TRELSTAR?**).

- are or may become pregnant. If taken during pregnancy, TRELSTAR may harm your unborn baby. If you become pregnant while taking TRELSTAR, talk to your healthcare professional immediately.
- are breastfeeding or planning to breastfeed. It is not known if TRELSTAR passes into breastmilk.
- have abnormal vaginal bleeding that has not been checked by your healthcare professional.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TRELSTAR. Talk about any health conditions or problems you may have, including if you:

- have kidney and/or liver problems.
- have a history of depression. Patients being treated with TRELSTAR have an increased risk of depression.

Other warnings you should know about:

Vaginal Bleeding: Since your period (menstruation) should stop while you are on TRELSTAR treatment, you should tell your healthcare professional if regular bleeding continues.

Pregnancy and Contraception:

- Avoid becoming pregnant while being treated with TRELSTAR. It may harm your unborn baby.
- You should not be pregnant at the beginning of treatment with TRELSTAR. Your healthcare professional should do a pregnancy test before you start TRELSTAR.
- You must use a non-hormonal method of birth control during treatment with TRELSTAR. Talk to your healthcare professional about the option that is best for you.
- Tell your healthcare professional right away if you become pregnant or think you are pregnant during treatment with TRELSTAR.

Bone Mineral Density Changes: Treatment with TRELSTAR can increase your risk of osteoporosis (thin, fragile bones) and bone fractures. You should talk with your healthcare professional about taking estrogen and progestogen therapy while taking TRELSTAR. Tell your healthcare professional about any risk factors you have including if you:

- or a family member have a history of osteoporosis or low bone mineral density (BMD)
- chronically use:
    - alcohol or tobacco
    - anticonvulsants; medicines used to control seizures
    - corticosteroids; medicines used to reduce inflammation and treat conditions like allergies, skin problems, arthritis and asthma

Driving and Using Machines: TRELSTAR can cause fatigue and dizziness. Before you do tasks that require special attention, wait until you know how you respond to TRELSTAR.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TRELSTAR:

- medicines used to treat high blood levels of the hormone prolactin

How to take TRELSTAR:

- TRELSTAR is injected into your muscle by your healthcare professional.

Usual dose:

One injection (3.75 mg) once a month.

Overdose:

If you think you, or a person you are caring for, have taken too much TRELSTAR, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss an injection of TRELSTAR contact your healthcare professional as soon as possible to reschedule.

What are possible side effects from using TRELSTAR?

These are not all the possible side effects you may have when taking TRELSTAR. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- nausea, vomiting
- stomach pain
- constipation
- diarrhea
- hot flushes, sweating
- headaches
- dizziness
- emotional changes (depression, irritability)
- trouble sleeping (insomnia)
- tiredness
- acne
- dandruff
- rash
- reduction in breast size
- vaginal dryness
- yellow/pale vaginal discharge
- low sex drive
- stopping of periods (menstruation)
- back pain, joint pain, muscle pain
- leg cramps

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Bone Mineral Density Changes (thin, fragile bones): broken bones, bone/joint pain, back pain that gets worse when standing or walking		✓	
Depression: sad mood, lack of interest in usual activities, change in sleep and appetite		✓	
Urinary Tract Infection: pain when urinating, urgent need to urinate, increased frequency of urination, blood in the urine, fever, chills		✓	
RARE			
Injection Site Reaction: pain, swelling, redness, itching, burning, hardening or bruising where TRELSTAR is injected		✓	
Edema: swelling of the legs or ankles	✓		
Vaginal Hemorrhage: severe bleeding from the vagina			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Pituitary Apoplexy: sudden headache, vomiting, vision-changes (loss of vision or double vision), paralysis or weakness of the eye muscles, altered mental status, severe low blood pressure (dizziness, lightheadedness, fainting)			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store TRELSTAR vial supplied with MIXJECT dose delivery system (with Pre-Filled Syringe Containing Sterile Water for Injection) at 15-30°C.
- Store TRELSTAR vial (without Pre-Filled Syringe Containing Sterile Water for Injection) at 15-30°C.
- Protect from light.
- Do not freeze.

Keep out of reach and sight of children.

