

PRODUCT MONOGRAPH

**Pr TRELSTAR™ 3.75 mg (1 month slow-release)
Triptorelin Pamoate for Injectable Suspension
Microgranules for depot suspension**

3.75 mg triptorelin (as pamoate) per vial (1 month slow release)
with single dose delivery system
and Sterile Water for Injection (2mL)

3.75 mg triptorelin (as pamoate) per vial (1 month slow release)
without Sterile Water for Injection (2mL)

**Pr TRELSTAR™ 11.25 mg (3 month slow-release)
Triptorelin Pamoate for Injectable Suspension
Microgranules for depot suspension**

11.25 mg triptorelin per vial (3 month slow release)
with single dose delivery system
and Sterile Water for Injection (2mL)

11.25 mg triptorelin per vial (3 month slow release)
without Sterile Water for Injection (2mL)

Luteinizing Hormone-Releasing Hormone (LHRH) Analog

Watson Laboratories, Inc.
311 Bonnie Circle
Corona, CA, USA, 92880

Date of Revision: November 24, 2009

Distributed by:
Paladin Labs Inc.
Montreal, QC H4P 2T4

Control No. 134095

Trelstar is a trademark of Watson Laboratories Inc.

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION.....	3
INDICATIONS AND CLINICAL USE	3
WARNINGS AND PRECAUTIONS	4
ADVERSE REACTIONS	6
DRUG INTERACTIONS	9
DOSAGE AND ADMINISTRATION	10
OVERDOSAGE.....	13
ACTION AND CLINICAL PHARMACOLOGY.....	14
STORAGE AND STABILITY	16
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	16
PART II: SCIENTIFIC INFORMATION	18
PHARMACEUTICAL INFORMATION.....	18
CLINICAL TRIALS	18
DETAILED PHARMACOLOGY	21
TOXICOLOGY.....	22
REFERENCES.....	24
PART III: CONSUMER INFORMATION.....	26

Pr TRELSTAR™ 3.75 mg (1 month slow-release)
Pr TRELSTAR™ 11.25 mg (3 month slow-release)
Triptorelin Pamoate 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	<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

TRELSTAR (triptorelin pamoate 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).

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

TRELSTAR must be administered under the supervision of a physician.

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 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 the Dosage Forms, Composition and Packaging sections of the Product Monograph.
- TRELSTAR is 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

General

TRELSTAR (triptorelin pamoate for injection), like other LH-RH agonists, cause 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 LH-RH 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 triptorelin therapy under close supervision.

Hypersensitivity and anaphylactic reactions have been reported with triptorelin as with other LHRH agonists (see Post-Market Adverse Drug Reactions).

Carcinogenesis and Mutagenesis

Carcinogenicity and mutagenicity studies have been performed in animals (see TOXICOLOGY section).

Endocrine and Metabolism

Changes in bone density: Bone loss can be expected as part of natural aging and can also be anticipated during the hypoandrogenic state caused by long-term use of triptorelin. In patients with significant risk factors for decreased bone mineral content and/or bone mass such as family history of osteoporosis, chronic use of corticosteroids or anticonvulsants or chronic abuse of alcohol or tobacco, triptorelin may pose additional risk. In these patients, risk versus benefit must be weighed carefully before initiation of triptorelin therapy.

Long-term administration of triptorelin 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.

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.

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 triptorelin 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% Colored patients.

Monitoring and Laboratory Tests

During therapy with TRELSTAR, patients should be routinely monitored by physical examinations and appropriate laboratory tests. Response to TRELSTAR may be monitored by periodically measuring serum concentrations of testosterone and prostate specific antigen. Results of testosterone determinations are dependant on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Triptorelin pamoate 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 triptorelin treatment. Three postmarketing reports of anaphylactic shock and seven postmarketing reports of angioedema related to triptorelin administration have been reported since 1986 (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 triptorelin 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 LH-RH 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).

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)

Clinical Study with Triptorelin Pamoate

The safety of triptorelin 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 triptorelin pamoate 3-month formulation (11.25 mg), administered i.m. every 84 days for 9 months, or nine injections of triptorelin pamoate 1-month formulation (3.75 mg), administered i.m. every 28 days for 9 months.

