**DESCRIPTION**

TRELSTAR™ LA contains a pamoate salt of triptorelin, and triptorelin is a synthetic decapeptide agonist analog of luteinizing hormone releasing hormone (LHRH or GnRH) with greater potency than the naturally occurring LHRH. The chemical name of triptorelin pamoate is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-lysyl-L-arginyl-L-prolylglycine amide (pamoate salt); the empirical formula is C₆₄H₈₂N₁₈O₁₃ · C₂₃H₁₆O₆ and the molecular weight is 1699.9. The structural formula is shown below.

![Structural formula of triptorelin pamoate](image)

TRELSTAR™ LA is a sterile, lyophilized biodegradable microgranule formulation supplied as a single-dose vial containing triptorelin pamoate (11.25 mg as the peptide base), 145 mg poly (d,l-lactide-co-glycolide), 85 mg mannitol USP, 30 mg carboxymethylcellulose sodium USP, 2 mg polysorbate 80 NF. When 2 mL sterile water for injection, USP (Debioclip™) is added to the vial containing TRELSTAR™ LA and mixed, a suspension is formed which is intended as an intramuscular injection to be administered every 84 days (ie, every 12 weeks). TRELSTAR™ LA is available in 2 packaging configurations: (a) TRELSTAR™ LA vial alone or (b) TRELSTAR™ LA vial plus a separate pre-filled syringe that contains 2 mL of sterile water for injection, USP (Debioclip™).

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

Triptorelin is a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. 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). 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 and ovarian steroidogenesis is observed. In men, 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 (IM) injection of TRELSTAR™ LA to men with advanced prostate cancer, serum testosterone levels first increased, peaking on days 2-3, and declined thereafter to low levels by weeks 3-4.

**Pharmacokinetics**

Results of pharmacokinetic investigations conducted in healthy men indicate that after intravenous (IV) 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:** Triptorelin pamoate is not active when given orally. The pharmacokinetic parameters following a single IM injection of 11.25 mg of TRELSTAR™ LA to 13 patients with prostate cancer are listed in Table 1. Triptorelin did not accumulate over 9 months of treatment.

**Pharmacokinetic Parameters (Mean ± SD)**

Following a single intramuscular (IM) injection of 11.25 mg of TRELSTAR™ LA to patients with prostate cancer, the following parameters were observed:

<table>
<thead>
<tr>
<th>Dose (No. of subjects)</th>
<th>Cmax (0-85d) (ng/mL)</th>
<th>Tmax (1-85d) (h)</th>
<th>AUC (1-85d) (h·ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.25 mg (n=13)</td>
<td>38.3 ± 18.5</td>
<td>2.9 ± 1.3</td>
<td>2158.0 ± 444.0</td>
</tr>
</tbody>
</table>

**Distribution:** The volume of distribution following a single IV bolus administration 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.

**Metabolism:** The metabolism of triptorelin in humans is unknown, but is unlikely to involve hepatic microsomal enzymes (cytochrome P-450). However, the effect of triptorelin on the activity of other drug metabolizing enzymes is 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 IV administration of 0.5 mg triptorelin peptide to healthy male volunteers with a creatinine clearance of 140 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 (39.9 mL/min). It has also been observed that the non-renal elimination of triptorelin (patient anuric, Clcreat = 0) was 76.2 mL/min, thus indicating that the nonrenal elimination of triptorelin is mainly dependent on the liver (see Special Populations).

**Special Populations:**

**Renal and Hepatic Impairment:** After an IV bolus 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
drug interaction studies have been conducted with triptorelin (See existing treatment). Patients with renal or hepatic impairment had 2- to 4-fold higher exposure (AUC values) than young healthy males. 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) 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. Pharmacokinetic Drug-Drug Interactions: No pharmacokinetic drug-drug interaction studies have been conducted with triptorelin (See PRECAUTIONS, Drug Interactions).

Clinical Trials: TRELSTAR™ LA was studied in a randomized, active control trial of 146 men with advanced prostate cancer in South Africa. The clinical trial population consisted of 48% Caucasian, 38% Black, and 15% Other. Men were between 45 and 96 years of age (71 mean). Patients received either TRELSTAR™ LA (n = 174) every 84 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 levels of serum testosterone from Day 57 through Day 253.

INDICATIONS AND USAGE: TRELSTAR™ LA is indicated in the palliative treatment of advanced prostate cancer. It offers an alternative treatment for prostate cancer when orchectomy or estrogen administration are either not indicated or unacceptable to the patient.

