PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] TRELSTAR®

Triptorelin 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

Knight Therapeutics Inc.
3400 De Maisonneuve W., Suite 1055
Montreal, QC
Canada H3Z 3B8

Date of Revision:
January 25, 2021

Submission Control No: 239594

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TRELSTAR (triptorelin for injectable suspension) is indicated for:

- The palliative treatment of hormone dependent advanced carcinoma of the prostate gland (stage D2).

TRELSTAR must be administered under the supervision of a health professional.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of TRELSTAR in pediatric patients has not been established (see WARNINGS AND PRECAUTIONS, Special Populations).

1.2 Geriatrics

Geriatrics (>65 years of age): The majority of the patients studied in the clinical trials for TRELSTAR were 65 years and older (see CLINICAL TRIALS).

2 CONTRAINDICATIONS

TRELSTAR is contraindicated in:

- Patients with hypersensitivity to gonadotropin releasing hormone or luteinizing hormone-releasing hormone (GnRH or LHRH), GnRH agonist analogs or any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. Anaphylactic reactions to synthetic GnRH or GnRH agonist analogs have been reported (see WARNINGS AND PRECAUTIONS). For a complete listing, see 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 WARNINGS AND PRECAUTIONS).
- Nursing women (see WARNINGS AND PRECAUTIONS).

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. TRELSTAR should be administered by a health professional.
The following are clinically significant adverse events:

- Clinical testosterone flare reaction in men with prostate cancer (see WARNINGS AND PRECAUTIONS, General)
- Osteoporosis (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

TRELSTAR should be administered by a health professional. TRELSTAR is administered as an intramuscular injection.

4.2 Recommended Dose and Dosage Adjustment

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

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

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, monthly. The lyophilized powder is to be reconstituted either with 2 mL of sterile water for injection utilizing a 21-gauge needle or using the single dose delivery system, MIXJECT. Administer monthly as a single intramuscular injection, in accordance with the Instructions for Use (see below).

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. The lyophilized powder is to be reconstituted either with 2 mL of sterile water for injection utilizing a 21-gauge needle or using the single dose delivery system, MIXJECT. Administer every 3 months as a single intramuscular injection, in accordance with the Instructions for Use (see below).

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. The lyophilized powder is to be reconstituted either with 2 mL of sterile water for injection utilizing a 21-gauge needle or using the single dose delivery system, MIXJECT. Administer every 6 months as a single intramuscular injection, in accordance with the Instructions for Use (see below).

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. Instructions are provided (see below) for reconstitution using the TRELSTAR dose delivery system (with Sterile Water for Injection), MIXJECT and the TRELSTAR vial (without Sterile Water for Injection).

When 2 mL of Sterile Water for Injection is added to the lyophilized triptorelin powder and mixed, a suspension is formed. For TRELSTAR 3.75 mg (1 month sustained-release

formulation) this is equivalent to 3.75 mg of triptorelin peptide base units intended as a single monthly intramuscular injection. For TRELSTAR 11.25 mg (3 month sustained-release formulation) this is equivalent to 11.25 mg of triptorelin peptide base units intended as a single 3 month intramuscular injection. For TRELSTAR 22.5 mg (6 month sustained-release formulation) this is equivalent to 22.5 mg of triptorelin peptide base units intended as a single 6 month intramuscular 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

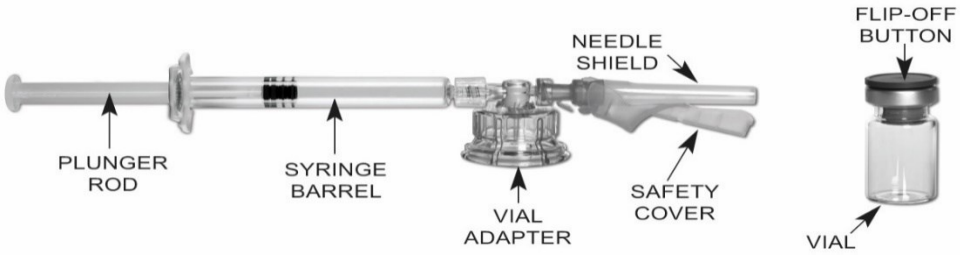
The suspension should be discarded if not used immediately after reconstitution.

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.

Single use only. Inject immediately after reconstitution and discard unused portion.