The following possibly or probably related systemic adverse events were reported by 1% or more of patients in this study:

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) AND TRELSTAR 11.25 MG (1 INJECTION EVERY 84 DAYS FOR 9 MONTHS)		
	TRELSTAR (3.75 mg) N = 172 n (%)	TRELSTAR (11.25 mg) N=174 n (%)
Application Site Disorders		
Injection site pain	2 (1.2)	7 (4.0)
Body as a Whole		
Hot flushes*	114 (66.3)	127 (73.0)
Back pain	6 (3.5)	5 (2.9)
Pain	10 (5.8)	6 (3.4)
Leg pain	5 (2.9)	9 (5.2)
Fatigue	5 (2.9)	4 (2.3)
Chest pain	0 (0.0)	3 (1.7)
Asthenia	2 (1.2)	2 (1.1)
Oedema peripheral	3 (1.7)	2 (1.1)
Allergic reaction	2 (1.2)	0 (0.0)
Cardiovascular Disorders		
Hypertension	8 (4.7)	7 (4.0)
Oedema dependant	0 (0.0)	4 (2.3)
Central and Peripheral Nervous System Disorders		
Headache	7 (4.1)	12 (6.9)
Dizziness	5 (2.9)	5 (2.9)
Cramps legs	1 (0.6)	3 (1.7)
Endocrine Disorders		
Breast pain male	5 (2.9)	4 (2.3)
Gynecomastia	0 (0.0)	3 (1.7)
Gastro-intestinal System Disorders		
Constipation	4 (2.3)	3 (1.7)
Nausea	7 (4.1)	5 (2.9)
Diarrhoea	4 (2.3)	2 (1.1)
Abdominal pain	1 (0.6)	2 (1.1)
Dyspepsia	2 (1.2)	3 (1.7)

* Expected pharmacological consequence of testosterone suppression

(Continued)

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) AND TRELSTAR 11.25 MG (1 INJECTION EVERY 84 DAYS FOR 9 MONTHS) (CONTINUED)

	TRELSTAR (3.75 mg) N = 172 n (%)	TRELSTAR (11.25 mg) N=174 n (%)
Heart Rate and Rhythm Disorders		
Palpitation	3 (1.7)	0 (0.0)
Liver and Biliary System Disorders		
Hepatic function abnormal	0 (0.0)	2 (1.1)
Metabolic and Nutritional Disorders		
Oedema legs	14 (8.1)	11 (6.3)
Diabetes mellitus	2 (1.2)	1 (0.6)
Musculo-skeletal Disorders		
Skeletal pain	20 (11.6)	23 (13.2)
Arthralgia	4 (2.3)	4 (2.3)
Myalgia	1 (0.6)	2 (1.1)
Psychiatric Disorders		
Insomnia	2 (1.2)	3 (1.7)
Depression*	3 (1.7)	1 (0.6)
Impotence*	7 (4.1)	4 (2.3)
Anorexia	1 (0.6)	3 (1.7)
Libido decreased*	1 (0.6)	4 (2.3)
Respiratory System Disorders		
Coughing	1 (0.6)	3 (1.7)
Dyspnoea	3 (1.7)	2 (1.1)
Pharyngitis	0 (0.0)	2 (1.1)
Skin and Appendages Disorders		
Rash	1 (0.6)	3 (1.7)
Pruritus	2 (1.2)	0 (0.0)
Urinary System Disorders		
Urinary tract infection	3 (1.7)	0 (0.0)
Dysuria	3 (1.7)	8 (4.6)
Urinary retention	0 (0.0)	2 (1.1)
Vision Disorders		
Eye pain	1 (0.6)	2 (1.1)
Conjunctivitis	0 (0.0)	2 (1.1)

* Expected pharmacological consequence of testosterone suppression

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.

Abnormal Hematologic and Clinical Chemistry Findings

The incidence rate 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.

Post-Market Adverse Drug Reactions

During post-marketing surveillance, three cases of anaphylatic shock and two cases of angioedema have been reported that were related to triptorelin.

