HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRELSTAR safely and effectively. See full prescribing information for TRELSTAR.

TRELSTAR® (triptorelin pamoate for injectable suspension), for intramuscular use
Initial U.S. Approval: 2000

----------RECENT MAJOR CHANGES ----------
Warnings and Precautions, Embryo-Fetal Toxicity (5.9) 12/2018

----------INDICATIONS AND USAGE ----------
TRELSTAR is a gonadotropin releasing hormone (GnRH) agonist indicated for the palliative treatment of advanced prostate cancer. (*1*)

----------DOSAGE AND ADMINISTRATION ----------
TRELSTAR is administered as a single intramuscular injection in either buttock. Due to different release characteristics, the dosage strengths are not additive and must be selected based upon the desired dosing schedule. (*2.1*)

- 3.75 mg every 4 weeks. (*2.1*)
- 11.25 mg every 12 weeks. (*2.1*)
- 22.5 mg every 24 weeks. (*2.1*)

----------DOSAGE FORMS AND STRENGTHS----------
Injectable suspension: 3.75 mg, 11.25 mg, 22.5 mg. (*3*)

----------CONTRAINDICATIONS ----------

- Known hypersensitivity to triptorelin or any other component of the product, or other GnRH agonists or GnRH. (*4*)

----------WARNINGS AND PRECAUTIONS ----------

- Hypersensitivity: Anaphylactic shock, hypersensitivity, and angioedema have been reported. In the event of a reaction, discontinue TRELSTAR and initiate appropriate medical management. (*5.1*)
- Tumor Flare: Transient increase in serum testosterone levels can occur within the first few weeks of treatment. This may worsen prostate cancer and result in spinal cord compression and urinary tract obstruction. Monitor patients at risk and manage as appropriate. (*5.2* and *5.3*)
- Effect on QT/QTc Interval: Androgen deprivation therapy may prolong the QT interval. Consider risks and benefits. (*5.4*)
- Hyperglycemia and Diabetes: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH analogs. Monitor blood glucose level and manage according to current clinical practice. (*5.5*)
  Cardiovascular Diseases: Increased risk of myocardial infarction, sudden cardiac death and stroke has been reported in men. Monitor for cardiovascular disease and manage according to current clinical practice. (*5.6*)

----------ADVERSE REACTIONS ----------

- 3.75 mg: The most common adverse reactions (≥ 5%) during TRELSTAR 3.75 mg therapy included hot flushes, skeletal pain, impotence, and headache. (*6.1*)
- 11.25 mg: The most common adverse reactions (≥ 5%) during TRELSTAR 11.25 mg therapy included hot flushes, skeletal pain, headache, edema in legs, and leg pain. (*6.1*)
- 22.5 mg: The most common adverse reactions (≥ 5%) during TRELSTAR 22.5 mg therapy included hot flushes, erectile dysfunction, and testicular atrophy. (*6.1*)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: TRELSTAR can cause fetal harm. (*5.9, 8.1*)
- Females and males of reproductive potential: TRELSTAR may impair fertility. (*8.3*)

----------DRUG INTERACTIONS ----------
None. (*7*)

See *17* for PATIENT COUNSELING INFORMATION

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS *

* Sections or subsections omitted from the full prescribing information are not listed

---

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TRELSTAR is indicated for the palliative treatment of advanced prostate cancer [*see Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

TRELSTAR m*ust be administered under the supervision of a physician.*

TRELSTAR is administered by a single intramuscular injection in either buttock. Dosing schedule depends on the product strength selected (Table 1). The lyophilized microgranules are to be reconstituted in ***sterile water***. ***No other diluent should be used.***

Table 1. TRELSTAR Recommended Dosing

Dosage	3.75 mg	11.25 mg	22.5 mg
Recommended dose	1 injection every 4 weeks	1 injection every 12 weeks	1 injection every 24 weeks

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

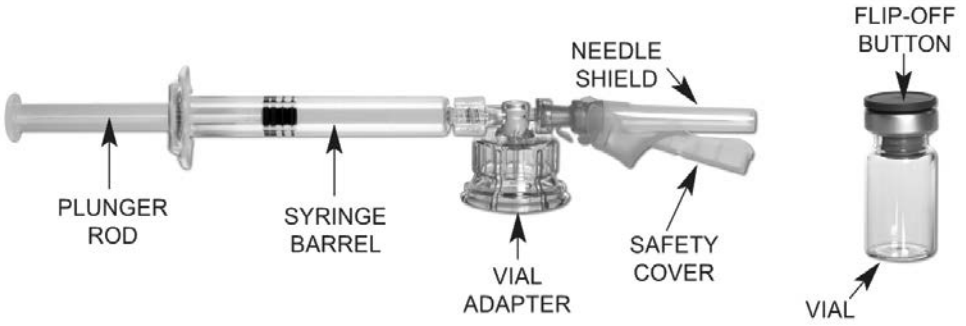
The suspension should be administered immediately after reconstitution.

