PRODUCT MONOGRAPH

Pr TRELSTAR® 3.75 mg
Triptorelin for Injectable Suspension
Microgranules for depot suspension

3.75 mg triptorelin (as pamoate) per vial (1 month slow-release)

Pr TRELSTAR® 11.25 mg
Triptorelin for Injectable Suspension
Microgranules for depot suspension

11.25 mg triptorelin (as pamoate) per vial (3 month slow-release)

Pr TRELSTAR® 22.5 mg
Triptorelin for Injectable Suspension
Microgranules for depot suspension

22.5 mg triptorelin (as pamoate) per vial (6 month slow-release)

Luteinizing Hormone-Releasing Hormone (LHRH) Analog

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Control No. 189866

Table of Contents

Pr TRELSTAR® 3.75 mg (1 month slow-release)
Pr TRELSTAR® 11.25 mg (3 month slow-release)
Pr TRELSTAR® 22.5 mg (6 month slow-release)
Triptorelin for Injectable Suspension

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular	Powder (microgranules) for slow-release suspension 3.75 mg of triptorelin peptide base units/vial; 11.25 mg of triptorelin peptide base units/vial; 22.5 mg of triptorelin peptide base units/vial	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

TRELSTAR (triptorelin for injectable suspension) is indicated for:
- the palliative treatment of hormone dependent advanced carcinoma of the prostate gland (stage D2).

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 section).

Pediatrics (<18 years of age): The safety and effectiveness of TRELSTAR in pediatric patients have not been established (see WARNINGS AND PRECAUTIONS section).

TRELSTAR must be administered under the supervision of a physician.

CONTRAINDICATIONS

- TRELSTAR are 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 or component of the container. Anaphylactic reactions to synthetic GnRH or GnRH agonist analogs have been reported (see WARNINGS AND PRECAUTIONS section). For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- TRELSTAR are contraindicated in 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 section).

- TRELSTAR is contraindicated in nursing women (see WARNINGS AND PRECAUTIONS section).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

TRELSTAR (triptorelin for injectable suspension) should be prescribed by a qualified physician 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 General below)**
- **Osteoporosis (see Endocrine and Metabolism below)**

General

TRELSTAR (triptorelin for injectable suspension), 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 Drug Reactions section).

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 TOXICOLOGY section).

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 (see the References section). Reports of events related to cardiovascular ischemia including myocardial infarction, stroke and cardiovascular-related deaths have been received in patients treated with LHRH agonists. Physicians 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 below).

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. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risk in patients with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure and in patients taking Class IA (e.g. quinidine, procainamide), Class III (e.g. aminodarone, sotalol, dofetilide, ibutilide), or Class IC (e.g. flecainide, propafenone) antiarrhythmic medications.

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.

Neurologic

No studies on the effects of TRELSTAR on the ability to drive and use machines have been performed. However, fatigue and dizziness are common adverse reactions that might influence the ability to drive and use machines.

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 and Hepatic

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

Special Populations

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 section).

Nursing Women: 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 section).

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

Pediatrics (< 18 years of age): The safety and effectiveness of TRELSTAR in pediatric patients have not been established.

Race: The effects of race on triptorelin pharmacokinetics, safety, and efficacy have not been systematically studied. In the three controlled clinical studies conducted to compare a controlled release formulation of triptorelin acetate with orchiectomy, no race data were collected. The study that compared TRELSTAR (1-month, 3.75 mg triptorelin pamoate formulation) and TRELSTAR (3-month, 11.25 mg triptorelin pamoate formulation), included 47.7% Caucasian, 37.6% Black, and 14.7% Other patients. In the non-comparative clinical study conducted to determine the safety and efficacy of TRELSTAR (6-month, 22.5 mg triptorelin pamoate formulation), 64.2% of the patients were Caucasian, 22.5% were Black, and 13.3% were Other.

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 slow-release). 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 section).