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 triptorelin pamoate since hyperprolactinemia reduces the number of pituitary GnRH receptors.

Drug-Drug Interactions

Interactions with other drugs have not been established.

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

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Triptorelin pamoate is intended for long-term administration unless clinically inappropriate.

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 one of the single dose delivery systems (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 one of the single dose delivery systems (MIXJECT™). Administer every 3 months as a single intramuscular injection, in accordance with the Instructions for use (see below).

Administration

TRELSTAR is administered as a single intramuscular injection.

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.

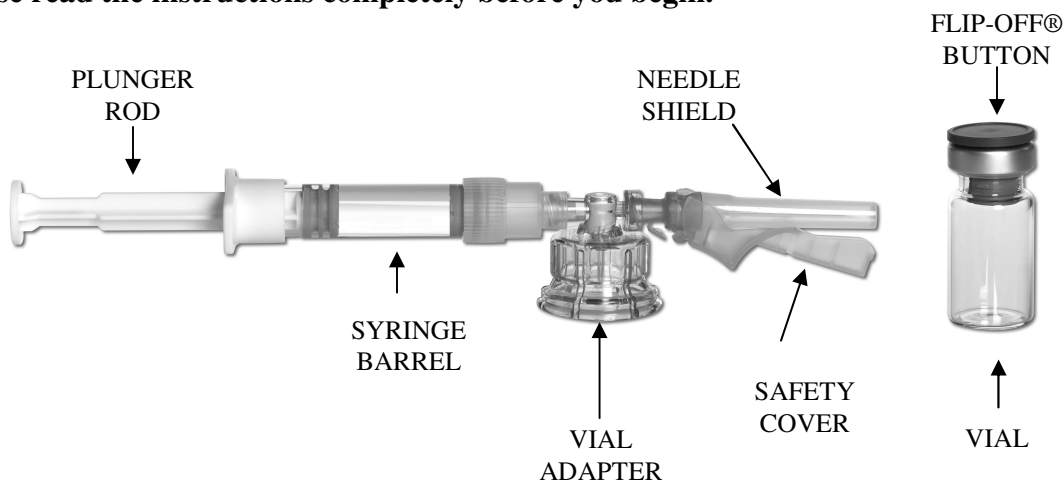
The suspension should be discarded if not used immediately after reconstitution. As with other drugs administered by intramuscular injection, the injection site should be varied periodically.

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 vial (with Sterile Water for Injection), MIXJECT™:

Please read the instructions completely before you begin.

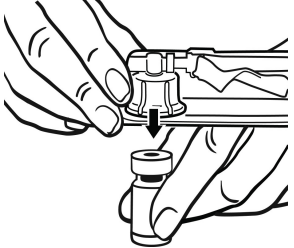


MIXJECT™ Preparation

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*.

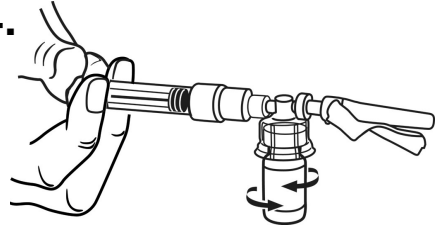
MIXJECT™ Activation

1.



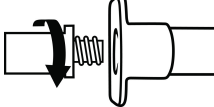
Peel the cover away from the blister pack containing the vial adapter. *Do not remove the vial adapter from the blister pack.* Place the blister pack containing the vial adapter firmly on the vial top, piercing the vial. Push down gently until you feel it snap in place. Remove the blister pack from the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

4.



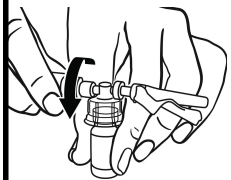
Keeping the plunger rod depressed, gently swirl the vial so that the diluent rinses the sides of the vial. This will ensure complete mixing of TRELSTAR® and the sterile water diluent. The suspension will now have a milky appearance. In order to avoid separation of the suspension, proceed to the next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

2a.



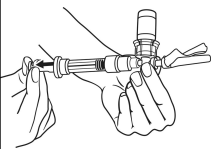
(a) Screw the plunger rod into the barrel end of the syringe. Remove the cap from the syringe barrel.