Instructions for Use – TRELSTAR Dose Delivery System (with Sterile Water for Injection), MIXJECT

Please read the instructions completely before you begin.



MIXJECT Preparation

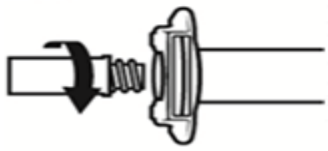
Wash your hands with soap and hot water and put on gloves immediately prior to preparing the injection. Place the sealed tray on a clean, flat surface that is covered with a sterile pad or cloth. Peel the cover away from the tray and remove the MIXJECT components and the TRELSTAR vial. Remove the Flip-Off 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.

Peel the cover away from the blister pack containing the vial adapter. *Do not remove the vial adapter from the blister pack.* Place the blister pack containing the vial adapter firmly on the vial top, piercing the vial. Push down gently until you feel it snap in place. Remove the blister pack from the vial adapter.

2a.

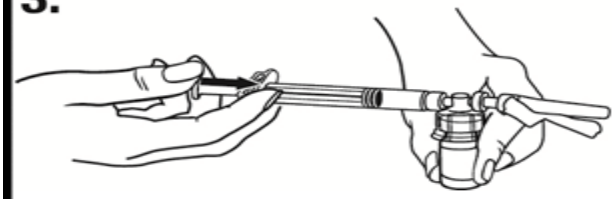


(a) Screw the plunger rod into the barrel end of the syringe. Remove the cap from the syringe barrel.

2b.

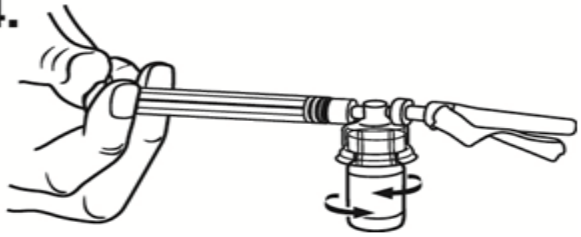
(b) Connect the syringe to the vial adapter by screwing it clockwise into the opening on the side of the vial adapter. Be sure to gently twist the syringe until it stops turning to ensure a tight connection.

3.



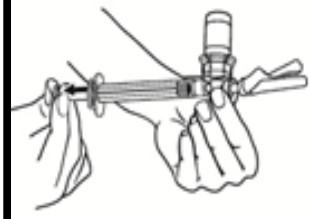
While holding the vial, place your thumb on the plunger rod and push the plunger rod in all the way to transfer the diluent from the pre-filled syringe into the vial. Do not release the plunger rod.

4.



Keeping the plunger rod depressed, gently swirl the vial so that the diluent rinses the sides of the vial. This will ensure complete mixing of TRELSTAR and the sterile water diluent. The suspension will now have a milky appearance. In order to avoid separation of the suspension, proceed to the next steps without delay.

5a.

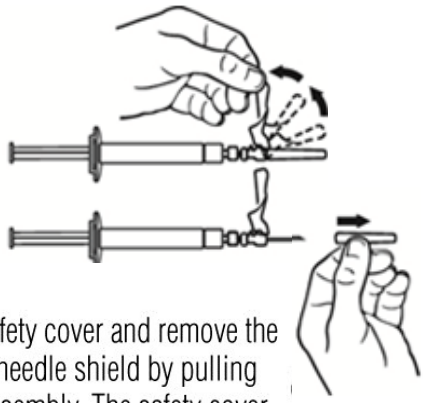


(a) Invert the MIXJECT system so that the vial is at the top. Grasp the MIXJECT system firmly by the syringe and pull back the plunger rod slowly to draw the reconstituted TRELSTAR into the syringe.

5b.

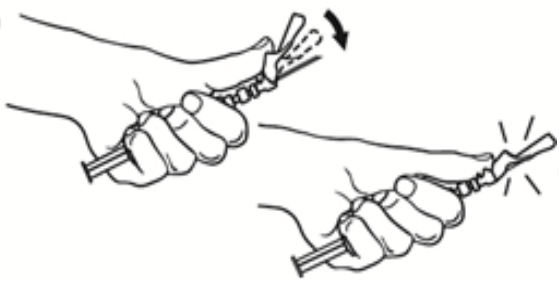
(b) Return the vial to its upright position, and disconnect the vial adapter and vial from the MIXJECT syringe assembly by turning the plastic cap of the vial adapter clockwise. *Grasp only the plastic cap when removing.*

6.



