Drug Monograph

A - Drug Name

triptorelin

SYNONYM(S): 6-D-Tryptophan-LH-RH

COMMON TRADE NAME(S): Trelstar® (Paladin Labs)

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B - Mechanism of Action and Pharmacokinetics

Triptorelin is a synthetic decapeptide agonist analogue of naturally occurring luteinizing hormone-releasing hormone (LHRH). LHRH is also known as gonadotropin releasing hormone (GnRH). It acts as a potent inhibitor of gonadotropin secretion, initially producing a transient rise in LH, FSH, and testosterone levels. Continuous triptorelin pamoate administration desensitizes pituitary LHRH receptors and inhibits LH and FSH secretion, resulting in chemical castration within ~ 3-4 weeks. In a randomized controlled trial comparing triptorelin to leuprolide, time-to-castrate levels were longer for triptorelin, although the outcomes were otherwise similar for both arms.

Absorption	Oral: not absorbed After IM injection, peak levels are reached on days 2 to 4.	
Distribution	Triptorelin is distributed and eliminated according to a 3 compartmental model.	
	Cross blood brain barrier?	no information found
	PPB	low / absent
Metabolism	Undetermined, suggested that it is either completely degraded by peptidases in the pituitaries, liver or kidneys, or rapidly further degraded in plasma.	

	Active metabolites	unknown
	Inactive metabolites	yes
Elimination	Triptorelin is eliminated by both renal and hepatic clearance. Renal and hepatic impairment lead to decrease in total clearance of triptorelin, consequently resulting in an increase in elimination half-life.	
	Urine	42 % (unchanged), increased in patients with hepatic impairment
	Half-life	3 hours (0.5 mg IV)

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C - Indications and Status

Health Canada Approvals:

- Palliative treatment of hormone dependent advanced carcinoma of the prostate gland (stage D2)

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D - Adverse Effects

Emetogenic potential: Not applicable

Extravasation Potential: None

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (rare)	E
	Hypertension (5%)	E
	Palpitations (2%)	E
	QT interval prolonged (rare)	
	Venous thromboembolism (rare)	E
Dermatological	Rash (2%)	E
Gastrointestinal	Abdominal pain (1%)	E
	Anorexia (2%)	E
	Constipation (2%)	E
	Diarrhea (2%)	E
	Dyspepsia (2%)	E

	Nausea (4%)	I	E	
General	Edema (8%)		E	
	Fatigue (4%)		E	
	Tumour flare	I		
Hematological	Anemia (>15%)			D
	Other (14%) (↑ prothrombin time)		E	
Hepatobiliary	↑ LFTs (1%)		E	
Hypersensitivity	Hypersensitivity (1%)	I		
Injection site	Injection site reaction (4%)		E	
Metabolic / Endocrine	Glucose intolerance (>15%) (diabetes 1%)		E	D
	Pituitary apoplexy (rare, observed with other GnRH agonists)	I	E	
Musculoskeletal	Musculoskeletal pain (13%)		E	
	Osteoporosis (may be severe)		E	
Nervous System	Depression (2%) (may be severe)		E	
	Dizziness (3%)		E	
	Headache (7%)		E	
	Insomnia (2%)		E	
	Seizure (rare)			
Ophthalmic	Conjunctivitis (1%)		E	
	Eye pain (1%)		E	
Reproductive and breast disorders	Hypogonadism (testosterone depletion symptoms up to 73%)		E	
Respiratory	Cough, dyspnea (2%)		E	
Urinary	Urinary symptoms (5%)		E	

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Most common side effects associated with triptorelin are pharmacological consequences of testosterone suppression – **hot flashes, impotence**, and **decrease in libido**.

Long-term use results in **hypogonadism**; it's unknown whether this is reversible.

In non-orchidectomized patients, the initial stimulation of the pituitary caused by triptorelin produces an acute increase in the concentration of testosterone, usually during the first week of

treatment. This is accompanied by disease flare in <10% of patients. Increased bone pain and less frequently, neuropathy, symptoms of urinary tract obstruction (e.g. renal failure) and/or spinal cord compression (e.g. weakness of lower extremities) occur. Patients with metastatic vertebral lesions and/or with urinary tract obstruction should begin triptorelin therapy under close supervision. Alternatively, cyproterone 100 mg bid, flutamide 250 mg tid, bicalutamide 50mg daily or nilutamide 150mg daily may be given concurrently with the first administration of triptorelin in prostate cancer patients. Since the danger of a flare reaction abates in the second week following triptorelin administration, there is no strong reason for continuing antiandrogens much beyond this time.

Bone loss may occur during the hypoandrogenic state caused by long-term use of triptorelin. Risk factors such as older age, pre-existing osteopenia, family history of osteoporosis, chronic use of corticosteroids, anticonvulsants, or other drugs that may lead to osteoporosis or chronic alcohol/tobacco abuse should be carefully considered before starting treatment.