2b.



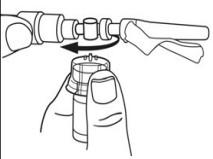
(b) Connect the syringe to the vial adapter by screwing it clockwise into the opening on the side of the vial adapter. Be sure to gently twist the syringe until it stops turning to ensure a tight connection.

5a.



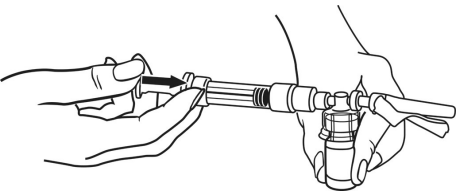
(a) Invert the MIXJECT® system so that the vial is at the top. Grasp the MIXJECT® system firmly by the syringe and pull back the plunger rod slowly to draw the reconstituted TRELSTAR® into the syringe.

5b.



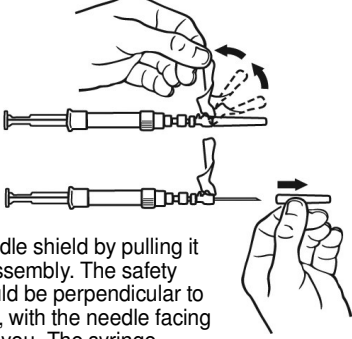
(b) Return the vial to its upright position, and disconnect the vial adapter and vial from the MIXJECT® syringe assembly by turning the plastic cap of the vial adapter clockwise. *Grasp only the plastic cap when removing.*

3.

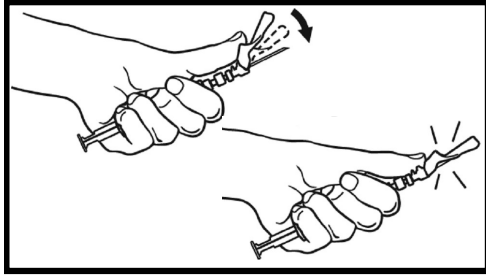


While holding the vial, place your thumb on the plunger rod and push the plunger rod in all the way to transfer the diluent from the pre-filled syringe into the vial. Do not release the plunger rod.

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.*



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

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 pamoate 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 pamoate for injectable suspension) 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 every 3 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 and 11.25 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)	F (%)* (No. of days)
3.75 mg 20 healthy male volunteers	28.43 ± 7.31	1.0 (1.0 - 3.0)	223.15 ± 46.96 ^a	83 (28 d)
11.25 mg 13 prostate cancer patients	38.5 ± 10.5	2.0 (2.0 - 4.0)	2268.0 ± 444.63 ^b	103 (85 d)

* Computed as the mean AUC of the study divided by the mean AUC of healthy volunteers corrected for dose (AUC = 36.1 h·ng/mL; 500 µg IV bolus of triptorelin).

^a AUC (0-28 d), ^b AUC (0-85 d)

Distribution: The volume of distribution of triptorelin following IV administration of 0.5 mg triptorelin was approximately 30L 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.

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).

Special Populations:

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.

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, Renal and Hepatic Impairment) 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 and TRELSTAR 11.25 mg vial supplied with MIXJECT™ Dose Delivery System (with Sterile Water for Injection) at 20 - 25 °C (68 - 77 °F); excursions permitted: 15 - 30 °C (59 - 86 °F).

Store TRELSTAR 3.75 mg and TRELSTAR 11.25 mg vial (without Sterile Water for Injection) at 4 - 25 °C (39 - 77 °F).

No refrigeration necessary. Protect from freezing. Protect from light.

Unused portion of reconstituted TRELSTAR should be discarded immediately.

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 (170 mg), mannitol, USP (85 mg), carboxymethylcellulose sodium, USP (30 mg), and polysorbate 80, USP (2 mg). When 2 mL Sterile Water for Injection is added to the microgranules and mixed, a suspension is formed, which is intended as a single, monthly intramuscular injection.