Lift up the safety cover and remove the clear plastic needle shield by pulling it from the assembly. The safety cover should be perpendicular to the needle, with the needle facing away from you. The syringe containing the TRELSTAR suspension is now ready for administration. *The suspension should be administered immediately after reconstitution.*

7.



MIXJECT Disposal

1. 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.
2. Immediately discard the syringe assembly after a single use into a suitable sharps container.

Instructions for Use – TRELSTAR vial (without 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 into the vial.
2) Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.
3) Withdraw the entire content of the reconstituted suspension into the syringe and inject it immediately.

Disposal

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

4.4 Administration

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 testosterone suppression is important 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	Packaging
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	TRELSTAR dose delivery system (with Sterile Water for Injection), MIXJECT: The accompanying pre-filled syringe contains 2 mL Sterile Water for Injection. TRELSTAR vial (without Sterile Water for Injection)
Intramuscular injection	Sterile vial of powder for injectable	Carboxymethylcellulose sodium, mannitol, poly-	TRELSTAR dose delivery system (with Sterile Water

	suspension, 11.25 mg (as triptorelin base), triptorelin pamoate	*d*,*l*-lactide-co-glycolide, and polysorbate 80	for Injection), MIXJECT: The accompanying pre-filled syringe contains 2 mL Sterile Water for Injection. TRELSTAR vial (without Sterile Water for Injection)
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 dose delivery system (with Sterile Water for Injection), MIXJECT: The accompanying pre-filled syringe contains 2 mL Sterile Water for Injection. TRELSTAR vial (without Sterile Water for Injection)

7 WARNINGS AND PRECAUTIONS

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.

Hypersensitivity and anaphylactic reactions have been reported with TRELSTAR as with other LHRH agonists (see ADVERSE REACTIONS, Post-Market Adverse Reactions).

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 gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, 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.

Carcinogenesis and Mutagenesis

Carcinogenicity and mutagenicity studies have been performed in animals (see NON-CLINICAL TOXICOLOGY).

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 WARNINGS AND PRECAUTIONS, 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. 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 Class IA (e.g. quinidine, procainamide), Class III (e.g. amiodarone, sotalol, dofetilide, ibutilide), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medications.

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

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.

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.

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.

Hepatic

Triptorelin 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.

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/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 WARNINGS AND PRECAUTIONS, 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 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Psychiatric

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

Patients with known depression should be monitored closely during therapy.

Renal

Triptorelin 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.

7.1 Special Populations

7.1.1 Pregnant Women

The safe use of TRELSTAR during pregnancy has not been established clinically. 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 (see CONTRAINDICATIONS).

7.1.2 Breast-feeding

It is not known to what extent triptorelin is excreted into human milk and caution should be exercised when TRELSTAR is administered to nursing women. (see CONTRAINDICATIONS).

7.1.3 Pediatrics (< 18 years of age)

The safety and efficacy of TRELSTAR in pediatric patients have not been established.

7.1.4 Geriatrics (> 65 years of age)

The majority of the patients studied in the clinical trials for TRELSTAR were 65 years and older.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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 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, impotence, and decreased libido. TRELSTAR, like other LHRH analogs, caused a transient increase in serum testosterone concentrations during the first weeks of treatment. Therefore, potential exacerbations of signs and symptoms of the disease during the first few weeks of treatment are of concern in patients with vertebral metastases and/or urinary obstruction or hematuria. If these conditions are aggravated, it may lead to neurological problems such as weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms (see WARNINGS AND PRECAUTIONS).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, 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 is useful for identifying drug-related adverse events and for approximating rates.

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 i.m. injection of 3.75 mg triptorelin and every month thereafter for 24 months, with the exception of 3 patients who received 100 µg triptorelin s.c. for the first month. In the second study, all patients received 100 µg triptorelin s.c. for the first 7 days, and 3.75 mg i.m. on Days 8, 28, and every month thereafter for up to 18 months. In the third study, all patients received an i.m. 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: impotence (50.0% in the triptorelin group and 41.2% in the orchiectomy group), decreased libido (44.9% of patients in the triptorelin group and 39.2% in the orchiectomy group), hot flushes (44.9% in the triptorelin group and 43.3% in the orchiectomy group), and reduced size of genitalia (12.2% in the triptorelin group). These events are known to be related to biochemical or surgical castration (see 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 3.