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.2 Reconstitution Instructions for TRELSTAR with MIXJECT SYSTEM

Please read the instructions completely before you begin.



MIXJECT Preparation

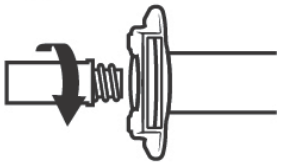
Wash your hands with soap and hot water and put on gloves immediately prior to preparing the injection. Place the sealed tray on a clean, flat surface that is covered with a sterile pad or cloth. Peel the cover away from the tray and remove the MIXJECT components and the TRELSTAR vial. Remove the Flip-Off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

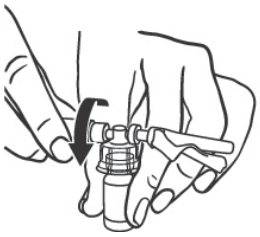
Peel the cover away from the blister pack containing the vial adapter. *Do not remove the vial adapter from the blister pack.* Place the blister pack containing the vial adapter firmly on the vial top, piercing the vial. Push down gently until you feel it snap in place. Remove the blister pack from the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

2a.



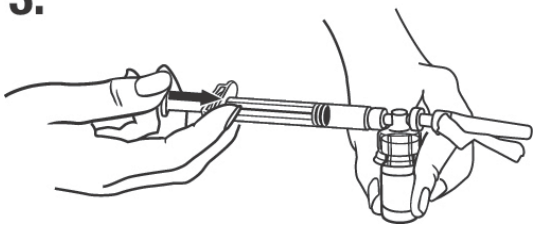
(a) Screw the plunger rod into the barrel end of the syringe. Remove the cap from the syringe barrel.

2b.



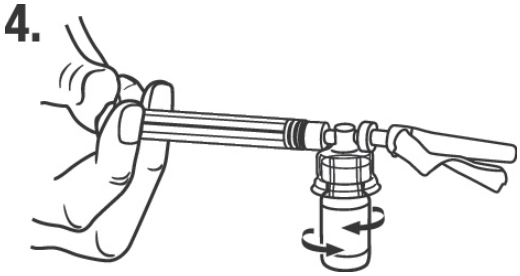
(b) Connect the syringe to the vial adapter by screwing it clockwise into the opening on the side of the vial adapter. Be sure to gently twist the syringe until it stops turning to ensure a tight connection.

3.



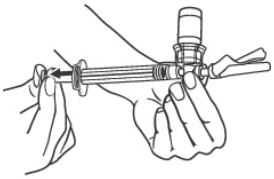
While holding the vial, place your thumb on the plunger rod and push the plunger rod in all the way to transfer the diluent from the pre-filled syringe into the vial. Do not release the plunger rod.

4.

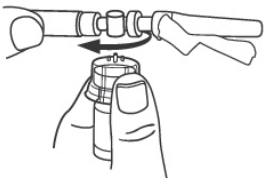


Keeping the plunger rod depressed, gently swirl the vial so that the diluent rinses the sides of the vial. This will ensure complete mixing of TRELSTAR and the sterile water diluent. The suspension will now have a milky appearance. In order to avoid separation of the suspension, proceed to the next steps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

5a.



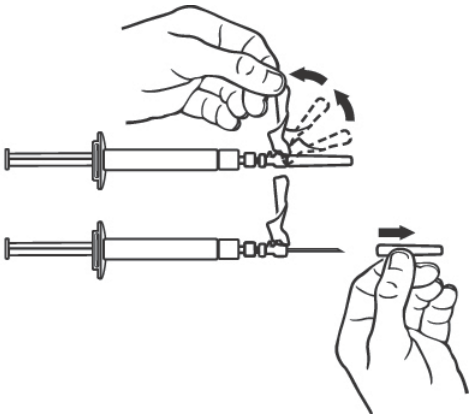
5b.



(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.

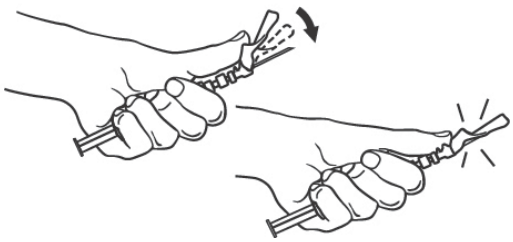
(b) Return the vial to its upright position, and disconnect the vial adapter and vial from the MIXJECT syringe assembly by turning the plastic cap of the vial adapter clockwise.
Grasp only the plastic cap when removing.

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.