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 section).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

TRELSTAR has been found to be generally well tolerated in clinical trials. Adverse reactions reported in these trials 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 section). 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 section).

Clinical Trial Adverse Drug 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 drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical Studies with Triptorelin Acetate

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 section).

Clinical Studies with Triptorelin Pamoate

TRELSTAR 3.75 mg (1-month, 3.75 mg triptorelin pamoate formulation) and TRELSTAR 11.25 mg (3-month, 11.25 mg triptorelin pamoate formulation)

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

The safety results showed that the two formulations of TRELSTAR were well tolerated.

TRELSTAR 22.5 mg (6-month, 22.5 mg triptorelin pamoate formulation)

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

The safety results showed that the 6-month formulation (TRELSTAR 22.5 mg) was well tolerated.
The safety profile was similar to the 1-month (TRELSTAR 3.75 mg) and 3-month (TRELSTAR 11.25 mg) formulations.

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

TABLE 1. 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), AND TRELSTAR 22.5 MG (1 INJECTION ON DAY 1 AND 1 INJECTION ON DAY 169)

Adverse Events	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)

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Adverse Events	TRELSTAR (3.75 mg)[1] N = 172 n (%)	TRELSTAR (11.25 mg)[1] N=174 n (%)	TRELSTAR (22.5 mg)[2] N = 120 n (%)
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)
Oedema 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)
Oedema 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)
Diarrhoea	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)
Metabolic and Nutritional Disorders			
Oedema 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)

TABLE 1. 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), AND TRELSTAR 22.5 MG (1 INJECTION ON DAY 1 AND 1 INJECTION ON DAY 169)			
Adverse Events	**TRELSTAR (3.75 mg)[1] N = 172 n (%)**	**TRELSTAR (11.25 mg)[1] N=174 n (%)**	**TRELSTAR (22.5 mg)[2] N = 120 n (%)**
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)
Dyspnoea	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)

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Adverse drug reactions that were reported by 1% or less of subjects in both the TRELSTAR 3.75 mg and TRELSTAR 11.25 mg treatment groups, and were considered to be possibly or probably related to study drug, included the following: injection site reaction, malaise, muscle weakness, rhinitis, skin disorder, and hematuria. Adverse drug reactions that were reported by 1% or less of subjects (N = 1; 0.83%) in the TRELSTAR 22.5 mg study, and were considered to be possibly or probably related to study drug, included the following: abdominal discomfort, abdominal pain, constipation, nausea, injection site erythema, injection site pruritus, injection site swelling, alanine aminotransferase increased, aspartate aminotransferase increased, prostatic antigen increased, weight increased, anorexia, arthralgia, back pain, musculoskeletal stiffness, myalgia, pain in extremity, metastatic pain, paraesthesia, syncope vasovagal, insomnia, loss of libido, orchitis noninfective, pruritus, rash, and hypertension.

Abnormal Hematologic and Clinical Chemistry Findings

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.

Post-Market Adverse Drug 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.

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

Interactions with other drugs have not been established.

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, dropedarone), 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).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

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.

DOSAGE AND ADMINISTRATION

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 slow-release) 3.75 mg triptorelin/vial: The recommended dose of TRELSTAR 3.75 mg (triptorelin for injectable suspension) is 3.75 mg (as peptide base) incorporated in a depot formulation, monthly. The lyophilized microgranules are 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 slow-release) 11.25 mg triptorelin/vial: The recommended dose of TRELSTAR 11.25 mg (triptorelin for injectable suspension) is 11.25 mg (as peptide base), incorporated in a depot formulation, every 3 months. The lyophilized microgranules are 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 slow-release) 22.5 mg triptorelin/vial: The recommended dose of TRELSTAR 6 month slow-release (triptorelin for injectable suspension) is 22.5 mg (as peptide base), incorporated in a depot formulation, every 6 months. The lyophilized microgranules are 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).

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.

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.

Reconstitution

TRELSTAR is supplied in single-dose vials containing lyophilized microgranules. These microgranules are 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).