Table 3 – Incidence (%) of possibly or probably related systemic adverse events reported by 1% or more 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 (%)
Application Site Disorders		
Injection site pain	6 (3.8)	NA
Body as a Whole		
Hot flushes*	70 (44.9)	42 (43.3)
Edema	6 (3.8)	2 (2.1)
Asthenia	6 (3.8)	3 (3.1)

Back pain	3 (1.9)	0 (0.0)
Fatigue	2 (1.3)	0 (0.0)
Pain	2 (1.3)	2 (2.1)
Cardiovascular Disorders		
Heart disorder	5 (3.2)	1 (1.0)
Angina pectoris	1 (0.6)	3 (3.1)
Flushing	0 (0.0)	2 (2.1)
Hypertension	2 (1.3)	0 (0.0)
Hypotension	0 (0.0)	1 (1.0)
Palpitation	1 (0.6)	1 (1.0)
Gastro-intestinal		
Vomiting	4 (2.6)	4 (4.1)
Constipation	3 (1.9)	1 (1.0)
Diarrhea	3 (1.9)	1 (1.0)
Bad defecation	0 (0.0)	1 (1.0)
Endocrine		
Reduced size of genitalia*	19 (12.2)	NA
Gynecomastia	2 (1.3)	0 (0.0)
Metabolic and Nutritional Disorders		
Weight increase	8 (5.1)	4 (4.1)
Weight decrease	2 (1.3)	2 (2.1)
Cachexia	2 (1.3)	0 (0.0)
Neoplasms		
Tumor flare	4 (2.6)	0 (0.0)
Nervous System		
Vertigo	0 (0.0)	1 (1.0)
Psychiatric Disorders		
Impotence*	78 (50.0)	40 (41.2)
Libido decreased*	70 (44.9)	38 (39.2)
Nervousness	4 (2.6)	1 (1.0)
Depression*	3 (1.9)	2 (2.1)
Anorexia	2 (1.3)	1 (1.0)
Aggressive reaction	0 (0.0)	1 (1.0)

Adverse Event	Triptorelin Acetate (3.75 mg) N = 156 n (%)	Orchiectomy N = 97 n (%)
Respiratory System Disorders		
Dyspnea	6 (3.8)	0 (0.0)
Respiratory disorder	1 (0.6)	1 (1.0)
Hemoptysis	0 (0.0)	1 (1.0)
Resistance Mechanism Disorder		
Infection	0 (0.0)	1 (1.0)
Skin and Appendages Disorders		
Pruritus	2 (1.3)	0 (0.0)
Rash	0 (0.0)	1 (1.0)
Sweating increased	1 (0.6)	1 (1.0)
Urinary System Disorders		
Micturition frequency	3 (1.9)	2 (1.3)
Urinary incontinence	2 (1.3)	1 (1.0)
Unknown**		
Unknown	3 (1.9)	0 (0.0)

NA = not applicable; * Expected pharmacological consequence of testosterone suppression; ** Data were insufficiently clear to be coded in three patients

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 (3 month sustained-release formulation), administered i.m. every 84 days for 9 months, or nine injections of TRELSTAR 3.75 mg (1- month sustained-release formulation), administered i.m. 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 (6 month sustained-release formulation), with the first injection administered i.m. on Day 1 and the second injection administered i.m. on Day 169.

The safety profile was similar to TRELSTAR 3.75 mg (1 month sustained-release formulation) and TRELSTAR 11.25 mg (3 month sustained-release formulation) 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 4 – Incidence (%) of possibly or probably related systemic adverse events reported by 1% or more of patients in either treatment group treated with TRELSTAR 3.75 mg (1 injection every 28 days for 9 months), TRELSTAR 11.25 mg (1 injection every 84 days for 9 months), or TRELSTAR 22.5 mg (1 injection on day 1 and 1 injection on day 169).