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

3 DOSAGE FORMS AND STRENGTHS

Injectable suspension: 3.75 mg, 11.25 mg, 22.5 mg.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

TRELSTAR is contraindicated in individuals with a known hypersensitivity to triptorelin or any other component of the product, or other GnRH agonists or GnRH [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Anaphylactic shock, hypersensitivity, and angioedema related to triptorelin administration have been reported. In the event of a hypersensitivity reaction, therapy with TRELSTAR should be discontinued immediately and the appropriate supportive and symptomatic care should be administered.

5.2 Transient Increase in Serum Testosterone

Initially, triptorelin, like other GnRH agonists, causes a transient increase in serum testosterone levels. As a result, isolated cases of worsening of signs and symptoms of prostate cancer during the first weeks of treatment have been reported with GnRH agonists. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, hematuria, or urethral or bladder outlet obstruction [*see Clinical Pharmacology (12.2)*].

5.3 Metastatic Vertebral Lesions and Urinary Tract Obstruction

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

Patients with metastatic vertebral lesions and/or with upper or lower urinary tract obstruction should be closely observed during the first few weeks of therapy.

5.4 Effect on QT/QTc Interval

Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

5.5 Hyperglycemia and Diabetes

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

5.6 Cardiovascular Diseases

Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

5.7 Laboratory Tests

Response to TRELSTAR should be monitored by measuring serum levels of testosterone periodically or as indicated.

5.8 Laboratory Test Interactions

Chronic or continuous administration of triptorelin in therapeutic doses results in suppression of pituitary-gonadal axis. Diagnostic tests of the pituitary-gonadal function conducted during treatment and after cessation of therapy may therefore be misleading.

5.9 Embryo-Fetal Toxicity

Based on findings from animal studies and mechanism of action, TRELSTAR can cause fetal harm when administered to a pregnant woman *[Clinical Pharmacology (12.1)]*. In animal developmental and reproductive toxicology studies, daily administration of triptorelin to pregnant rats during the period of organogenesis caused maternal toxicity and embryo-fetal toxicities, including loss of pregnancy, at doses as low as 0.2, 0.8, and 8 times the estimated human daily dose based on body surface area. Advise pregnant patients and females of reproductive potential of the potential risk to the fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of the three TRELSTAR formulations was evaluated in clinical trials involving patients with advanced prostate cancer. Mean testosterone levels increased above baseline during the first week following the initial injection, declining thereafter to baseline levels or below by the end of the second week of treatment. The transient increase in testosterone levels may be associated with temporary worsening of disease signs and symptoms, including bone pain, neuropathy, hematuria, and urethral or bladder outlet obstruction. Isolated cases of spinal cord compression with weakness or paralysis of the lower extremities have occurred [*see Warnings and Precautions (5.3)*].

Adverse reactions reported for each of the three TRELSTAR formulations in the clinical trials, are presented in Table 2, Table 3, and Table 4. Often, causality is difficult to assess in patients with metastatic prostate cancer. The majority of adverse reactions related to triptorelin are a result of its pharmacological action, i.e., the induced variation in serum testosterone levels, either an increase in testosterone at the initiation of treatment, or a decrease in testosterone once castration is achieved. Local reactions at the injection site or allergic reactions may occur.

The following adverse reactions were reported to have a possible or probable relationship to therapy as

ascribed by the treating physician in at least 1% of patients receiving TRELSTAR 3.75 mg.

Table 2. TRELSTAR 3.75 mg: Treatment-Related Adverse Reactions Reported by 1% or More of Patients During Treatment

Adverse Reactions*	TRELSTAR 3.75 mg N = 140	
	N	%
Application Site Disorders		
Injection site pain	5	3.6
Body as a Whole		
Hot flush	82	58.6
Pain	3	2.1
Leg pain	3	2.1
Fatigue	3	2.1
Cardiovascular Disorders		
Hypertension	5	3.6
Central and Peripheral Nervous System Disorders		
Headache	7	5.0
Dizziness	2	1.4
Gastrointestinal Disorders		
Diarrhea	2	1.4
Vomiting	3	2.1
Musculoskeletal System Disorders		
Skeletal pain	17	12.1
Psychiatric Disorders		
Insomnia	3	2.1
Impotence	10	7.1
Emotional lability	2	1.4
Red Blood Cell Disorders		
Anemia	2	1.4
Skin and Appendages Disorders		
Pruritus	2	1.4
Urinary System Disorders		
Urinary tract infection	2	1.4
Urinary retention	2	1.4

* Adverse reactions for TRELSTAR 3.75 mg are coded using the WHO Adverse Reactions

Terminology (WHOART)

The following adverse reactions were reported to have a possible or probable relationship to therapy as ascribed by the treating physician in at least 1% of patients receiving TRELSTAR 11.25 mg.