If you want more information about TRELSTAR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.gud-knight.com/), by emailing medinfo@knighttx.com, or by calling 1-844-483-5636.

This leaflet was prepared by Knight Therapeutics Inc.

Last Revised SEP 07, 2022

PATIENT MEDICATION INFORMATION FOR PROSTATE CANCER PATIENTS

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr TRELSTAR®

Triptorelin for Injectable Suspension

Read this carefully before you start taking **TRELSTAR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TRELSTAR**.

Serious Warnings and Precautions

TRELSTAR should be prescribed by a qualified healthcare professional experienced in the use of hormonal therapy in prostate cancer. TRELSTAR should be administered by a healthcare professional.

TRELSTAR may cause the following serious side effects:

- **Testosterone flare reaction:** worsening of symptoms of prostate cancer at the beginning of treatment
- **Bone mineral density changes:** osteoporosis (thin, fragile bones) and bone fractures
- **Pituitary apoplexy:** bleeding into the pituitary gland or lack of blood flow to the pituitary gland

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

What is TRELSTAR used for?

TRELSTAR is used in adult men as part of the treatment for advanced hormone-dependent prostate cancer.

How does TRELSTAR work?

TRELSTAR belongs to a class of drugs called luteinizing hormone-releasing hormone (LHRH) analogs. It works by lowering the levels of sex hormones, like testosterone, in your body. This may help reduce the bone pain, urinary problems and other symptoms of prostate cancer.

What are the ingredients in TRELSTAR?

Medicinal ingredients: triptorelin pamoate

Non-medicinal ingredients: carboxymethylcellulose sodium, mannitol, poly-*d,l*-lactide-co-glycolide and polysorbate 80.

TRELSTAR comes in the following dosage forms:

Powder for injectable suspension: 3.75 mg (1 month sustained-release formulation), 11.25 mg (3 month sustained-release formulation), 22.5 mg (6 month sustained-release formulation).

Do not use TRELSTAR if you:

- are allergic (hypersensitive) to triptorelin, or to drugs called LHRH agonists or gonadotropin releasing hormone (GnRH) agonists, LHRH agonist analogs or GnRH agonist analogs, or to any other ingredient in TRELSTAR (see **What are the ingredients in TRELSTAR?**).

- are a woman who is or may become pregnant. If taken during pregnancy, TRELSTAR may harm your unborn baby. If you become pregnant while taking TRELSTAR, talk to your healthcare professional immediately.
- are a woman who is breastfeeding or planning to breastfeed. It is not known if TRELSTAR passes into breastmilk.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TRELSTAR. Talk about any health conditions or problems you may have, including if you:

- have or have had kidney and/or liver problems.
- have a history of heart problems, or have a genetic heart condition called "long QT syndrome".
- have high blood sugar (diabetes). You may need to test your blood sugar more frequently while receiving treatment with TRELSTAR.
- have low levels of red blood cells (anemia).
- have a history of depression. Patients being treated with TRELSTAR have an increased risk of depression.

Other warnings you should know about:

Testosterone Flare Reaction (worsening of prostate cancer symptoms): TRELSTAR may cause an increase in the blood levels of testosterone during the first weeks after treatment begins. As a result, symptoms related to your prostate cancer may temporarily get worse. This increase in blood levels of testosterone and any associated symptoms should decrease over time after the first injection of TRELSTAR. **Talk to your healthcare professional immediately if you develop severe or increased pain, numbness or weakness of the limbs, or persistent difficulty in urinating.**

Bone Mineral Density Changes: Treatment with TRELSTAR can increase your risk of osteoporosis (thin, fragile bones) and bone fractures. Tell your healthcare professional about any risk factors you have including if you:

- or a family member have a family history of osteoporosis or low bone mineral density (BMD)
- chronically use:
    - alcohol or tobacco
    - anticonvulsants; medicines used to control seizures
    - corticosteroids; medicines used to reduce inflammation and treat conditions like allergies, skin problems, arthritis and asthma

Blood Tests and Monitoring: You will need blood tests before you start TRELSTAR and during treatment. These will help your healthcare professional see how TRELSTAR is affecting your blood, blood glucose levels, hormones and other areas of your body (such as your heart, liver and kidneys). You may also have blood pressure tests, ECGs, ultrasounds, CT scans and other examinations during your treatment.