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 (%)
Application Site Disorders			
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)
Body as a Whole			
Hot flushes*	114 (66.3)	127 (73.0)	86 (71.7)
Back pain	6 (3.5)	5 (2.9)	0 (0.0)
Pain	10 (5.8)	6 (3.4)	0 (0.0)
Leg pain	5 (2.9)	9 (5.2)	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)
Allergic reaction	2 (1.2)	0 (0.0)	0 (0.0)
Cardiovascular Disorders			
Hypertension	8 (4.7)	7 (4.0)	0 (0.0)
Edema dependant	0 (0.0)	4 (2.3)	0 (0.0)
Central and Peripheral Nervous System Disorders			
Headache	7 (4.1)	12 (6.9)	2 (1.7)
Dizziness	5 (2.9)	5 (2.9)	2 (1.7)
Cramps legs	1 (0.6)	3 (1.7)	0 (0.0)
Endocrine Disorders			
Breast pain male	5 (2.9)	4 (2.3)	0 (0.0)
Gynecomastia	0 (0.0)	3 (1.7)	0 (0.0)
Gastro-intestinal System 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)
Heart Rate and Rhythm Disorders			
Palpitation	3 (1.7)	0 (0.0)	0 (0.0)
Liver and Biliary System Disorders			
Hepatic function abnormal	0 (0.0)	2 (1.1)	0 (0.0)

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 (%)
Metabolic and Nutritional Disorders			
Edema legs	14 (8.1)	11 (6.3)	0 (0.0)
Diabetes mellitus	2 (1.2)	1 (0.6)	0 (0.0)
Musculo-skeletal Disorders			
Skeletal pain	20 (11.6)	23 (13.2)	0 (0.0)
Arthralgia	4 (2.3)	4 (2.3)	0 (0.0)
Myalgia	1 (0.6)	2 (1.1)	0 (0.0)
Psychiatric Disorders			
Insomnia	2 (1.2)	3 (1.7)	0 (0.0)
Depression*	3 (1.7)	1 (0.6)	2 (1.7)
Impotence*	7 (4.1)	4 (2.3)	12 (10.0)
Anorexia	1 (0.6)	3 (1.7)	0 (0.0)
Libido decreased*	1 (0.6)	4 (2.3)	2 (1.7)
Reproductive System and Breast Disorders			
Testicular atrophy*	0 (0.0)	0 (0.0)	9 (7.5)
Respiratory System 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 Appendages Disorders			
Rash	1 (0.6)	3 (1.7)	0 (0.0)
Pruritus	2 (1.2)	0 (0.0)	0 (0.0)
Urinary System 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)
Vision Disorders			
Eye pain	1 (0.6)	2 (1.1)	0 (0.0)
Conjunctivitis	0 (0.0)	2 (1.1)	0 (0.0)

* 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 the Medical Dictionary for Regulatory Activities (MedDRA)

8.3 Less Common Clinical Trial Adverse Reactions

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:

Application Site Disorders: Injection site erythema, Injection site pruritus, Injection site reaction, Injection site swelling
Gastro-intestinal System Disorders: Abdominal discomfort, Abdominal pain, Nausea
General Disorders and Administration Site Condition: Malaise
Investigations: Alanine aminotransferase increased, Aspartate aminotransferase increased, Prostatic antigen increased, Weight increased
Musculo-skeletal Disorders: Metastatic pain, Muscle weakness, Musculoskeletal stiffness, Pain in extremity
Nervous System Disorders: Paresthesia
Psychiatric Disorders: Loss of libido
Reproductive system and Breast disorders: Orchitis noninfective
Respiratory, Thoracic and Mediastinal Disorders: Rhinitis
Skin and Appendages Disorders: Skin disorder
Urinary System Disorders: Hematuria
Vascular Disorders: Syncope vasovagal

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

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). An increase in prothrombin time was observed in 4.9%, 10.5% and 13.6% of the patients for TRELSTAR 3.75 mg, 11.25 mg and 22.5 mg, respectively (change from baseline to worst-case on-treatment). The relationship of these changes to drug treatment is difficult to assess in this population.

8.6 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.

Cases of anaphylactic shock and angioedema that were related to TRELSTAR have been reported during post-marketing surveillance.

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 GnRH agonists, including TRELSTAR.

9 DRUG INTERACTIONS

9.2 Overview

No formal drug interaction studies have been conducted with TRELSTAR and no data are available on the interaction with alcohol.

9.3 Drug-Drug Interactions

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 GnRH receptors.

Since androgen deprivation treatment may prolong the QTc interval, 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).

9.4 Drug-Food Interactions

Interactions with food have not been established.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Administration of LHRH analogs, including TRELSTAR, 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 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Triptorelin is a synthetic decapeptide agonist analog of naturally occurring luteinizing hormone-releasing hormone (LHRH), also called gonadotropin releasing hormone (GnRH). This analog possesses greater potency than the natural hormone.