PRECAUTIONS: Pregnancy, Teratogenic Effects: Pregnancy Category X (see CONTRAINDICATIONS). TRELSTAR™ LA is contraindicated in women who are or may become pregnant while receiving the drug. Studies in pregnant rats administered triptorelin at doses of 2, 10, and 100 mcg/kg/day (approximately equivalent to 0.2, 2, and 20 mg/d in humans) failed to show embryotoxicity, but no fetotoxicity or teratogenicity. Similarly, no teratogenic effects were observed when mice were administered doses of 2, 20, and 200 mcg/kg/day (approximately equivalent to 0.1, 0.7, and 7 mg/d in humans), respectively.

WARNINGS: Rare reports of anaphylactic shock and angioedema related to triptorelin administration have been reported. In the event of a reaction, therapy with TRELSTAR™ LA should be discontinued immediately and the appropriate supportive and symptomatic care should be administered. Initially, triptorelin, like other LHRH agonists, causes a transient increase in serum testosterone levels. As a result, isolated cases of worsening of symptoms and signs of prostate cancer during the first weeks of treatment have been reported with LHRH agonists. Patients may experience worsening of symptoms or onset of new symptoms, including bone pain, neuropathy, hematuria, or urethral or bladder outlet obstruction. Cases of spinal cord compression, which may contribute to paralysis with or without fatal complications, have been reported with LHRH agonists.

If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted, and in extreme cases an immediate orchectomy considered.

Table 2. Pharmacokinetic Parameters (Mean ±SD) in Healthy Volunteers and Special Populations

<table>
<thead>
<tr>
<th>Group</th>
<th>Cmax (ng/mL)</th>
<th>AUC (h·ng/mL)</th>
<th>Clp (mL/min)</th>
<th>Clrenal (mL/min)</th>
<th>t1/2 (h)</th>
<th>Clcreat (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 healthy male volunteers</td>
<td>48.2 ± 11.8</td>
<td>36.3 ± 9.0</td>
<td>211.9 ± 31.6</td>
<td>90.6 ± 35.6</td>
<td>2.81 ± 1.2</td>
<td>14.9 ± 7.3</td>
</tr>
<tr>
<td>6 males with moderate renal impairment</td>
<td>45.6 ± 20.5</td>
<td>60.9 ± 24.6</td>
<td>120.0 ± 45.0</td>
<td>23.3 ± 17.6</td>
<td>6.56 ± 2.1</td>
<td>19.7 ± 12.5</td>
</tr>
<tr>
<td>6 males with severe renal impairment</td>
<td>46.5 ± 14.0</td>
<td>80.0 ± 18.4</td>
<td>88.6 ± 19.7</td>
<td>4.3 ± 2.9</td>
<td>7.65 ± 2.1</td>
<td>8.9 ± 6.0</td>
</tr>
<tr>
<td>6 males with liver disease</td>
<td>54.1 ± 3.3</td>
<td>131.9 ± 18.1</td>
<td>57.8 ± 8.0</td>
<td>35.9 ± 5.0</td>
<td>7.18 ± 1.7</td>
<td>69.9 ± 13.1</td>
</tr>
</tbody>
</table>
and 7 times the recommended human therapeutic dose based on body surface area). 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 PRECAUTIONS, and Pregnancy).

Carcinogenesis, Mutagenesis, Impairment of Fertility: In rats, doses of 120, 600, and 3000 mcg/kg given every 28 days (approximately 0.3, 2, and 8 times the recommended human therapeutic dose based on body surface area) resulted in increased mortality with a drug treatment period of 13-19 months. The incidence 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 600 mcg/kg every 28 days (approximately 8 times the human therapeutic 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 microsome test) provided no evidence of mutagenic potential.

After 60 days of 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, 2.0, and 16 times the recommended human therapeutic dose based on body surface area) or 20 mcg/kg/day in slow release microspheres, had no effect on the fertility or general reproductive performance of female rats. Treatment did not elicit embryotoxicity, teratogenicity, or any effects on the development of the offspring (F1 generation) or their reproductive performance.

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

Geriatric Use: Prostate cancer occurs primarily in an older patient population. Clinical studies with TRELSTAR™ LA have been conducted primarily in patients ≥65 years old.

Use in Women: TRELSTAR™ LA has not been studied in women and is not indicated for use in women.