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 (145 mg), mannitol, USP (85 mg), carboxymethylcellulose sodium, USP (30 mg), and polysorbate 80, USP (2 mg). When 2 mL Sterile Water for Injection is added to the microgranules and mixed, a suspension is formed, which is intended as a single, 3 month intramuscular injection.

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).

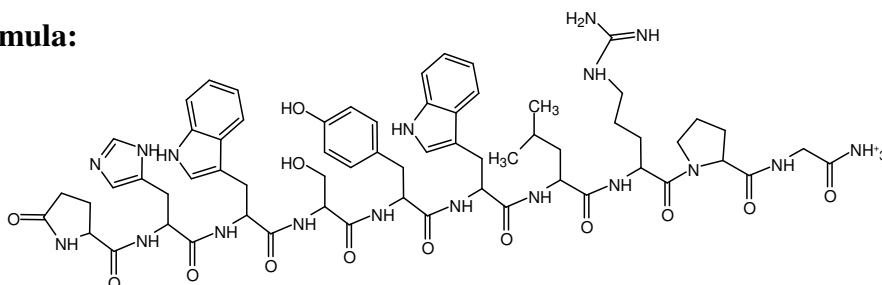
PART II: SCIENTIFIC INFORMATION

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:



• Pamoic acid

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 $[\alpha]_D^{25} = -23.0^\circ \pm 2.5^\circ$
Physicochemical properties:	Soluble in DMSO (660 mg/mL), pyridine (440 mg/mL) and water (60 μ g/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 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)

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 (%)
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)
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 Study with Triptorelin Pamoate

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 Colored. 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.

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

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.

REFERENCES

1. Adamopoulos DA, Nicopoulou S, Kapolla N, Vassilopoulos P, Keramertzanis M: Testicular secretion after pulsatile human menopausal gonadotropin therapy in gonadotropin-releasing hormone agonist desensitized dysspermic men. *Fertil Steril* 62:155-161, 1994.
2. Banik UK, Givner ML. Comparative ovulation-inducing capacity of a synthetic luteinizing hormone-releasing hormone and two analogs in adult rats and mice. *Fertil Steril* 11:1243-1249, 1977.
3. Barron JL, Millar RP, Searle D: Metabolic clearance and plasma half-disappearance time of D-Trp6 and exogenous luteinizing hormone-releasing hormone. *J Clin Endocrinol Metab* 54: 1169-1173, 1982.
4. Boccardo FA, Decensi D, Guarneri A, Rubagotti T, Massa G, Martorana C et al: Long-term results with a long-acting formulation of D-Trp6LH-RH in patients with prostate cancer: an Italian prostatic cancer project study (P.O.N.C.A.P.). *Prostate* 11: 243-255, 1987.
5. Coy DH, Labrie F, Savary M, Coy EJ, Schally AV. LH-releasing activity of potent LH-RH analogs in vitro. *Biochem Biophys Res Commun* 67:576-582, 1975.
6. Coy DH, Vilchez-Martinez JA, Coy EJ, Schally AV. Analogs of luteinizing hormone-releasing hormone with increased biological activity produced by D-amino acid substitutions in position 6. *J Med Chem* 19:423-425, 1976.
7. De Sy WA, De Wild P, De Meyer JM, Casselman J, Desmet R, Renders G, Schelfhout W. Long term experience in the treatment of prostatic cancer with Decapeptyl®, compared to orchiectomy. *Acta Urologica Belgica* 56:581-588, 1986.
8. De Sy WA, De Meyer JM, Casselman J, De Smet R, Renders G, Schelfhout W, De Wild P. A comparative study of a long acting leuteinizing hormone releasing hormone agonist (Decapeptyl®) and orchiectomy in the treatment of advanced prostate cancer. *Acta Urologica Belgica* 54:221-229, 1988.
9. Gonzalez-Barcena D, Perez-Sanchez PL, Graef A, Gomez AM, Barea H, et al. Inhibition of the pituitary-gonadal axis by a single intramuscular administration of D-Trp6-LHRH (Decapeptyl®) in a sustained release formulation in patients with prostatic carcinoma *Prostate* 14: 291-300, 1989.
10. Jacobi GH, Wenderoth UK, Ehrenthal W, v Wallenberg H, Spindler HW, Hohenfellner R: Endocrine and clinical evaluation of 107 patients with advanced prostatic carcinoma under long-term pernasal buserelin or intramuscular Decapeptyl® depot treatment. *Am J Clin Oncol* 11(suppl 1): S36-S43, 1988.
11. Mason-Garcia M, Vigh S, Comaru-Schally AM, Rading TW, Somogyvari-Vigh SA, Horvath J et al. Radioimmunoassay for 6-D-tryptophan analog of luteinizing hormone-releasing