Triptorelin, a LHRH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses. The potency relative to native LHRH has been demonstrated both in vitro and in vivo. Triptorelin was more active in stimulating 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.

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.

On administration of triptorelin there is an initial and transient increase in circulating levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone. However, chronic and continuous administration of triptorelin results in decreased LH and FSH secretion and suppression of testicular steroidogenesis. A reduction of serum testosterone levels into the range normally seen in surgically castrated men occurs approximately 2 to 4 weeks after initiation of therapy. This results in accessory sexual organ atrophy which is generally reversible upon discontinuation of drug therapy.

10.2 Pharmacodynamics

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

Following a single intramuscular 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 intramuscular injection.

Following intramuscular 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. Intramuscular injection of TRELSTAR 11.25 mg every 3 months ensures that exposure to triptorelin is maintained with no clinically significant accumulation.

Following intramuscular 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. Intramuscular injection of TRELSTAR (22.5 mg) every 6 months ensures that exposure to triptorelin is maintained with no clinically significant accumulation.

10.3 Pharmacokinetics

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 5. The plasma concentrations for the 3.75 mg formulation declined to 0.084 ng/mL at 4 weeks.

Table 5 – Pharmacokinetic Parameters of Triptorelin (Mean ± SD or Median (Range) for T_{max}).

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]

[a] AUC (0-28 d), [b] AUC (0-85 d), [c] AUC (0-169 d)

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

Special Populations and Conditions

***Renal and Hepatic Insufficiency*:** After an IV injection of 0.5 mg triptorelin peptide, the two distribution half-lives were unaffected by renal and hepatic 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 6). The decrease in triptorelin clearance was more pronounced in subjects with liver insufficiency, but the half-life was prolonged similarly in subjects with renal insufficiency, since the volume of distribution was only minimally increased.

Table 6 – 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

***Age and Ethnic Origin*:** The effects of age and ethnic origin 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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, *Renal and 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.

11 STORAGE, STABILITY AND DISPOSAL

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

Store TRELSTAR 3.75 mg, TRELSTAR 11.25 mg and TRELSTAR 22.5 mg vials (without 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.

Keep out of sight and reach of children.

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

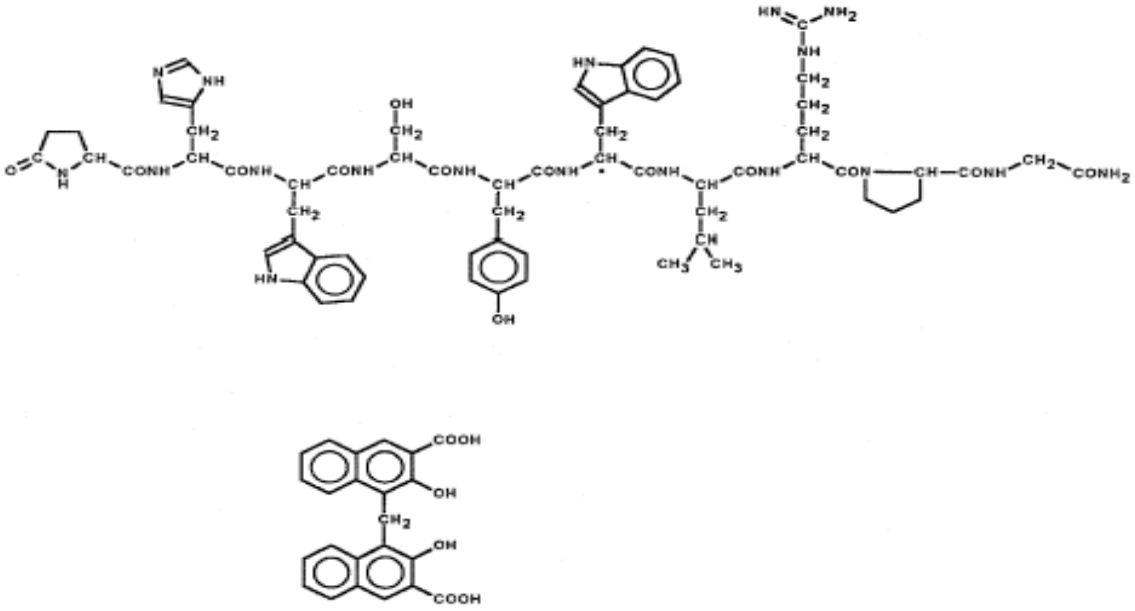
Molecular formula: $C_{64}H_{82}N_{18}O_{13} \cdot C_{23}H_{16}O_6$

