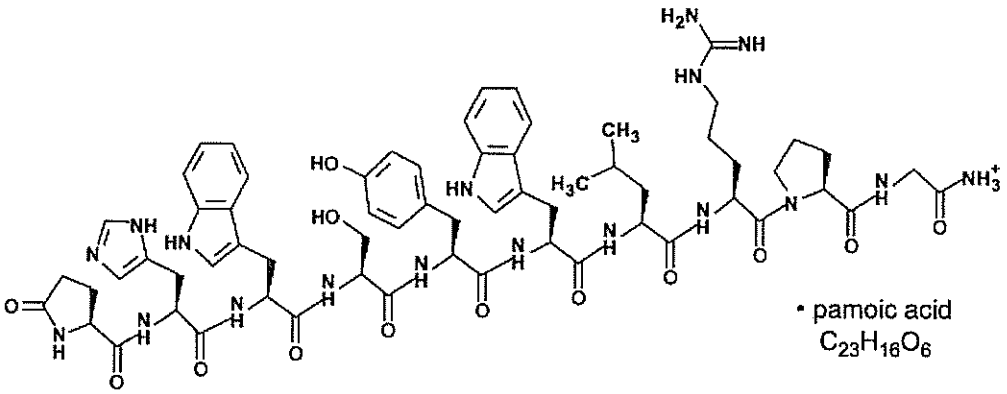
(Part Number) Revised: September 2005

(Place for bar code)

Watson Pharma, Inc.
TRELSTAR® DEPOT 3.75 mg
(triptorelin pamoate for injectable suspension)

DESCRIPTION
TRELSTAR DEPOT 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-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 shown below.



TRELSTAR DEPOT is a sterile, lyophilized biodegradable microgranule formulation supplied as a single-dose vial containing triptorelin pamoate (3.75 mg as the peptide base), 170 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 is added to the vial containing **TRELSTAR DEPOT** and mixed, a suspension is formed which is intended as a monthly intramuscular injection. **TRELSTAR DEPOT** is available in 2 packaging configurations: (a) **TRELSTAR DEPOT** vial alone or (b) **TRELSTAR DEPOT** vial plus a separate pre-filled syringe that contains sterile water for injection, USP, 2 mL, pH 6 to 8.5 (Clip'n'Ject®).

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 DEPOT** to healthy male volunteers, serum testosterone levels first increased, peaking on day 4, and declined thereafter to low levels by week 4. Similar testosterone profiles were observed in patients with advanced prostate cancer, when injected with **TRELSTAR DEPOT**. In healthy volunteers, testosterone serum levels returned to near baseline by week 8.

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. Intramuscular injection of the depot formulation provides plasma concentrations of triptorelin over a period of 1 month. The pharmacokinetic parameters following a single IM injection of 3.75 mg of **TRELSTAR DEPOT** to 20 healthy male volunteers are listed in Table 1. The plasma concentrations declined to 0.084 ng/mL at 4 weeks.

TABLE 1. PHARMACOKINETIC PARAMETERS FOLLOWING INTRAMUSCULAR ADMINISTRATION OF TRELSTAR DEPOT TO HEALTHY MALE VOLUNTEERS

Dose (No. of subjects)	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}28d}$ (h·ng/mL)	F (%)[3] (No. of days)
3.75 mg (n=20)	28.43 ± 7.31[1]	1.0 (1.0 - 3.0)[2]	223.15 ± 46.96[1]	83 (28 d)

[1] Mean ± SD

[2] Median (range)

[3] Computed as the mean AUC of the study divided by the mean AUC of healthy volunteers corrected for dose where AUC=36.1 h·ng/mL and 500 µg IV bolus dose of triptorelin was administered.

Distribution: The volume of distribution following an IV 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.

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 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, CI_{creat}=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 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 2). The decrease in triptorelin clearance was more pronounced in subjects with liver insufficiency, but the half-life was prolonged similarly in subjects with renal insufficiency, since the volume of distribution was only minimally increased.

TABLE 2. PHARMACOKINETIC PARAMETERS (MEAN ±SD) IN HEALTHY VOLUNTEERS AND SPECIAL POPULATIONS

Group	C_{max} (ng/mL)	AUC_{inf} (h·ng/mL)	CI_p (mL/min)	CI_{renal} (mL/min)	$t_{1/2}$ (h)	CI_{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 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 DEPOT 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 (71 mean). Patients received either **TRELSTAR DEPOT** 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) were achieved in 91.2% of **TRELSTAR DEPOT** patients at Day 29 and in 97.7% of patients at Day 57.

Maintenance of castration levels of serum testosterone from Day 57 through Day 253 was found in 96.4% of **TRELSTAR DEPOT** patients.

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 DEPOT** administration on Days 85 and 169. One hundred twenty-four of 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.

INDICATIONS AND USAGE

TRELSTAR DEPOT is indicated in the palliative treatment of advanced prostate cancer. It offers an alternative treatment for prostate cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient.