Nursing Mothers: It is not known whether TRELSTAR™ LA is excreted in human milk. Because many drugs are excreted in human milk and because the effects of TRELSTAR™ LA on lactation and/or the breastfed child have not been determined, TRELSTAR™ LA should not be used by nursing mothers.

Pediatric Use: TRELSTAR™ LA has not been studied in pediatric patients and is not indicated for use in pediatric patients.

ADVERSE REACTIONS

In the majority of patients, 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, hematuria, and bladder outlet obstruction. Isolated cases of spinal cord compression with weakness or paralysis of the lower extremities have occurred (see WARNINGS).

In a controlled, comparative clinical trial, the following adverse reactions were reported to have a possible or probable relationship to therapy as ascribed by the treating physicians in 1% or more of the patients receiving triptorelin (Table 3). Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug-related or unlikely to be related are excluded.

Changes in Laboratory Values During Treatment: The following abnormalities in laboratory values not present at baseline were observed in 10% or more of patients at the Day 25 visit: decreased hemoglobin and RBC count and increased glucose, BUN, SGOT, SGPT, and alkaline phosphatase. The relationship of these changes to drug treatment is difficult to assess in this population.
OVERDOSAGE
There is no experience of overdosage in clinical trials. In single
dose toxicity studies in mice and rats, the subcutaneous LD₅₀ of triptorelin was 400 mg/kg in mice and 250 mg/kg in rats, approximately
7000 and 4000 times, respectively, the usual human dose. If over-
dosage occurs however, therapy should be discontinued immediately
and the appropriate supportive and symptomatic treatment adminis-
tered.

DOSAGE AND ADMINISTRATION
TRELSTAR™ LA Must Be Administered Under the Supervision of a
Physician.
The recommended dose of TRELSTAR™ LA is 11.25 mg incorporated
in a long acting formulation administered every 84 days as a single
intramuscular injection administered in either buttock. The lyophilized
microgranules are to be reconstituted in sterile water. No other
diluent should be used. Reconstitute in accord with the following:
For TRELSTAR™ LA:
1. Using a syringe fitted with a sterile 20-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. Slowly withdraw the entire contents of the reconstituted sus-
pension into the syringe.
4. Inject the patient in either buttock with the contents of the
syringe.
The suspension should be discarded if not used immediately after
reconstitution.
For the TRELSTAR™ LA Debioclip™ single-dose delivery system:
1. Remove the Tyvek® cover from the blister pack.
2. Remove the vial from its case. Remove the flip-off vial cover
and place the vial in the vertical position.
3. Hold the lower part of the TRELSTAR™ LA
Debioclip™ and press it firmly onto the top
of the vial (See Figure).
4. Hold firmly the syringe barrel. Push the
finger grip in the direction of the vial as far
as it will go (until you hear a click).
5. Take the plunger rod and screw it into the
upper joint of the syringe.
6. Press the plunger rod to release the con-
tents of the syringe into the vial.
7. Mix and withdraw the contents of the vial into the syringe.
8. Remove the syringe from the TRELSTAR™ LA Debioclip™.
9. Inject the patient in either buttock with the contents of the
syringe.
The suspension should be discarded if not used immediately after
reconstitution.
As with other drugs administered by intramuscular injection, the
injection site should be altered periodically.

HOW SUPPLIED
TRELSTAR™ LA (NDC 0009-5215-01) is supplied in a single-dose vial
with a flip-off seal containing sterile lyophilized triptorelin pamoate
microgranules equivalent to 11.25 mg triptorelin peptide base, incor-
oporated in a biodegradable copolymer of lactic and glycolic acids. A
single dose vial of TRELSTAR™ LA contains triptorelin pamoate
(11.25 mg as peptide base units), poly-D,L-lactide-co-glycolide, (145 mg),
mannitol, USP (85 mg), carbomethoxy cellulose sodium, USP
(30 mg), and polysorbate 80, NF (2 mg).
TRELSTAR™ LA Debiclip™ single-dose delivery system consisting of
a vial with a flip-off seal containing sterile lyophilized triptorelin
microgranules equivalent to 11.25 mg of triptorelin peptide base,
incorporated in a biodegradable copolymer of lactic and glycolic
acids, and a pre-filled syringe containing 2 mL sterile water for injec-
tion, USP.

When mixed with sterile water for injection, TRELSTAR™ LA is
administered every 84 days as a single intramuscular injection.
Store at 20-25°C (68-77°F); excursions permitted to 15-30°C
(59-86°F) [see USP Controlled Room Temperature]. Do not freeze.