Molecular mass: 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 Trial Design and Study Demographics

Clinical Studies with Triptorelin Acetate

TRELSTAR 3.75 mg (1 month sustained-release formulation)

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). 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)

A study involving 348 patients was conducted to compare TRELSTAR 3.75 mg (173 patients) and TRELSTAR 11.25 mg (175 patients) in subjects with advanced prostate cancer.

The primary objectives of this study were to demonstrate that TRELSTAR 11.25 mg (3 month sustained-release formulation) is at least as effective as TRELSTAR 3.75 mg (1 month sustained-release formulation) 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.

The mean age of the 346 patients in the safety population was 70.5 years (range: 45 to 96 years). One hundred and sixty-five (165) of these patients 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 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. One hundred eighty-three (183) of the patients had prostate cancer at stage C and 162 had prostate cancer at stage D.

TRELSTAR 22.5 mg (6 month sustained-release formulation)

TRELSTAR 22.5 mg (6 month sustained-release formulation), was studied in a non-comparative trial of 120 men with advanced prostate cancer in South Africa. Patients received TRELSTAR 22.5 mg (6 month sustained-release formulation) (N = 120) 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. Men were between 51 and 93 years of age (mean = 71 years).

14.2 Study Results

Clinical Studies with Triptorelin Acetate

TRELSTAR 3.75 mg (1 month sustained-release formulation)

The efficacy results of the studies showed that monthly i.m. 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: 73% of the patients in the triptorelin group and 74% of the patients in the orchiectomy group were at the castration level (≤ 1.735 nmol/L) at Month 1; 75% of the patients in the triptorelin group and 80% of the patients in the orchiectomy group were at the castration level (≤ 1.735 nmol/L) of testosterone at Month 24. 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)

The efficacy results showed that TRELSTAR 11.25 mg (3 month sustained-release formulation) was able to induce a chemical castration (≤ 1.735 nmol/L) in 162 out of 166 patients (97.6%) 28 days after the first i.m. injection. In the TRELSTAR 3.75 mg (1 month sustained-release formulation) group, 147 out of 159 (92.5%) patients were chemically castrated (≤ 1.735 nmol/L) 28 days after the first injection. It was concluded that TRELSTAR 11.25 mg (3 month sustained-release formulation) is at least as effective as TRELSTAR 3.75 mg (1 month sustained-release formulation) in achieving castration on Day 29.

TRELSTAR 22.5 mg (6 month sustained-release formulation)

The efficacy results showed that castration levels of serum testosterone (≤ 1.735 nmol/L) were achieved at Day 29 in 117 of 120 (97.5%) patients treated with TRELSTAR 22.5 mg (6 month sustained-release formulation). Maintenance of castration levels of serum testosterone from Day 57 through Day 337 was found in 93.0% of patients treated with TRELSTAR 22.5 mg (6 month sustained-release formulation).

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 Studies

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.

Reproduction Studies

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.

Mutagenicity Studies

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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

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:
- worsening of symptoms of prostate cancer at the beginning of treatment
- bone thinning (osteoporosis)

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 gonadotropin-releasing hormone (GnRH) agonists. 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 GnRH agonists or luteinizing hormone-releasing hormone (LHRH) agonists, GnRH agonist analogs, or to any other ingredient in the medication.
- 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, contact 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:

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. **Contact 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 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
- 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 adult 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 have been given too much TRELSTAR, contact your 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.

What are possible side effects from using TRELSTAR?
These are not all the possible side effects you may feel when taking TRELSTAR. If you experience any side effects not listed here, contact 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 (impotence)
- 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			
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		✓	
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		✓	

If you have troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to 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 healthcare 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 Sterile Water for Injection) at 15-30°C.
- Store TRELSTAR 3.75 mg, TRELSTAR 11.25 mg and TRELSTAR 22.5 mg vials (without Sterile Water for Injection) at 15-30°C.
- Do not freeze.
- Protect from light.

Keep out of sight and reach 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: January 25, 2021