CONTRAINDICATIONS

TRELSTAR DEPOT is contraindicated in individuals with a known hypersensitivity to triptorelin or any other component of the product, other LHRH agonists or LHRH. Three postmarketing reports of anaphylactic shock and seven postmarketing reports of angioedema related to triptorelin administration have been reported since 1986 (see WARNINGS).

TRELSTAR DEPOT may cause fetal harm when administered to a pregnant woman.

WARNINGS

Initially, triptorelin, like other LHRH 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 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 orchiectomy considered.

TRELSTAR DEPOT should not be administered to individuals who are hypersensitive to triptorelin, other LHRH agonists, or LHRH. In the event of a hypersensitivity reaction, therapy with **TRELSTAR DEPOT** should be discontinued immediately and the appropriate supportive and symptomatic care should be administered.

PRECAUTIONS

General: 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 (see WARNINGS). Hypersensitivity and anaphylactic reactions have been reported with triptorelin with other LHRH agonists (see CONTRAINDICATIONS and WARNINGS).

Laboratory Tests: Response to **TRELSTAR DEPOT** should be monitored by measuring serum levels of testosterone and prostate-specific antigen.

Drug Interactions: No drug-drug interaction studies involving triptorelin have been conducted. In the absence of relevant data as a precaution, hyperprolactinemic drugs should not be prescribed concomitantly with **TRELSTAR DEPOT** since hyperprolactinemia reduces the number of pituitary GnRH receptors.

Drug/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.

Pregnancy, Teratogenic Effects: **Pregnancy Category X (see CONTRAINDICATIONS). TRELSTAR DEPOT** 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 µg/kg/day (approximately equivalent to 0.2, 0.8, and 8 times the recommended human therapeutic dose based on body surface area) during the period of organogenesis displayed maternal toxicity and embryotoxicity, but no fetotoxicity or teratogenicity. Similarly, no teratogenic effects were observed when mice were administered doses of 2, 20, and 200 µg/kg/day (approximately equivalent to 0.1, 0.7, 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In rats, doses of 120, 600, and 3000 µg/kg given every 28 days (approximately 0.3, 2.0, 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 6000 μg/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 micronucleus 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 μg/kg/day in saline (approximately 0.2, 2.0, and 16 times the recommended human therapeutic dose based on body surface area) or 20 μg/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 (F_1 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 DEPOT** have been conducted primarily in patients ≥ 65 years.

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

Pediatric Use: **TRELSTAR DEPOT** has not been studied 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 physician 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 are excluded.

TABLE 3. RELATED ADVERSE EVENTS REPORTED BY 1% OR MORE OF PATIENTS DURING TREATMENT WITH TRELSTAR DEPOT

	TRELSTAR DEPOT N=140	
Adverse Event	**N**	**%**
Application Site Disorders		
Injection site pain	5	3.6

Body As A Whole		
Hot Flushes*	82	58.6
Pain	3	2.1
Leg Pain	3	2.1
Fatigue	3	2.1
Cardiovascular		
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		
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		
Urinary retention	2	1.4
Urinary tract infection	2	1.4

*Expected pharmacologic consequences of testosterone suppression.

Changes in Laboratory Values During Treatment: There were no clinically meaningful changes in laboratory values during or following therapy with **TRELSTAR DEPOT**.

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.

OVERDOSAGE

The pharmacological properties of triptorelin and its mode of administration make accidental or intentional overdosage unlikely. There were no reported overdoses 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 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.

DOSAGE AND ADMINISTRATION

TRELSTAR DEPOT *Must Be Administered Under the Supervision of a Physician.*

The recommended dose of **TRELSTAR DEPOT** is 3.75 mg incorporated in a depot formulation and is administered monthly as a single intramuscular injection. The lyophilized microgranules are to be reconstituted in **sterile water. No other diluent should be used.**

Reconstitute in accord with the following:

For **TRELSTAR DEPOT**:

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) Withdraw the entire content of the reconstituted suspension into the syringe and inject it immediately.

For the **TRELSTAR DEPOT** 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.

Dosage Adjustments: Patients with renal or hepatic impairment showed 2- to 4-fold higher exposure than young healthy males. The clinical consequences of this increase, as well as the potential need for dose adjustment, is unknown.

HOW SUPPLIED

TRELSTAR DEPOT (NDC 52544-153-02) is supplied in a single-dose vial with a flip-off seal containing sterile lyophilized triptorelin pamoate microgranules equivalent to 3.75 mg triptorelin peptide base, incorporated in a biodegradable copolymer of lactic and glycolic acids. A single dose vial of **TRELSTAR DEPOT** contains triptorelin pamoate (3.75 mg as peptide base units), poly-*d,l*-lactide-co-glycolide (170 mg), mannitol, USP (85 mg), carboxymethylcellulose sodium, USP (30 mg), and polysorbate 80, NF (2 mg).