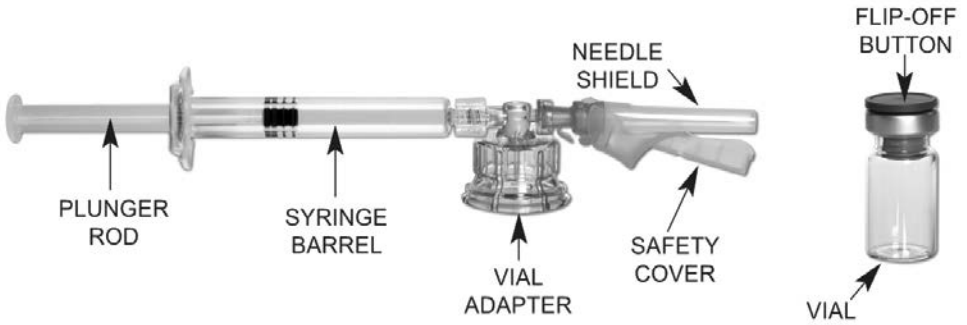
When 2 mL of Sterile Water for Injection is added to the lyophilized triptorelin pamoate microgranules and mixed, a suspension is formed. For TRELSTAR 3.75 mg (1 month slow-release) this is equivalent to 3.75 mg of triptorelin peptide base units intended as a single monthly intramuscular injection. For TRELSTAR 11.25 mg (3 month slow-release) 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 slow-release) this is equivalent to 22.5 mg of triptorelin peptide base units intended as a single 6 month intramuscular injection.

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

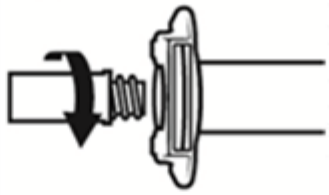
Wash your hands with soap and hot water and put on gloves immediately prior to preparing the injection. Place the sealed tray on a clean, flat surface that is covered with a sterile pad or cloth. Peel the cover away from the tray and remove the MIXJECT components and the TRELSTAR vial. Remove the Flip-Off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

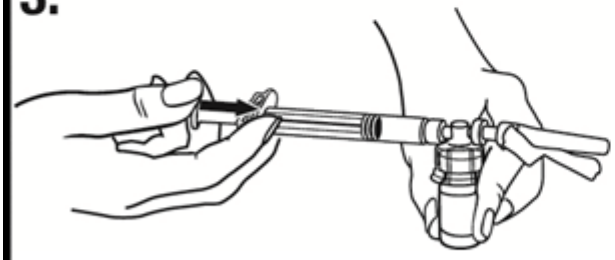


(a) Screw the plunger rod into the barrel end of the syringe. Remove the cap from the syringe barrel.

2b.

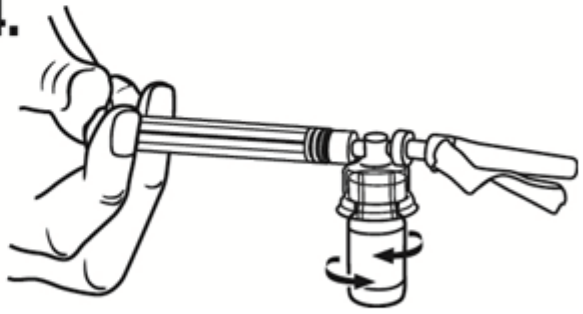
(b) Connect the syringe to the vial adapter by screwing it clockwise into the opening on the side of the vial adapter. Be sure to gently twist the syringe until it stops turning to ensure a tight connection.

3.



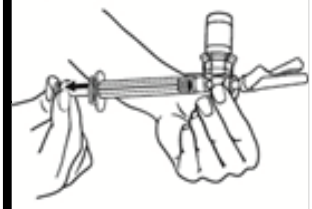
While holding the vial, place your thumb on the plunger rod and push the plunger rod in all the way to transfer the diluent from the pre-filled syringe into the vial. Do not release the plunger rod.