Table 3. TRELSTAR 11.25 mg: Treatment-Related Adverse Reactions Reported by 1% or More of Patients During Treatment

Adverse Reactions*	TRELSTAR 11.25 mg N = 174	
	N	%
Application Site		
Injection site pain	7	4.0
Body as a Whole		
Hot flush	127	73.0
Leg pain	9	5.2
Pain	6	3.4
Back pain	5	2.9
Fatigue	4	2.3
Chest pain	3	1.7
Asthenia	2	1.1
Peripheral edema	2	1.1
Cardiovascular Disorders		
Hypertension	7	4.0
Dependent edema	4	2.3
Central and Peripheral Nervous System Disorders		
Headache	12	6.9
Dizziness	5	2.9
Leg cramps	3	1.7
Endocrine		
Breast pain	4	2.3
Gynecomastia	3	1.7
Gastrointestinal Disorders		
Nausea	5	2.9
Constipation	3	1.7
Dyspepsia	3	1.7
Diarrhea	2	1.1
Abdominal pain	2	1.1
Liver and Biliary System		
Abnormal hepatic function	2	1.1

Metabolic and Nutritional Disorders		
Edema in legs	11	6.3
Increased alkaline phosphatase	3	1.7
Musculoskeletal System Disorders		
Skeletal pain	23	13.2
Arthralgia	4	2.3
Myalgia	2	1.1
Psychiatric Disorders		
Decreased libido	4	2.3
Impotence	4	2.3
Insomnia	3	1.7
Anorexia	3	1.7
Respiratory System Disorders		
Coughing	3	1.7
Dyspnea	2	1.1
Pharyngitis	2	1.1
Skin and Appendages		
Rash	3	1.7
Urinary System Disorders		
Dysuria	8	4.6
Urinary retention	2	1.1
Vision Disorders		
Eye pain	2	1.1
Conjunctivitis	2	1.1

* Adverse reactions for TRELSTAR 11.25 mg are coded using the WHO Adverse Reactions Terminology (WHOART)

The following adverse reactions occurred in at least 5% of patients receiving TRELSTAR 22.5 mg. The table includes all reactions whether or not they were ascribed to TRELSTAR by the treating physician. The table also includes the incidence of these adverse reactions that were considered by the treating physician to have a reasonable causal relationship or for which the relationship could not be assessed.

Table 4. TRELSTAR 22.5 mg: Adverse Reactions Reported by 5% or More of Patients During Treatment

Adverse Reactions*	TRELSTAR 22.5 mg N = 120			
	Treatment-Emergent		Treatment-Related	
	N	%	N	%
General Disorders and Administration Site Conditions				
Edema peripheral	6	5.0	0	0
Infections and Infestations				
Influenza	19	15.8	0	0
Bronchitis	6	5.0	0	0
Endocrine				
Diabetes Mellitus/Hyperglycemia	6	5.0	0	0
Musculoskeletal and Connective Tissue Disorders				
Back pain	13	10.8	1	0.8
Arthralgia	9	7.5	1	0.8
Pain in extremity	9	7.5	1	0.8
Nervous System Disorders				
Headache	9	7.5	2	1.7
Psychiatric Disorders				
Insomnia	6	5.0	1	0.8
Renal and Urinary Disorders				
Urinary tract infection	14	11.6	0	0
Urinary retention	6	5.0	0	0
Reproductive System and Breast Disorders				
Erectile dysfunction	12	10.0	12	10.0
Testicular atrophy	9	7.5	9	7.5
Vascular Disorders				
Hot flush	87	72.5	86	71.7
Hypertension	17	14.2	1	0.8

* Adverse reactions for TRELSTAR 22.5 mg are coded using the Medical Dictionary for Regulatory Activities (MedDRA)

Changes in Laboratory Values During Treatment

The following abnormalities in laboratory values not present at baseline were observed in 10% or more of patients:

TRELSTAR 3.75 mg: There were no clinically meaningful changes in laboratory values detected during therapy.

TRELSTAR 11.25 mg: Decreased hemoglobin and RBC count and increased glucose, BUN, SGOT, SGPT, and alkaline phosphatase at the Day 253 visit.

TRELSTAR 22.5 mg: Decreased hemoglobin and increased glucose and hepatic transaminases were detected during the study. The majority of the changes were mild to moderate.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of gonadotropin releasing hormone agonists. 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.

During postmarketing surveillance, 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.

During postmarketing experience, convulsions, interstitial lung disease, and thromboembolic events including, but not limited to, pulmonary emboli, cerebrovascular accident, myocardial infarction, deep venous thrombosis, transient ischemic attack, and thrombophlebitis have been reported.

7 DRUG INTERACTIONS

No drug-drug interaction studies involving triptorelin have been conducted.

