

Drug Monograph

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A - Drug Name

leuprolide

COMMON TRADE NAME(S): Lupron®; Lupron Depot®; Eligard®

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B - Mechanism of Action and Pharmacokinetics

Leuprolide is a synthetic analog of gonadotropin releasing hormone (GnRH) acting mainly on the pituitary gland in humans. Continuous treatment produces initial stimulation of FSH and LH (3-4 days), then suppression, with reduction of gonadal hormones to castrate or post-menopausal levels. In males, the net effect is a reduction of testosterone to castration levels within two to four weeks. In females, both ovarian estrogen and androgen synthesis are inhibited.

Absorption	Destroyed in gastrointestinal tract	
Distribution	Undetermined. There was no evidence of accumulation after repeated administration.	
	Cross blood brain barrier?	yes
	PPB	43-49% (in vitro)
Metabolism	Extensive, by peptidases, to inactive peptides.	
	Active metabolites	none reported
	Inactive metabolites	yes
Elimination	Urine	< 5 %, parent and main inactive metabolite
	Half-life	3 hours (after 1mg IV dose).

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C - Indications and Status

Health Canada Approvals:

- Prostate cancer

Refer to the product monograph for a full list and details of approved indications

Other Uses:

- Breast cancer

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D - Adverse Effects

Emetogenic Potential: Not applicable

Extravasation Potential: None

The following table contains adverse effects reported in prostate cancer patients.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Hearing impaired (<5%)	E
Cardiovascular	Arrhythmia (<5%)	E
	Arterial thromboembolism (<5%)	E
	Cardiotoxicity (<5%)	E D
	Hypertension (<5%)	E
	Hypotension (<5%)	E
	QT interval prolonged	E
	Venous thromboembolism (<5%)	E
Dermatological	Alopecia (<5%)	E
	Hypertrichosis (<5%)	E

	Photosensitivity	E
	Rash (12%)	E
Gastrointestinal	Appetite changes (<5%)	E
	Constipation (<5%)	E
	Dysphagia (<5%)	E
	GI hemorrhage (<5%)	E
	GI obstruction (<5%)	E
	GI ulcer (<5%)	E
	Nausea, vomiting (5%)	I
	Weight changes (<5%)	E
General	Edema (21%)	E
	Fatigue (12%)	I E
	Tumour flare (including pain)	E
Hematological	Myelosuppression (<5%) (mild)	E
Hepatobiliary	↑ LFTs (<5%) (may be severe)	E
Hypersensitivity	Hypersensitivity (rare)	I
Injection site	Injection site reaction (38%)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (increased/decreased Na, PO4, K, Ca)	E
	Hyperglycemia (5%)	E
	Hyperlipidemia (5%)	D
	Pituitary apoplexy / adenoma (rare)	I E
Musculoskeletal	Musculoskeletal pain (33%)	E
	Osteoporosis	D
Nervous System	Anxiety (<5%)	E
	Dizziness (8%)	E
	Headache (10%)	E
	Mood changes (<5%) (including depression, may be severe)	E
	Paresthesia (8%)	E
	Seizure (<5%)	E
	Sleep disorder (9%)	E
Ophthalmic	Eye disorders (<5%) (and abnormal vision)	E
Renal	Creatinine increased (<5%)	I E

Reproductive and breast disorders	Androgen deprivation symptoms and hypogonadism (59%)	E
Respiratory	Cough, dyspnea (5%)	E
	Pneumonitis (<5%)	E D
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.

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

Leuprolide-induced **hot flashes** range in severity from mild to severe, with frequent sweating. They usually decrease with continued therapy and do not usually require treatment discontinuation. Adverse **CNS effects** occur in 3% or more of patients and include dizziness, pain, headache and paresthesia.

In non-orchidectomized patients, the initial stimulation of the pituitary caused by leuprolide produces an acute increase in the concentration of testosterone, usually during the first week of treatment. This is accompanied by **disease flare** in 5-10% of patients and transient prostatic enlargement in 30-50%. 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 leuprolide 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 leuprolide in prostate cancer patients. Since the danger of a flare reaction abates in the second week following leuprolide 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 leuprolide. 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 leuprolide 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 in patients using GHRH agonists, 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.

Hypersensitivity reaction and anaphylaxis have been described. Long-term use results in hypogonadism; it is unknown whether this is reversible. Second malignancies have been described but the relationship to leuprolide is unclear.

Rare cases of serious **hepatotoxicity**, including fatal cases, have been described.

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E - Dosing

Refer to protocol by which patient is being treated. Do not use formulations for shorter or longer periods (for e.g., dividing 3-monthly dose between more than one patient monthly or using 3 x monthly preparations q3m) as the pharmacokinetics are quite different. Delays of 14 days or more (for the monthly dose) will result in increased testosterone levels, so the schedule must be maintained.