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.

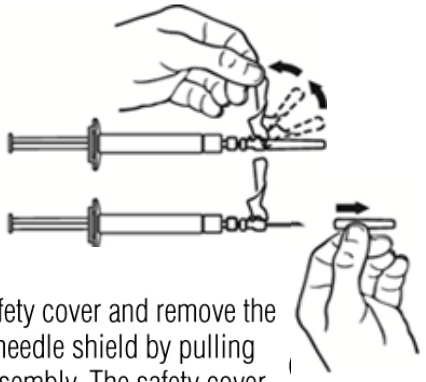


(a) Invert the MIXJECT system so that the vial is at the top. Grasp the MIXJECT system firmly by the syringe and pull back the plunger rod slowly to draw the reconstituted TRELSTAR into the syringe.

5b.

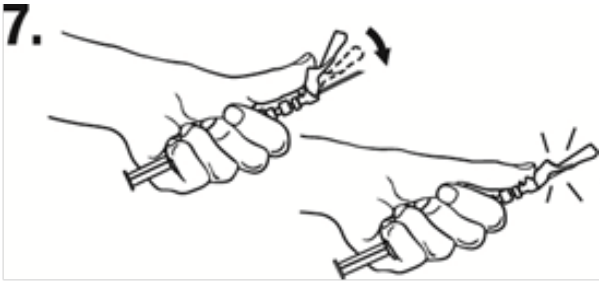
(b) Return the vial to its upright position, and disconnect the vial adapter and vial from the MIXJECT syringe assembly by turning the plastic cap of the vial adapter clockwise. *Grasp only the plastic cap when removing.*

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.

<u>Instructions for Use – TRELSTAR vial (without Sterile Water for Injection)</u>

The lyophilized microgranules are to be reconstituted **in sterile water**. **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.

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.

ACTION AND CLINICAL PHARMACOLOGY

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. 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.

Following a single intramuscular injection of TRELSTAR 3.75 mg (triptorelin for injectable suspension) as a 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 (triptorelin for injectable suspension) as a 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 (triptorelin for injectable suspension) as a 6 month sustained release formulation (22.5 mg) 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.

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

TABLE 2. PHARMACOKINETIC PARAMETERS OF TRIPTORELIN
(mean ± SD or median (range) for T_{max})

Triptorelin Pharmacokinetics			
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 section).

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.

Excretion: 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 dependant on the liver (see Special Populations and Conditions section).

Special Populations and Conditions:

Renal and Hepatic Impairment: 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 3). 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 3. 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 Race: The effects of age and race on triptorelin pharmacokinetics have not been systematically studied. However, pharmacokinetic data obtained in young healthy male volunteers aged 20 to 22 years with an elevated creatinine clearance (approximately 250 mL/min) indicates that triptorelin was eliminated twice as fast in this young population (see Special Populations and Conditions, Renal and Hepatic Impairment, section) 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.

STORAGE AND STABILITY

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 20-25°C: excursions permitted: 15 - 30°C.

Store TRELSTAR 3.75 mg, TRELSTAR 11.25 mg and TRELSTAR 22.5 mg vials (without Sterile Water for Injection) at 20-25°C; excursions permitted: 15 - 30 °C.

Do Not Freeze. Protect from light.

Unused portion of reconstituted TRELSTAR should be discarded immediately.

Keep out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TRELSTAR (1 month slow-release) 3.75 mg triptorelin/vial

TRELSTAR 3.75 mg is supplied in a vial containing sterile lyophilized triptorelin pamoate microgranules which are equivalent to 3.75 mg triptorelin peptide base, poly-*d*,l-lactide-co-glycolide, mannitol, carboxymethylcellulose sodium, and polysorbate 80. When 2 mL Sterile Water for Injection is added to the microgranules and mixed, a suspension is formed, which is intended as a single, intramuscular injection administered monthly.