Human pharmacokinetic data with triptorelin suggest that C-terminal fragments produced by tissue degradation are either degraded completely within tissues or are rapidly degraded further in plasma, or cleared by the kidneys. Therefore, hepatic microsomal enzymes are unlikely to be involved in triptorelin metabolism. However, in the absence of relevant data and as a precaution, hyperprolactinemic drugs should not be used concomitantly with triptorelin since hyperprolactinemia reduces the number of pituitary GnRH receptors.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal studies and mechanism of action, TRELSTAR can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Expected hormonal changes that occur with TRELSTAR treatment increase the risk for pregnancy loss. In animal developmental and reproductive toxicology studies, daily administration of triptorelin to pregnant rats during the period of organogenesis caused maternal toxicity and embryo-fetal toxicities, including loss of pregnancy, at doses as low as 0.2, 0.8, and 8 times the estimated human daily dose based on body surface area. Advise pregnant patients and females of reproductive potential of the potential risk to the fetus.

Data

Animal Data

Studies in pregnant rats administered triptorelin at doses of 2, 10, and 100 mcg/kg/day (approximately equivalent to 0.2, 0.8, and 8 times the estimated human daily dose based on body surface area) during the period of organogenesis demonstrated maternal toxicity and embryo-fetal toxicities. Embryo-fetal toxicities consisted of pre-implantation loss, increased resorption, and reduced mean number of viable fetuses at the high dose. Teratogenic effects were not observed in viable fetuses in rats or mice. Doses administered to mice were 2, 20, and 200 mcg/kg/day (approximately equivalent to 0.1, 0.7, and 7 times the estimated human daily dose based on body surface area).

8.2 Lactation

The safety and efficacy of TRELSTAR have not been established in females. There are no data on the presence of triptorelin in human milk, the effects of the drug on milk production, or the effects of the drug on the breastfed child. Because of the potential for serious adverse reactions in a breastfed child from TRELSTAR, a decision should be made to either discontinue breastfeeding, or discontinue the drug taking into account the importance of the drug to the mother.

8.3 Females and Males of Reproductive Potential

Infertility

Males

Based on mechanism of action, TRELSTAR may impair fertility in males of reproductive potential *[see Clinical Pharmacology (12.1)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Prostate cancer occurs primarily in an older population. Clinical studies with TRELSTAR have been conducted primarily in patients ≥ 65 years [*see Clinical Pharmacology (12.3) and Clinical Studies (14)*].

8.6 Renal Impairment

Subjects with renal impairment had higher exposure than young healthy males [*see Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

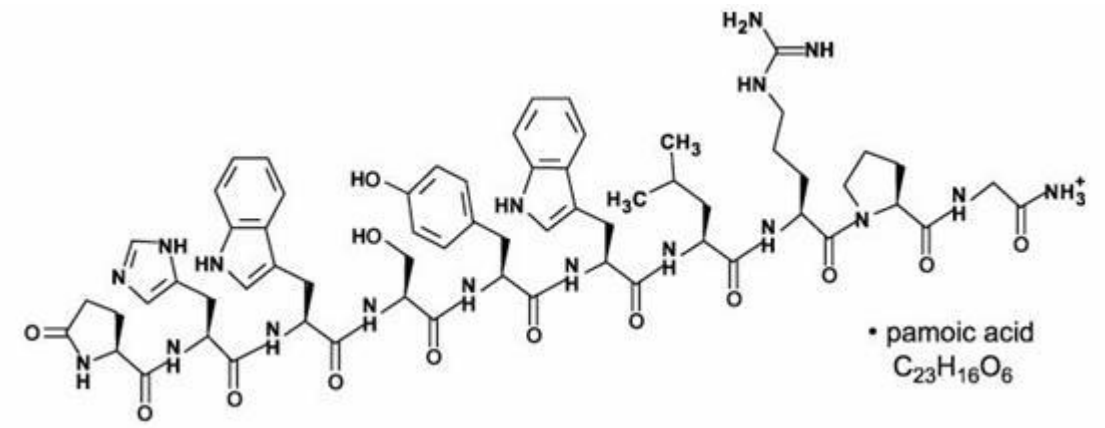
Subjects with hepatic impairment had higher exposure than young healthy males [*see Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

There is no experience of overdosage in clinical trials. In single dose toxicity studies in mice and rats, the subcutaneous LD_{50} of triptorelin was 400 mg/kg in mice and 250 mg/kg in rats, approximately 500 and 600 times, respectively, the estimated monthly human dose based on body surface area. If overdosage occurs, therapy should be discontinued immediately and the appropriate supportive and symptomatic treatment administered.

11 DESCRIPTION

TRELSTAR is a white to slightly yellow lyophilized cake. When reconstituted, TRELSTAR has a milky appearance. It contains a pamoate salt of triptorelin, a synthetic decapeptide agonist analog of gonadotropin releasing hormone (GnRH). The chemical name of triptorelin pamoate is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycine amide (pamoate salt). The empirical formula is $C_{64}H_{82}N_{18}O_{13} \cdot C_{23}H_{16}O_6$ and the molecular weight is 1699.9. The structural formula is:



Structural formula for TRELSTAR (triptorelin pamoate).