Adults:

Daily schedule: 1 mg (0.2 mL of leuprolide 5mg/mL injection) subcutaneously
Use for about 2 weeks prior to beginning monthly treatments in those patients at risk of worsening signs and symptoms.

Long-acting:

Route of administration varies depending on brand and formulation*
Monthly SR: 7.5 mg

3-monthly SR: 22.5mg

4-monthly SR: 30mg

6-monthly SR: 45mg

* NOTE: Eligard® 7.5mg, 22.5mg, 30mg, and 45mg are for Subcutaneous use only.
Lupron Depot® 7.5mg, 22.5mg and 30mg are for Intramuscular use only.

Dosage with Toxicity:

Toxicity	Dose modification
Myelosuppression	No dose reduction needed
↑ LFTs	Hold until ≤ grade 1. If no recovery then discontinue
Arterial and venous thromboembolism	Discontinue
Pituitary apoplexy	Discontinue
Pneumonitis	Discontinue

Dosage with Hepatic Impairment:

No adjustment required. See table above for management of drug-related hepatotoxicity.

Dosage with Renal Impairment:

No adjustment required.

Dosage in the elderly:

No adjustment required

Children:

No oncologic indications. Safety and efficacy have not been established.

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F - Administration Guidelines

- Outpatient prescription; administer in Cancer Centre or physician's office
- Vary injection site.
- For long-acting preparations, reconstitute with supplied diluent immediately before injection as directed (see product monograph).
- Do not give multiple monthly injections together to make up a q3 or q4 month dose, as the release characteristics are different.

Lupron® 5 mg/mL injection:

- For Subcutaneous use only.
- Usual sites of injection include the abdomen and anterior thigh.
- Keep refrigerated.

Lupron Depot® 7.5 mg, 22.5 mg and 30 mg:

- For Intramuscular use only.
- Usual sites of injection include the anterior thigh, gluteal area or deltoid. Vary injection sites.
- Store at room temperature.

Eligard® 7.5 mg, 22.5 mg, 30 mg, and 45 mg:

- For Subcutaneous use only. Choose an injection site on the abdomen, upper buttocks, or anywhere with adequate amounts of subcutaneous tissue.
- Keep refrigerated, or may be stored at room temperature in original packaging for a period of 8 weeks before administration.
- Allow product to reach room temperature before using.

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug, any of its components, or similar nonapeptides

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, and in patients at risk of convulsions.
- Some brands may contain benzyl alcohol and may cause local reactions.

Other Drug Properties:

- Carcinogenicity: Unlikely

Pregnancy and Lactation:

- Mutagenicity: No
- Fetotoxicity: Documented in animals
- Teratogenicity: Probable
- Abortifacient effects: Probable
- Pregnancy:
Leuprolide is **contraindicated** for use in patients who are or may become pregnant. Adequate contraception (non-hormonal) should be used by patients and their partners during treatment, and for at least **6 months** after the last dose (general recommendation).
- Breastfeeding: Contraindicated
- Fertility effects:
Leuprolide may suppress fertility; the effects were reversible in patients who can get pregnant (treated up to 24 weeks), but there were no data in patients who can get others pregnant.

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H - Interactions

Leuprolide may interfere with diagnostic tests of pituitary-gonadal function; these tests should be conducted at more than 8 weeks after discontinuing treatment.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Drugs that increase QT interval	↑ risk of QT prolongation or Torsades de pointes	Additive	Caution

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Blood glucose levels/HbA1c	baseline and periodic, especially in diabetic patients
PSA	baseline and periodic
EKG, Electrolytes, (including K, Ca, Mg)	baseline, also regular for at risk patients
Liver function tests	periodic
Clinical assessment of disease flare, local reactions, thromboembolism, cardiovascular effects, osteoporosis, psychiatric effects, hot flashes and injection site reactions	At each visit

Grade toxicity using the current [NCI-CTCAE \(Common Terminology Criteria for Adverse Events\) version](#)

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Renal function tests	periodic

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J - Supplementary Public Funding

ODB - General Benefit ([ODB Formulary](#))

- leuprolide - long-acting formulation ()

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K - References

Leuprolide acetate [Internet]; 2012 [cited 2012 September 4]. Available from <http://www.ahfsdruginformation.com>

NCI Drug Dictionary [Internet] [cited 2012 September 4]. Available from <http://www.cancer.gov/drugdictionary>

Prescribing Information: Lupron® Depot (leuprolide). Abbvie Inc. (US), June 2014.

Product Monograph: Eligard® (leuprolide). Sanofi-aventis Canada Inc. May 31, 2011.

Product Monograph : Lupron® / Lupron® depot (leuprolide). AbbVie Corporation, August 9, 2013.

May 2025 Updated Special precautions section

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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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