TRELSTAR (3 month slow-release) 11.25 mg triptorelin/vial

TRELSTAR 11.25 mg is supplied in a vial containing sterile lyophilized triptorelin pamoate microgranules which are equivalent to 11.25 mg triptorelin peptide base, poly-*d*,l-lactide-co-glycolide, mannitol, carboxymethylcellulose sodium, and polysorbate 80. When 2 mL Sterile Water for Injection is added to the microgranules and mixed, a suspension is formed, which is intended as a single, intramuscular injection administered every 3 months.

TRELSTAR (6 month slow-release) 22.5 mg triptorelin/vial

TRELSTAR 22.5 mg is supplied in a vial containing sterile lyophilized triptorelin pamoate microgranules which are equivalent to 22.5 mg triptorelin peptide base, poly-*d*,l-lactide-co-glycolide, mannitol, carboxymethylcellulose sodium, and polysorbate 80. When 2 mL Sterile Water for Injection is added to the microgranules and mixed, a suspension is formed, which is intended as a single, intramuscular injection administered every 6 months.

TRELSTAR is available in two presentations:

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).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

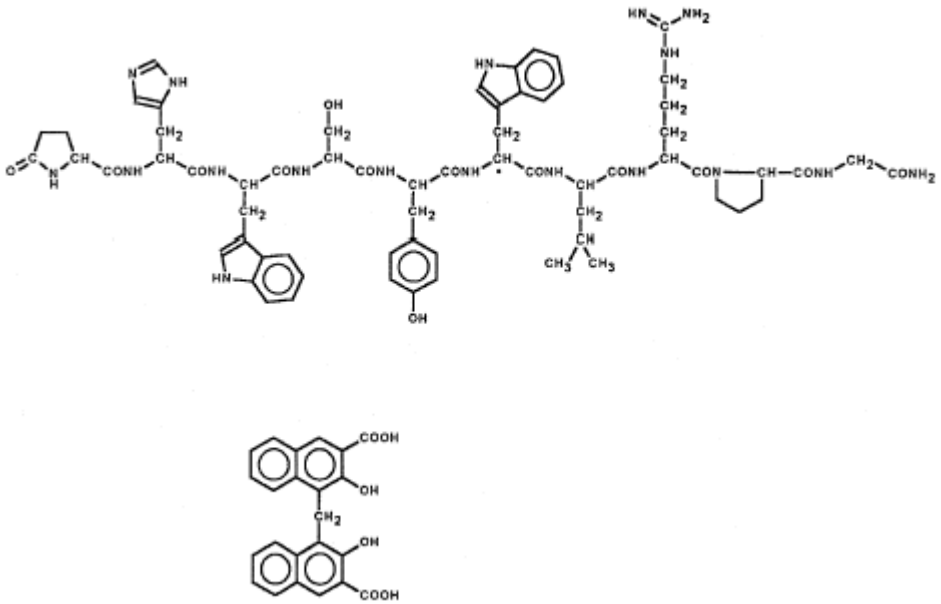
Proper Name: Triptorelin pamoate

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

Structural Formula: Upper formula (D-Trp6)-LHRH

Lower formula Pamoic acid (embonic acid)

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



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

Molecular Weight: 1699.9

Description: Yellowish powder, specific optical rotation $[\alpha]_D^{25} = -23.0^o \pm 2.5^o$

Physicochemical Properties: Soluble in DMSO (660 mg/mL), pyridine (440 mg/mL) and water (60 µg/mL)

CLINICAL TRIALS

Clinical Studies with Triptorelin Acetate

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.

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.