The TRELSTAR products are sterile, lyophilized biodegradable microgranule formulations supplied as single dose vials. Refer to Table 5 for the composition of each TRELSTAR product.

Table 5. TRELSTAR Composition

Ingredients	**TRELSTAR 3.75 mg**	**TRELSTAR 11.25 mg**	**TRELSTAR 22.5 mg**
triptorelin pamoate (base units)	3.75 mg	11.25 mg	22.5 mg
poly-*d*,*l*-lactide-co-glycolide	138 mg	120 mg	183 mg
mannitol, USP	71 mg	74 mg	74 mg
carboxymethylcellulose sodium, USP	25 mg	26 mg	26 mg
polysorbate 80, NF	1.7 mg	1.7 mg	1.7 mg

When 2 mL sterile water is added to the vial containing TRELSTAR and mixed, a suspension is formed which is intended as an intramuscular injection. TRELSTAR is available in a vial plus a MIXJECT vial adapter, and a separate pre-filled syringe that contains sterile water for injection, USP, 2 mL, pH 6 to 8.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Triptorelin is a synthetic decapeptide agonist analog of gonadotropin releasing hormone (GnRH). Comparative *in vitro* studies showed that triptorelin was 100-fold more active than native GnRH in stimulating luteinizing hormone release from monolayers of dispersed rat pituitary cells in culture and 20-fold more active than native GnRH in displacing ^{125}I-GnRH from pituitary receptor sites. In animal studies, triptorelin pamoate was found to have 13−fold higher luteinizing hormone-releasing activity and 21-fold higher follicle-stimulating hormone-releasing activity compared to the native GnRH.

12.2 Pharmacodynamics

Following the first administration, there is a transient surge in circulating levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and estradiol [*see Adverse Reactions (6)*]. After chronic and continuous administration, usually 2 to 4 weeks after initiation of therapy, a sustained decrease in LH and FSH secretion and marked reduction of testicular steroidogenesis are observed. A reduction of serum testosterone concentration to a level typically seen in surgically castrated men is obtained. Consequently, the result is that tissues and functions that depend on these hormones for maintenance become quiescent. These effects are usually reversible after cessation of therapy.

Following a single intramuscular injection of TRELSTAR:

TRELSTAR 3.75 mg: serum testosterone levels first increased, peaking on Day 4, and declined thereafter to low levels by Week 4 in healthy male volunteers.

TRELSTAR 11.25 mg: serum testosterone levels first increased, peaking on Days 2 – 3, and declined thereafter to low levels by Weeks 3 – 4 in men with advanced prostate cancer.

TRELSTAR 22.5 mg: serum testosterone levels first increased, peaking on Day 3, and declined thereafter to low levels by Weeks 3 – 4 in men with advanced prostate cancer.

12.3 Pharmacokinetics

Results of pharmacokinetic investigations conducted in healthy men indicate that after intravenous bolus administration, triptorelin is distributed and eliminated according to a 3-compartment model and corresponding half-lives are approximately 6 minutes, 45 minutes, and 3 hours.

Absorption

Following a single intramuscular injection of TRELSTAR to patients with prostate cancer, mean peak serum concentrations of 28.4 ng/mL, 38.5 ng/mL, and 44.1 ng/mL occurred in 1 to 3 hours after the 3.75 mg, 11.25 mg, and 22.5 mg formulations, respectively.

Triptorelin did not accumulate over 9 months (3.75 mg and 11.25 mg) or 12 months (22.5 mg) of treatment.

Distribution

The volume of distribution following a single intravenous bolus dose of 0.5 mg of triptorelin peptide was 30 – 33 L in healthy male volunteers. There is no evidence that triptorelin, at clinically relevant concentrations, binds to plasma proteins.

Elimination

Metabolism

The metabolism of triptorelin in humans is unknown, but is unlikely to involve hepatic microsomal enzymes (cytochrome P-450). The effect of triptorelin on the activity of other drug metabolizing enzymes is also unknown. Thus far, no metabolites of triptorelin have been identified. Pharmacokinetic data suggest that C-terminal fragments produced by tissue degradation are either completely degraded in the tissues, or rapidly degraded in plasma, or cleared by the kidneys.

Excretion

Triptorelin is eliminated by both the liver and the kidneys. Following intravenous administration of 0.5 mg triptorelin peptide to six 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 nonrenal clearance of triptorelin (patient anuric, $CI_{creat} = 0$) was 76.2 mL/min, thus indicating that the nonrenal elimination of triptorelin is mainly dependent on the liver.

Special Populations

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 150 mL/min) indicate that triptorelin was eliminated twice as fast in this young population as compared with 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 [*see Use in Specific Populations (8.6) and (8.7)*].

Pediatric

TRELSTAR has not been evaluated in patients less than 18 years of age [*see Use in Specific Populations (8.4)*].