- hormone: measurement of serum levels after administration of long-acting formulation administration. *Proc Natl Acad Sci USA* 82:1547-1551, 1985.
12. Milovanovic SR, Radulovic S, Groot K, Schally AV. Inhibition of growth of PC-82 human prostate cancer line xenografts in nude mice by bombesin antagonist RC-3095 or combination of [D-Trp6]-luteinizing hormone-releasing hormone and somatostatin analog RC-160. *Prostate* 20:269-280, 1992.
 13. Papadopoulos I, Merkel KH, Cramer B, Weissach L. Hodenhistologie nach 6monatiger therapie mit der depotform des LHRH-analogons Decapeptyl®. *Verh Deutsch Geselle Urologie* 38:274-277, 1987.
 14. Parmar H, Edwards L, Phillips RH, Allen L, Lightman SL. Orchiectomy versus long-acting D-Trp-6-LHRH in advanced prostatic cancer. *Br J Urol* 1987;59:248-4
 15. Redding TW, Schally AV. Inhibition of prostate tumor growth in two rat models by chronic administration of [D-Trp6] analogue of luteinizing hormone-releasing hormone. *Proc Natl Acad Sci USA* 78:6509-6512, 1981.
 16. Redding TW, Schally AV, Tice TR, Meyers WE. Long-acting delivery systems for peptides: Inhibition of rat prostate tumors by controlled release of [D-trp6] luteinizing hormone-releasing hormone from injectable microcapsules. *Proc Natl Acad Sci USA* 81:5845-5848, 1984.
 17. Roger M, Duchier J, Lahlou N, Nahoul K, Schally AV: Treatment of prostatic carcinoma with D-Trp-6-LHRH: plasma hormone levels after daily subcutaneous injections and periodic administration of delayed-release preparations. *The Prostate* 7:271-82, 1985.
 18. Schally AV, Redding TW. Somatostatin analogs as adjuncts to agonists of luteinizing hormone-releasing hormone in the treatment of experimental prostate cancer. *Proc Natl Acad Sci USA* 84:7275-7259, 1987.
 19. Schally AV, Redding TW, Comaru-Schally AM. Inhibition of prostate tumors by agonistic and antagonistic analogs of LH-RH. *Prostate* 4:545-552, 1983.
 20. Stoffel-Wagner B, Sommer L, Bidlingmaier F, Klingmiller D: Effects of the gonadotropin-releasing hormone agonist, D-Trp-6-GnRH, on prolactin secretion in healthy young men. *Horm Res* 43:266-272, 1995.
 21. The Veterans Administration Cooperative Urological Research Group. Carcinoma of the Prostate: Treatment Comparisons. *J Urol* 98:516-522, 1967.
 22. Walker KJ, Turkes AO, Nicholson RI, Turkes A, Griffiths K. Therapeutic potential of the LHRH agonist ICI 118630 in the treatment of advanced prostatic carcinoma. *Lancet* 413-145; 20 August, 1983.

PART III: CONSUMER INFORMATION

Pr TRELSTAR™ 3.75 mg

Pr TRELSTAR™ 11.25 mg

Triptorelin Pamoate for Injectable Suspension

This leaflet is part III of a three-part "Product Monograph" published when TRELSTAR 3.75 mg (1 month slow release) and TRELSTAR 11.25 mg (3 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.

ABOUT THIS MEDICATION

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

What the medication is used for:

Your doctor has prescribed TRELSTAR to treat your advanced hormone-dependent prostate cancer.

What it does:

Triptorelin works like a hormone and reduces 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. The duration of your treatment will be determined by your doctor.

