is no evidence that triptorelin, at clinically rele-
vant concentrations, binds to plasma albumin.

Metabolism: The metabolism of triptorelin in humans is
unknown, but is unlikely to involve hepatic micro-
somal enzymes (cytochrome P-450). However, the effect
of triptorelin clearance by triptorelin metabolizing enzymes is unknown. Thus, far, no metabolites of triptorelin have been identified.

Pharmacokinetic data suggest that C-terminal fragments produced by complete degradation of triptorelin 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 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 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, Clcreaat=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 85 mg triptorelin peptide, the two distri-
bution half-lives were unaffected by renal and hepatic impairment, but renal insufficiency led to a proportional decrease in triptorelin clearance.

A decrease in triptorelin clearance was more pronounced in subjects with liver insuf-
ficiency, but the half-life was prolonged similarly in subjects with renal insufficiency. Since the vol-
ume of distribution was only minimally increased. 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 systemat-
cally 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 clearance was proportional to body weight in 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 proportional to body weight
and is related to total creatinine clearance, which is well
known to decrease with age.

Pharmacodynamic Drug-Drug Interactions: No phar-
macokinetic drug-drug interaction studies have been conducted with triptorelin (see PRECAU-
tIONS, Drug Interactions).

Clinical Trials
TRELSTAR LA was studied in a randomized, active
trial controlled trial of 346 men with advanced prostate
cancer in South Africa. The clinical trial population consisted of 46% Caucasian, 30% Black, and 15% Other. Men were between 45 and 96 years of age (1.735 nmol/L) were achieved at Day 29 in 167 of
1034 volunteers (n=13). Patients received either
TRELSTAR LA or (b) TRELSTAR LA via a single pre-
filled syringe that contains sterile water for injec-
tion, USP, 2 mL fluid to 6.5 (Clip n-Ject+
).
Trelstar® LA 11.25 mg triptorelin pamoate for injectable suspension

INSTRUCTIONS FOR CLIP’N’JECT® USE

Before you begin read complete instructions.

Clip’n’Ject® Preparation
Wash your hands with soap and hot water and put on gloves immediately prior to preparing the injection. Place the package containing the Clip’n’Ject® system and the Trelstar® vial on a clean, flat surface that is covered with a sterile pad or cloth. Peel the Tyvek® cover away from the blister package, and place the vial, connector, alcohol swab, and plunger rod on the prepared surface. Be sure to begin by removing the Flip-Off® button from the top of the vial, revealing the rubber stopper. Disinfect the rubber portion of the vial cap with the alcohol swab. Discard the alcohol swab and let the alcohol dry. Proceed to Clip’n’Ject Activation.

Clip’n’Ject® Activation

1. Holding the vial upright and flat on the table surface with one hand, place the plastic connector directly over the top of the Trelstar® vial with the other hand. Press the connector down firmly on the vial top. This will ensure proper positioning of the vial.

2. Still holding the vial with one hand, press the syringe barrel downward as far as it will go in the connector. This results in insertion of the needle into the rubber stopper in the vial top to the predetermined depth.

3. Check to make sure that the needle is inserted into the vial. Now, screw the plunger rod into the end of the plastic grip on the syringe barrel.

4a. (a) With the vial still on the flat surface, place your thumb on the plunger rod and depress the plunger rod to inject the sterile water diluent into the vial.

4b. (b) With your thumb on the plunger rod, place two fingers under the plastic tab on the connector to keep the assembly together. Gently rotate the system so that the diluent rinses the vials sides to ensure complete mixing of Trelstar® and the sterile water diluent. The solution will now have a milky appearance. In order to avoid separation of the solution, proceed to the next steps without delay.

5. Hold the Clip’n’Ject® system in a vertical position with the connector at 12 o’clock and the syringe plunger rod at 6 o’clock. Double check to make sure that the syringe is still as far forward as possible in the connector with the needle situated in the vial.

6. Grasp the Clip’n’Ject® system firmly by the syringe barrel and pull back the plunger rod to draw the reconstituted Trelstar® into the syringe.

Clip’n’Ject® Disposal
After administering Trelstar®, dispose of the Clip’n’Ject system as follows:

a. Place Clip’n’Ject with attached vial in standing upright position on a flat surface.

b. Using one hand, replace the syringe into the Clip’n’Ject connector.

c. Dispose of syringe and attached Clip’n’Ject connector with vial into a suitable sharps container.

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 253 visit: decreased hemoglobin and B/C count and increased glucose, BUN, Bilirubin, alkaline phosphatase. The relationship of these changes to drug administration is not known.

Pituitary apoplexy: During post-marketing 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.

OVERDOSE
There is no experience of overdose 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 overdosage occurs however, therapy should be discontinued immediately and the appropriate supportive and symptomatic treatment administered.

DOSE 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 4 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 suspension into the syringe.

4. Inject the patient in either buttock with the contents of the syringe.

For the TRELSTAR LA Clip’n’Ject® single-dose delivery system, see adjacent INSTRUCTIONS FOR CLIP’N’JECT® USE section.

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 52544-154-02) 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, incorporated 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-lactide-co-glycolide (145 mg), mannitol, USP (85 mg), carboxymethylcellulose sodium, USP (30 mg), and polysorbate 80, NF (2 mg).

TRELSTAR LA (NDC 52544-154-76) is also supplied in the TRELSTAR LA Clip’n’Ject® single-dose delivery system consisting of a vial with a flip-off seal containing sterile lyophilized triptorelin pamoate microgranules equivalent to 11.25 mg of triptorelin peptide base, incorporated in a biodegradable copolymer of lactic and glycolic acids, and a prefilled syringe containing sterile water for injection, USP, 2 mL, pH 6 to 8.5.

When mixed with sterile water for injection, TRELSTAR LA is administered every 4 days as a single intramuscular injection.

Store at 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Do not freeze.

MODERN
testosterone suppression.

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For TRELSTAR LA:

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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 suspension into the syringe.

4. Inject the patient in either buttock with the contents of the syringe.

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B only
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