These studies also showed that triptorelin acetate was well-tolerated. 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. 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

	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)
Oedema	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)
Diarrhoea	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)

NA = not applicable; * Expected pharmacological consequence of testosterone suppression (Continued)

Table 4 (Continued)

	Triptorelin Acetate (3.75 mg) N = 156 n (%)	Orchiectomy N = 97 n (%)
Respiratory System Disorders		
Dyspnoea	6 (3.8)	0 (0.0)
Respiratory disorder	1 (0.6)	1 (1.0)
Haemoptysis	0 (0.0)	1 (1.0)
Resistance Mechanism Disorder		
Infection	0 (0.0)	1 (1.0)
Skin and Appendages Disorders		
Pruritis	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, 3.75 mg triptorelin pamoate formulation) and TRELSTAR 11.25 mg (3-month, 11.25 mg triptorelin pamoate 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 the 3-month formulation (TRELSTAR 11.25 mg) of triptorelin pamoate is at least as effective as the 1-month formulation (TRELSTAR 3.75 mg) of triptorelin pamoate 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 of the patients had prostate cancer at stage C and 162 had prostate cancer at stage D.

The efficacy results showed that the 3-month formulation of triptorelin pamoate 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 1-month 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 the

3-month formulation (TRELSTAR 11.25 mg) is at least as effective as the 1-month formulation (TRELSTAR 3.75 mg) in achieving castration on Day 29.

TRELSTAR 22.5 mg (6-month, 22.5 mg triptorelin pamoate formulation)

The 6-month formulation, TRELSTAR 22.5 mg, was studied in a non-comparative trial of 120 men with advanced prostate cancer in South Africa. Patients received the 6-month 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).

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 the 6-month formulation. Maintenance of castration levels of serum testosterone from Day 57 through Day 337 was found in 93.0% of patients treated with the 6-month formulation.

DETAILED PHARMACOLOGY

Triptorelin is a potent agonist of LHRH. The potency relative to native LHRH has been demonstrated both *in vitro* and *in vivo*. Comparative *in vitro* studies showed that triptorelin was 100-fold more active than native LHRH in stimulating LH release from monolayers of dispersed rat pituitary cells in culture and 20-fold more active than native LHRH in displacing ^{125}I-LHRH from pituitary receptor sites. The increased potency was correlated with an increased resistance to degradation on exposure to enzyme preparations derived from rat hypothalamus or anterior pituitary. *In vivo* studies in immature male rats showed that triptorelin had 13-fold higher LH-releasing activity and 21-fold higher FSH-releasing activity compared to native LHRH. Compared with the ovulating-inducing capacity of native LHRH in adult Sprague-Dawley rats and Swiss albino mice, triptorelin was 84-fold more potent in proestrus rats (pretreated with fluphenazine to block ovulation), 372-fold more potent in pregnant rats, 85-fold more potent in diestrus rats, and 63-fold more potent in diestrus mice.

A series of experiments showed that long-term administration of triptorelin inhibited prostate cancer growth in male rats that had been inoculated subcutaneously with Segaloff 11095 rat prostate tumor, a chemically-induced, androgen-dependent squamous cell carcinoma; in male rats bearing Dunning R3227 rat prostate tumor, a spontaneous androgen-dependent adenocarcinoma with characteristics similar to human prostate adenocarcinoma; in male rats bearing an androgen-independent Dunning R3327_AT_1 prostate tumor; and in male nude mice bearing xenografts of the hormone-dependent human prostatic tumor PC-82.

In both rats and human prostate tumors, two classes of binding sites were found for triptorelin, one with high affinity and low binding capacity and the other with low affinity and high binding capacity. In rats with prostate tumors, chronic treatment with triptorelin produced down-regulation of membrane receptors for LHRH in the tumors. Additionally, direct antiproliferative effects of LHRH agonists were demonstrated *in vitro* for both androgen-independent Dunning

R3327-AT-1 rat prostate cancer cells and androgen-sensitive human LNCaP prostatic cancer cells.