Hepatic and Renal Impairment

After an intravenous bolus injection of 0.5 mg triptorelin, the two distribution half-lives were unaffected by renal and hepatic impairment. However, renal insufficiency led to a decrease in total triptorelin clearance proportional to the decrease in creatinine clearance as well as increases in volume of distribution and consequently, an increase in elimination half-life (see Table 6). In subjects with hepatic insufficiency, a decrease in triptorelin clearance was more pronounced than that observed with renal insufficiency. Due to minimal increases in the volume of distribution, the elimination half-life in subjects with hepatic insufficiency was similar to subjects with renal insufficiency. Subjects with renal or hepatic impairment had 2- to 4-fold higher exposure (AUC values) than young healthy males [*see Use in Specific Populations (8.6) and (8.7)*].

Table 6. Pharmacokinetic Parameters (Mean ± SD) in Healthy Volunteers and Special Populations Following an IV Bolus Injection of 0.5 mg Triptorelin

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In rats, triptorelin doses of 120, 600, and 3000 mcg/kg given every 28 days (approximately 0.3, 2, and 8 times the human monthly dose based on body surface area) resulted in increased mortality with a drug treatment period of 13 – 19 months. The incidences of benign and malignant pituitary tumors and histiosarcomas were increased in a dose-related manner. No oncogenic effect was observed in mice administered triptorelin for 18 months at doses up to 6000 mcg/kg every 28 days (approximately 8 times the human monthly dose based on body surface area).

Mutagenicity studies performed with triptorelin using bacterial and mammalian systems (*in vitro* Ames test and chromosomal aberration test in CHO cells and an *in vivo* mouse micronucleus test) provided no evidence of mutagenic potential.

After 60 days of subcutaneous treatment followed by a minimum of four estrus cycles prior to mating, triptorelin, at doses of 2, 20, and 200 mcg/kg/day in saline (approximately 0.2, 2, and 16 times the estimated human daily dose based on body surface area) or 2 monthly injections as slow release microspheres (~20 mcg/kg/day), had no effect on the fertility or general reproductive function of female rats.

No studies were conducted to assess the effect of triptorelin on male fertility.

14 CLINICAL STUDIES

TRELSTAR 3.75 mg

TRELSTAR 3.75 mg was studied in a randomized, active control trial of 277 men with advanced prostate cancer. The clinical trial population consisted of 59.9% Caucasian, 39.3% Black, and 0.8% Other. There was no difference observed with triptorelin response between racial groups. Men were between 47 and 89 years of age (mean = 71 years). Patients received either TRELSTAR 3.75 mg (N = 140) or an approved GnRH agonist monthly for 9 months. The primary efficacy endpoints were both achievement of castration by Day 29 and maintenance of castration from Day 57 through Day 253.

Castration levels of serum testosterone (≤ 1.735 nmol/L; equivalent to 50 ng/dL) in patients treated with TRELSTAR 3.75 mg were achieved at Day 29 in 125 of 137 (91.2%) patients and at Day 57 in 97.7% of patients. Maintenance of castration levels of serum testosterone from Day 57 through Day 253 was found in 96.2% of patients treated with TRELSTAR 3.75 mg.

The presence of an acute-on-chronic flare phenomenon was also studied as a secondary efficacy endpoint. Serum LH levels were measured at 2 hours after repeat TRELSTAR 3.75 mg administration on Days 85 and 169. One hundred twenty-four of the 126 evaluable patients (98.4%) on Day 85 had a serum LH level of ≤ 1.0 IU/L at 2 hours after dosing, indicating desensitization of the pituitary gonadotroph receptors.

TRELSTAR 11.25 mg

TRELSTAR 11.25 mg was studied in a randomized, active control trial of 346 men with advanced prostate cancer. The clinical trial population consisted of 48% Caucasian, 38% Black, and 15% Other. There was no difference observed with triptorelin response between racial groups. Men were between 45 and 96 years of age (mean = 71 years). Patients received either TRELSTAR 11.25 mg (N = 174) every 12 weeks for a total of up to 3 doses (maximum treatment period of 253 days) or TRELSTAR 3.75 mg (N = 172) every 28 days for a total of up to 9 doses. The primary efficacy endpoints were both achievement of castration by Day 29 and maintenance of castration from Day 57 through Day 253.

Castration levels of serum testosterone (≤ 1.735 nmol/L; equivalent to 50 ng/dL) were achieved at Day 29 in 167 of 171 (97.7%) patients treated with TRELSTAR 11.25 mg, and maintenance of castration levels of serum testosterone from Day 57 through Day 253 was found in 94.4% of patients treated with TRELSTAR 11.25 mg.