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

What the medicinal ingredient is:

Triptorelin pamoate

What the nonmedicinal 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. The powder will be mixed by your doctor with sterile water to make a suspension before injecting it into your muscle. The active ingredient contained in the microgranules will slowly be released from the injection site.

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

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

WARNINGS AND PRECAUTIONS

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 vial
- You have a history of chronic alcohol and/or tobacco use
- You have a history of chronic use of drugs such as anticonvulsants or corticosteroids
- You have kidney and/or liver disease

During treatment, your doctor should routinely give you appropriate physical examinations and laboratory tests.

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 before taking any other drugs, including nonprescription 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

How is TRELSTAR 3.75 mg given?

Usual Dose:

Your doctor will administer one injection of TRELSTAR 3.75 mg, containing 3.75 mg triptorelin, into your muscle on a specified day, generally once every 28 days.

Missed Dose:

If you forget to have TRELSTAR 3.75 mg administered on the specified day, have it administered as soon as you can.

How is TRELSTAR 11.25 mg given?

Usual Dose:

Your doctor will administer one injection of TRELSTAR 11.25 mg, containing 11.25 mg triptorelin, into your muscle on a specified day, generally once every 3 months.

Missed Dose:

If you forget to have TRELSTAR 11.25 mg administered on the specified day, have it administered as soon as you can.

It is very important that your doctor check your progress at regular medical visits. Don't stop your TRELSTAR treatment if you feel better; consult your doctor before you decide to change your treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, TRELSTAR may have, in addition to its beneficial effects, some unwanted effects.

TRELSTAR 3.75 mg treatment, given once a month, or TRELSTAR 11.25 mg treatment, given once every 3 months, results in suppression of your sex hormones. Any effects you experience may be related to this hormone-suppressing action of triptorelin. These effects may include hot flushes, reduction in sex drive, and impotence*. If these 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.

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

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

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	
Common	Difficulty breathing		✓	
	Racing/abnormal heartbeat		✓	
	Rash		✓	
	Infection of the bladder and/or kidneys		✓	
	Difficulty falling asleep		✓	
	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		✓	
Infection of the eye		✓		
Uncommon	Injection site reaction		✓	
	Feeling unwell/uneasy		✓	
	Muscle weakness		✓	
	Infection of the nose		✓	
	Abnormal skin changes		✓	
	Blood in the urine		✓	

* Are considered expected side effects related to the hormone-suppressing action of TRELSTAR.

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

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	
Common	Inability to develop and maintain an erection*	✓		
	Reduced sex drive*	✓		
	Hot flushes*	✓		
	Reduced size of genitalia		✓	
	Pain		✓	
	Bone pain		✓	
	Leg pain		✓	
	Injection site pain		✓	
	Back pain		✓	
	Breast pain		✓	
	Joint pain		✓	
	Chest pain		✓	
	Muscle pain		✓	
	Eye pain		✓	
	Headache		✓	
	High blood pressure		✓	
	Difficult/painful urination		✓	
	Nausea		✓	
	Tiredness		✓	
	Dizziness		✓	
Swelling in the limbs		✓		
Constipation		✓		
Diarrhea		✓		
Depression		✓		
Loss of appetite		✓		

(continued)

HOW TO STORE IT

Store TRELSTAR 3.75 mg and TRELSTAR 11.25 mg vial supplied with MIXJECT™ Dose Delivery System (with Sterile Water for Injection) at 20-25°C (68-77°F); excursions permitted: 15 – 30°C (59-86°F).

Store TRELSTAR 3.75 mg and TRELSTAR 11.25 mg (without Sterile Water for Injection) at 4-25°C (39-77°F).

No refrigeration is necessary. Protect from freezing. Protect from light.

Keep out of reach of children.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
Canadian Adverse Reaction Monitoring Program
(CADRMP)
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found by contacting the Distributor, Paladin Labs Inc., at 1-888-550-6060.

This leaflet was prepared by:
Watson Laboratories, Inc.
Corona, California
USA 92880

Distributed in Canada by:
Paladin Labs Inc.
Montreal, Quebec H4P 2T4

Date of Preparation: November 24, 2009.