TRELSTAR DEPOT (NDC 52544-153-76) is also supplied in the **TRELSTAR DEPOT** Clip'n'Ject® single-dose delivery system consisting of a vial with a flip-off seal containing sterile lyophilized triptorelin pamoate microgranules equivalent to 3.75 mg of triptorelin peptide base, incorporated in a biodegradable copolymer of lactic and glycolic acids, and a pre-filled syringe containing sterile water for injection, USP, 2 mL, pH 6 to 8.5.

When mixed with sterile water for injection, **TRELSTAR DEPOT** is administered every 28 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].

Rx only

Product No. 1119-02
Revised: September 2005

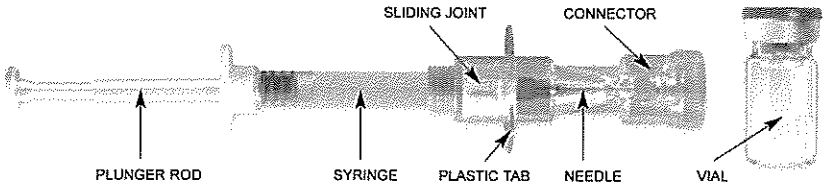
U.S. Patent Nos.: 5,134,122; 5,225,205; 5,192,741.

Clip'n'Ject® is manufactured by and is a registered trademark of West Pharmaceutical Services, Inc. Lionville, PA 19341 USA

Tyvek® is a registered trademark of E.I. du Pont de Nemours and Company

Manufactured for:
Watson Pharma, Inc.
A subsidiary of Watson Pharmaceuticals, Inc.
Corona, CA 92880 USA
by: Debio RP
CH-1920 Martigny, Switzerland

INSTRUCTIONS FOR CLIP'N'JECT® USE

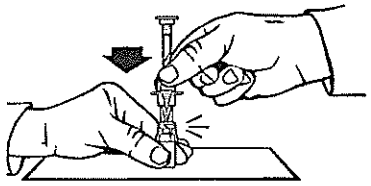


Clip'n'Ject® Preparation

Wash hands with soap and hot water immediately prior to preparing injection. Place the package containing the Clip'n'Ject® system and the drug product vial on a clean, flat surface that is covered with a sterile pad or cloth and peel the Tyvek® cover away from the blister package. Place the vial, connector, alcohol swab, and plunger rod on the prepared surface. Remove the flip-off button from the top of the vial and cleanse the rubber portion of the vial cap with the alcohol swab. Discard the alcohol swab.

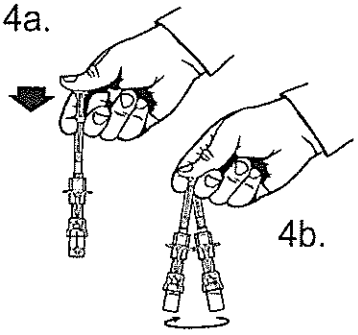
Clip'n'Ject® Activation

1.



Place the plastic connector directly over the top of the drug product vial. Press the connector down firmly on the vial top until the system attaches to the vial top and you hear a "click." This will ensure proper positioning of the vial.

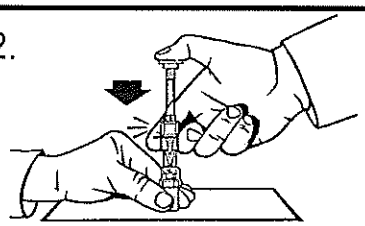
4a.



4b.

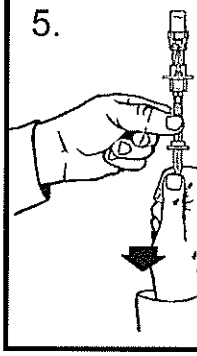
(a) Press the plunger rod to inject the diluent into the vial. (b) While holding the plunger rod in position, gently rotate the system so that diluent rinses the vial sides and to ensure that complete mixing of the product and diluent occurs.

2.



Press the barrel of the syringe forward until a second "click" is heard. The click indicates that the needle has been inserted to the appropriate predetermined depth through the rubber stopper in the vial top.

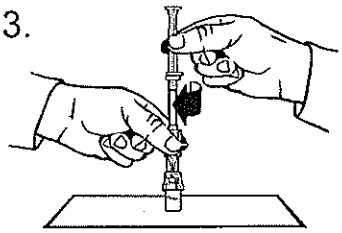
5.



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.

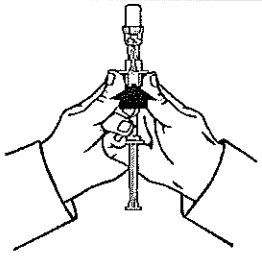
Grasp the Clip'n'Ject system firmly by the syringe barrel and pull back the plunger rod to draw the reconstituted product into the syringe.

3.



Screw the plunger rod into the end of the plastic grip on the syringe barrel.

6.



Remove the connector from the filled syringe by pressing your thumb against the plastic tab and pulling the syringe section from the connector.

Follow safe disposal procedures for all components.