TRELSTAR 22.5 mg

TRELSTAR 22.5 mg was studied in a non-comparative trial of 120 men with advanced prostate cancer. The clinical trial population consisted of 64% Caucasian, 23% Black, and 13% Other, with a mean age of 71.1 years (range 51-93). Patients received TRELSTAR 22.5 mg (N = 120) every 24 weeks for a total of 2 doses (maximum treatment period of 337 days). The primary efficacy endpoints included achievement of castration by Day 29 and maintenance of castration from Day 57 through Day 337.

Castration levels of serum testosterone (≤ 1.735 nmol/L; equivalent to 50 ng/dL) were achieved at Day 29 in 97.5% (117 of 120) of patients treated with TRELSTAR 22.5 mg. Castration was maintained in 93.3% of patients in the period from Day 57 to Day 337.

A summary of the clinical studies for TRELSTAR is provided in Table 7.

Table 7. Summary of TRELSTAR Clinical Studies

Product Strength	**3.75 mg**	**11.25 mg**	**22.5 mg**
Number of Patients	137	171	120
Treatment Schedule	every 4 weeks	every 12 weeks	every 24 weeks
Duration of Study	253 days	253 days	337 days
Castration Rate* on Day 29, % (n/N)	91.2% (125/137)	97.7% (167/171)	97.5% (117/120)
Rate of Castration Maintenance† from Days 57 – 253, %	96.2%	94.4%	not applicable
Rate of Castration Maintenance from Days 57 – 337, % (n/N)	not applicable	not applicable	93.3% (112/120)‡

* Maintenance of castration was calculated using a frequency distribution.
† Cumulative maintenance of castration was calculated using a survival analysis (Kaplan-Meier) technique.
‡ Calculation includes 5 patients who discontinued the study but who had castrate levels of testosterone prior to discontinuation.

16 HOW SUPPLIED/STORAGE AND HANDLING

TRELSTAR is supplied in the TRELSTAR MIXJECT single-dose delivery system consisting of a vial with a Flip-Off seal containing sterile lyophilized triptorelin pamoate microgranules incorporated in a biodegradable copolymer of lactic and glycolic acids, a MIXJECT vial adapter, and a pre-filled syringe containing sterile water for injection, USP, 2 mL, pH 6 to 8.5.

TRELSTAR 3.75 mg –NDC 0023-5902-04 (TRELSTAR 3.75 mg with MIXJECT single-dose delivery system)

TRELSTAR 11.25 mg –NDC 0023-5904-12 (TRELSTAR 11.25 mg with MIXJECT single-dose delivery system)

TRELSTAR 22.5 mg –NDC 0023-5906-23 (TRELSTAR 22.5 mg with MIXJECT single-dose delivery system)

Storage
Store at 20-25°C (68-77°F). [See USP Controlled Room Temperature.] Do not freeze TRELSTAR with MIXJECT.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity

- Inform patients that if they have experienced hypersensitivity with other GnRH agonist drugs like TRELSTAR, TRELSTAR is contraindicated *[see Contraindications (4)]*.

Tumor Flare

- Inform patients that TRELSTAR can cause tumor flare during the first weeks of treatment. Inform patients that the increase in testosterone can cause an increase in urinary symptoms or pain. Advise patients to contact their healthcare provider if uretral obstruction, spinal cord compression, paralysis, or new or worsened symptoms occur after beginning TRELSTAR treatment *[see Warnings and Precautions (5.2)]*.

Hyperglycemia and Diabetes

- Advise patients that there is an increased risk of hyperglycemia and diabetes with TRELSTAR therapy. Inform patients that periodic monitoring for hyperglycemia and diabetes is required when being treated with TRELSTAR *[see Warnings and Precautions (5.5)]*.

Cardiovascular Disease

- Inform patients that there is an increased risk of myocardial infarction, sudden cardiac death, and stroke with TRELSTAR treatment. Advise patients to immediately report signs and symptoms associated with these events to their healthcare provider for evaluation *[see Warnings and Precautions (5.6)]*.

Urogenital Disorders

- Advise patients that TRELSTAR may cause impotence.

Infertility

- Inform patients that TRELSTAR may cause infertility *[(see Use In Specific Populations (8.3)]*.

Continuation of TRELSTAR Treatment

- Inform patients that TRELSTAR is usually continued, often with additional medication, after the development of metastatic castration-resistant prostate cancer *[see Dosage and Administration (2.1)]*.

For all medical inquiries contact:
Allergan
Medical Communications
1-800-678-1605

Distributed By:
Allergan USA, Inc.
Madison, NJ 07940

Manufactured By:

Debiopharm Research & Manufacturing SA
CH-1920 Martigny, Switzerland

MIXJECT is manufactured by:
West Pharma. Services IL, Ltd.
Ra'anana, Israel

The pre-filled syringe containing sterile water for injection is manufactured by:
Baxter Pharmaceutical Solutions, LLC
927 South Curry Pike
Bloomington, Indiana 47403

V2.0USPI5902