Driving and Using Machines: TRELSTAR can cause fatigue and dizziness. Before you do tasks that require special attention, wait until you know how you respond to TRELSTAR.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TRELSTAR:

- antipsychotic medicines used to treat mental health problems such as: risperidone, chlorpromazine

- medicines that affect your heart rhythm such as: quinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide, dronedarone, flecainide, propafenone
- antibiotics, used to treat bacterial infections, such as: erythromycin, clarithromycin, azithromycin, moxifloxacin
- medicines used to treat malaria such as: quinine
- medicines used to treat fungal infections
- medicines used to treat high blood levels of the hormone prolactin
- ondansetron, used to prevent nausea and vomiting
- salbutamol, used to treat breathing problems like asthma and COPD

How to take TRELSTAR:

- TRELSTAR is injected into your muscle by your healthcare professional.

Usual dose:

3.75 mg: one injection, once a month

11.25 mg: one injection, once every 3 months

22.5 mg: one injection, once every 6 months

Overdose:

If you think you, or a person you are caring for, have taken too much TRELSTAR, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss an injection of TRELSTAR, contact your healthcare professional as soon as possible to reschedule.

What are possible side effects from using TRELSTAR?

These are not all the possible side effects you may have when taking TRELSTAR. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- nausea, vomiting
- stomach pain or discomfort, indigestion
- constipation
- diarrhea
- loss of appetite
- weight gain
- hot flushes, sweating
- headaches
- dizziness
- nervousness
- trouble sleeping (insomnia)
- tiredness, fatigue
- cough, throat inflammation
- rash, itching

- enlarged breasts
- reduced size of genitalia
- low sex drive
- inability to develop and maintain an erection, inability or difficulty ejaculating (erectile dysfunction)
- inflammation of the testicles
- eye pain, eye infection
- back, breast or leg pain
- joint pain, bone pain
- muscle pain, weakness or stiffness
- leg cramps
- numbness or tingling

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Bone Mineral Density Changes (thin, fragile bones): broken bones, bone/joint pain, back pain that gets worse when standing or walking		✓	
Testosterone Flare Reaction (worsening of prostate cancer symptoms): severe or increased pain, numbness or weakness of the limbs, persistent difficulty in urinating		✓	
Edema: swelling of the legs or ankles	✓		
Urinary Tract Infection: pain when urinating, urgent need to urinate, increased frequency of urination, blood in the urine, fever, chills		✓	
Urinary Problems: difficult or painful urination, unable to urinate, blood in the urine			✓
Depression: sad mood, lack of interest in usual activities, change in sleep and appetite		✓	
Increased Blood Sugar: frequent urination, thirst, hunger	✓		
Heart Problems: irregular heartbeat, fast heartbeat, palpitations		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Anemia: fatigue, loss of energy, weakness, shortness of breath		✓	
RARE			
Injection Site Reaction: pain, swelling, redness, itching, burning, hardening or bruising where TRELSTAR is injected		✓	
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Fainting		✓	
Pituitary Apoplexy: sudden headache, vomiting, vision-changes (loss of vision or double vision), paralysis or weakness of the eye muscles, altered mental status, severe low blood pressure (dizziness, lightheadedness, fainting)			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store TRELSTAR 3.75 mg, TRELSTAR 11.25 mg and TRELSTAR 22.5 mg vials supplied with MIXJECT dose delivery system (with Pre-Filled Syringe Containing Sterile Water for Injection) at 15-30°C.
- Store TRELSTAR 3.75 mg, TRELSTAR 11.25 mg and TRELSTAR 22.5 mg vials (without Pre-Filled Syringe Containing Sterile Water for Injection) at 15-30°C.

- Protect from light.
- Do not freeze.

Keep out of reach and sight of children.

If you want more information about TRELSTAR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.gud-knight.com/), by emailing medinfo@knighttx.com, or by calling 1-844-483-5636.

This leaflet was prepared by Knight Therapeutics Inc.

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