Androgen deprivation may increase **cardiovascular risk** (MI, sudden death, stroke) in men with prostate cancer since it can adversely affect cardiovascular risk factors, such as increased body weight, reduced insulin sensitivity and/or dyslipidemia. **QTc prolongation** has been described and triptorelin should be used with caution in patients with other risk factors such as congenital long QT syndrome, abnormal electrolytes and concomitant medications which prolong QTc. Reduction in glucose tolerance and increased risk of developing **diabetes** have been reported in men treated androgen deprivation therapy. **Anemia** is also a known physiologic effect of testosterone suppression.

There is an increased risk of **depression** in patients on GnRH agonist treatment. Worsening of depression, including suicidal attempts, have been reported.

Pituitary apoplexy has been reported rarely, usually in patients with pre-existing adenomas. Most occurred within 2 weeks of the first dose, and some within the first hour. Symptoms include sudden headache, vomiting, visual changes, altered mental status and sometimes cardiovascular collapse.

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E - Dosing

Refer to protocol by which patient is being treated.

Adults:

Intramuscular:

Monthly: 3.75 mg (depot formulation)

3-monthly LA: 11.25mg (depot formulation)

6-monthly LA: 22.5mg (depot formulation)

Dosage with Toxicity:

Worst grade of toxicity	Dose modification
Myelosuppression	No adjustment required
Grade 3 / 4 toxicity	Discontinue

Dosage with Hepatic Impairment:

Triptorelin exposure is increased in patients with hepatic insufficiency. Clinical consequences are unknown.

Dosage with Renal Impairment:

Triptorelin exposure is increased in patients with renal insufficiency. Clinical consequences are unknown.

Dosage in the elderly:

No adjustment required

Children:

Safety and efficacy not established

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F - Administration Guidelines

- Intramuscular injection only; to be given in Cancer Centre or physician's office, drug supplied by outpatient prescription.
- The dosage strengths are not additive, due to different release characteristics, and must be selected based on the desired dosing schedule.
- Vary injection sites.
- Reconstitute the drug vial with 2 mL sterile water for injection (forms a suspension) using a 21–gauge needle or using the single dose delivery system (MIXJECT®). Refer to the triptorelin (Trelstar®) product monograph for detailed instructions.
- Store triptorelin (Trelstar®) at room temperature and protected from light; administer triptorelin suspension right after reconstitution. Any unused portion should be discarded immediately.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to gonadotropin releasing hormone or luteinizing hormone-releasing hormone (GnRH or LHRH), GnRH agonist analogs, to this drug or any of its components.

Other Warnings/Precautions:

- Use with caution in patients with osteoporosis (or risk factors for osteoporosis), diabetes, risk factors for QT prolongation, history of depression, cardiovascular disease, metastatic vertebral lesions and/or urinary tract obstruction due to the risk of disease flare.

Pregnancy and Lactation:

- Teratogenicity: No
  Triptorelin is non-mutagenic, non-clastogenic and non-teratogenic; however, animal studies suggested triptorelin to have oncogenic effects on the pituitary gland and reduction in fertility. Triptorelin is contraindicated for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Yes

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Hyperprolactinemic drugs (e.g., chlorpromazine, haloperidol, olanzapine, prochlorperazine, risperidone, methyldopa, reserpine, metoclopramide,	no data	May reduce the number of pituitary GnRH receptors	Avoid concomitant use

domperidone, estrogens)			
Tests of pituitary-gonadal function (including testosterone)	Results might be misleading	Normal pituitary-gonadal function restores within 4-12 weeks after discontinuation of triptorelin	Conduct diagnostic tests of pituitary-gonadal function at least 12 weeks after discontinuation of triptorelin
Drugs that may prolong QT interval	↑ risk of QT prolongation	Additive effects with androgen deprivation	Caution

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- Blood glucose and/or HbA1c; baseline and periodic, more frequently in diabetic patients or patients at risk of hyperglycemia
- ECG, electrolytes, including calcium and magnesium; baseline, also regularly in patients at risk of electrolyte abnormality or QT prolongation
- PSA, bone and prostatic lesions; periodic
- Clinical assessment of disease flare, osteoporosis, symptoms of hypogonadism, injection site reactions, thromboembolism, depression, cardiovascular effects; regular
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Hemoglobin; baseline and periodic

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

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K - References

Heyns CF, Simonin MP, Grosgurin P et al. Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer. BJU International 2003;92:226-31.

Product Monograph: Trelstar® and Trelstar® LA (triptorelin). Paladin Labs Inc., September 6, 2013.

Product Monograph: Trelstar® (triptorelin). Watson Laboratories Inc (US), March 2011.

October 2014: updated adverse effects, dosing and precautions sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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