In male rats, chronic administration of triptorelin caused a decrease in weights of testes, seminal vesicles, and prostate; a fall in blood testosterone levels; inhibition of spermatogenesis; and a reduction of testicular LH/hCG and PRL receptors. Experiments in hypophysectomized animals showed that some of these effects result from the direct action of triptorelin on testicular LH receptors. In both adult and immature hypophysectomized male rats, daily injections of 2 µg triptorelin for 7 days decreased the number of testicular LH/hCG binding sites. The effects of triptorelin on testicular LH receptors were biphasic and could be nullified by LHRH antagonists. In hypophysectomized adult male rats primed with pregnant mare serum, daily administration of 200 ng triptorelin reduced the number of testicular LH receptors to 60% of control values, but a 1 ng dose increased receptors to 485% of control values. Both effects were nullified when an antagonist was administered concomitantly with triptorelin.

In female rats, chronic administration of triptorelin or other LHRH agonists caused a delay in vaginal opening, reduction in ovarian and uterine weight; interference with implantation and termination of gestation; and a decrease in the number of ovarian receptors for LH/hCG.

TOXICOLOGY

Acute Toxicity Studies

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

Subchronic and Chronic Toxicity Studies

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.

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PART III: CONSUMER INFORMATION

Pr TRELSTAR® (3.75 mg)
Pr TRELSTAR® (11.25 mg)
Pr TRELSTAR® (22.5 mg)
Triptorelin for Injectable Suspension

This leaflet is part III of a three-part "Product Monograph" published when TRELSTAR, 3.75 mg (1 month slow-release), TRELSTAR 11.25 mg (3 month slow-release) and TRELSTAR 22.5 mg (6 month slow-release) were approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TRELSTAR. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this leaflet before you start taking TRELSTAR (triptorelin pamoate). Also, read it each time you renew your prescription, just in case new information has been added.

ABOUT THIS MEDICATION

What the medication is used for:
Your doctor has prescribed TRELSTAR as part of the treatment for your advanced hormone-dependent prostate cancer.

What it does:
TRELSTAR belongs to a class of drugs called gonadotropin-releasing hormone (GnRH) agonists.

TRELSTAR works to reduce the level of sex hormones, such as testosterone, in your body. A reduction in testosterone may help reduce the bone pain, urinary problems and other symptoms of prostate cancer.

When it should not be used:
TRELSTAR should not be used if:

- You are allergic or oversensitive to triptorelin, or to drugs called LHRH agonists, or to any ingredients in the formulation or component of the vial.

- Do not use TRELSTAR for women who are or may become pregnant, for nursing mothers, and for women in general. In pregnant women, TRELSTAR may cause harm to the baby.

What the medicinal ingredient is:
Triptorelin pamoate

What the important non-medicinal ingredients are:
Poly-*d*,l-lactide-co-glycolide, mannitol, carboxymethylcellulose sodium and polysorbate 80.

What dosage forms it comes in:
TRELSTAR is sterile powders stored in vials.

TRELSTAR 3.75 mg 1 month slow-release (triptorelin for injectable suspension) contains 3.75 mg of triptorelin (as pamoate).

TRELSTAR 11.25mg 3 month slow-release (triptorelin for injectable suspension) contains 11.25 mg of triptorelin (as pamoate).

TRELSTAR 22.5 mg 6 month slow-release (triptorelin for injectable suspension) contains 22.5 mg of triptorelin (as pamoate).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

TRELSTAR should be prescribed by a doctor experienced with this type of drugs.
TRELSTAR may cause:

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

BEFORE you use TRELSTAR talk to your doctor or pharmacist if:

- You have any allergies to this drug, or its ingredients, or to components of the injection
- You have a strong family history of osteoporosis, have low bone density (BMD), or take any medication that causes thinning of the bones, or use alcohol or tobacco. TRELSTAR may increase your risk of osteoporosis and bone fractures
- You have or have had kidney and/or liver disease
- You have a history of heart disease or disorders, or have a genetic heart condition called “long QT syndrome”
- You have high blood sugar (diabetes), TRELSTAR may affect your blood sugar and you may need to test your blood sugar more frequently while receiving treatment with TRELSTAR
- You have low red blood cell counts, TRELSTAR may cause a decrease in red blood cells (anemia)

TRELSTAR has not been studied in children under 18 years of age.

You should know how TRELSTAR affects you before driving a vehicle or operating machinery.

INTERACTIONS WITH THIS MEDICATION

Before your treatment with TRELSTAR, check with your doctor or pharmacist if you are taking drugs for abnormal heart rhythms, psychosis, nausea resulting from chemotherapy, asthma, antibiotics, or antifungal drugs or any other drugs, including non prescription drugs (for colds, nausea, etc). During your treatment

with TRELSTAR, do not start taking a new medicine before checking with your doctor or pharmacist.

PROPER USE OF THIS MEDICATION

TRELSTAR is given into your muscle (intramuscular injection) by a healthcare professional under the supervision of your doctor.

Usual Dose:

TRELSTAR 3.75 mg on a specified day, generally once every 28 days

TRELSTAR 11.25 mg on a specified day, generally once every 84 days

TRELSTAR 22.5 mg on a specified day, generally once every 168 days.

Missed Dose:
If you forget to have TRELSTAR on the specified day, call your doctor as soon as you can.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, TRELSTAR may have some unwanted or side effects.

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. **Consult your doctor immediately if you develop severe or increased pain, numbness or weakness of the limbs, or persistent difficulty in urinating.**

Expected side effects related to decreased testosterone levels in your body may include hot flushes, reduction in sex drive and inability to develop and maintain an erection (impotence). If these side effects continue to make you feel uncomfortable, consult your doctor.

Occasionally, a local skin reaction may occur at the injection site such as itching, redness, burning and swelling. These reactions generally are mild and disappear after a few days. If they get worse or do not go away, tell your doctor.

Other side effects not listed above may also occur in some patients. If you notice any other effects, tell your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very common	Hot flushes	✓		
Common	Pain (Bone, leg, breast, back, joint, muscle)		✓	
	Injection site pain, hardening, or bruising		✓	
	Eye pain, eye infection		✓	
	Headache		✓	
	High blood pressure		✓	
	Difficult/painful urination		✓	
	Nausea		✓	
	Tiredness		✓	
	Dizziness		✓	
	Swelling in the limbs		✓	
	Constipation		✓	
	Diarrhea		✓	
	Depression		✓	
	Loss of appetite		✓	
	Difficulty breathing		✓	
	Racing/abnormal heartbeat		✓	
	Infection of the bladder and/or kidneys		✓	
	Indigestion		✓	
	Leg cramps		✓	
	Enlargement of breasts		✓	
	Coughing		✓	
	Abnormal liver function		✓	
	High blood sugar/diabetes		✓	
	Inflammation of the throat		✓	
	Itching of the skin		✓	
	Unable to urinate		✓	
	Reduced size of genitalia		✓	
Uncommon	Injection site reaction		✓	
	Feeling unwell/uneasy		✓	
	Muscle weakness		✓	
	Infection of the nose		✓	
	Abnormal skin changes		✓	
	Blood in the urine		✓	
	Abdominal discomfort or pain		✓	
	Increase in weight		✓	
	Muscle stiffness		✓	
	Pain associated with cancer		✓	
	Fainting		✓	
	Inflammation of the testicles		✓	
	Difficulty falling asleep		✓	
	Tingling or numbness		✓	
	Rash		✓	

This is not a complete list of side effects. For any unexpected effects while taking TRELSTAR, contact your doctor or pharmacist.

HOW TO STORE IT

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 20-25°C; excursions permitted: 15 - 30° C.

Store TRELSTAR 3.75 mg, TRELSTAR 11.25 mg and TRELSTAR 22.5 mg vials (without Sterile Water for Injection) at 20-25°C; excursions permitted: 15 - 30 °C.

Do not freeze. Protect from light.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario
  K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found at: www.allergan.ca or by contacting the sponsor, Allergan Pharma Co., at 1-800-668-6424

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