Drug Monograph

A - Drug Name

buserelin

COMMON TRADE NAME(S): Suprefact®; Suprefact Depot®; Suprefact Nasal Spray®

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B - Mechanism of Action and Pharmacokinetics

Buserelin is a synthetic analog of natural gonadotropin-releasing hormone (GnRH/LHRH). The effects of buserelin on follicle stimulating hormone (FSH) and luteinizing hormone (LH) release are 20 to 170 times greater than those of LHRH. Chronic administration of buserelin results in sustained inhibition of gonadotropin production, suppression of ovarian and testicular steroidogenesis, reduced circulating levels of gonadotropin and gonadal steroids.

Absorption	Oral: Not absorbed Nasal: 1-3% SC: 70% at 200 mcg	
Distribution	Well distributed to liver, kidneys, anterior pituitary lobe; trace present in breast milk	
	Cross blood brain barrier?	No information found
	PPB	15%
Metabolism	Metabolized and inactivated by peptidases in liver, kidneys, GI tract, pituitary gland	
	Active metabolites	None known
	Inactive metabolites	Buserelin (5-9) pentapeptide and others

Elimination	Mainly via kidney, some biliary	
	Urine	44% intact drug
	Half-life	SC: 80 min (20-30 days for 2-month depot implants) Intranasal: 1-2 h

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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.

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D - Adverse Effects

Emetogenic Potential: Not applicable

Extravasation Potential: None

The following table contains adverse effects reported mainly in prostate cancer patients and reported for depot buserelin ± cyproterone.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Heart failure (<1%)	E
	Hypertension (9%) (may be severe)	E
	Palpitations (5%)	E
	QT interval prolonged (rare)	E
	Venous thromboembolism (<1%)	E
Dermatological	Rash (<1%)	D

Gastrointestinal	Constipation (<1%)	E
	Diarrhea (<1%)	E
	Dry mouth (2%) (nasal route)	I
	Nausea, vomiting (5%)	I
	Weight changes (<1%)	D
General	Edema (1%)	E
	Fatigue (14%)	E
	Tumour flare (1%) (disease flare including urinary retention)	E
Hematological	Myelosuppression (anemia, mild)	D
Hypersensitivity	Hypersensitivity (rare)	I
Injection site	Injection site reaction (5%) (transient)	I E D
Metabolic / Endocrine	Hyperglycemia (<1%)	E
	Hyperlipidemia (rare)	E
	Other (pituitary adenoma- rare)	L
Musculoskeletal	Musculoskeletal pain (5%)	E
	Osteopenia (may be severe)	D L
Neoplastic	Other (<1%) (myeloid metaplasia)	E
Nervous System	Headache (29%) (nasal route)	E
	Insomnia (5%)	D
	Mood changes (2%)	D
Renal	Creatinine increased (rare)	E
Reproductive and breast disorders	Androgen deprivation symptoms (Up to 23%)	E
Respiratory	Dyspnea (<1%)	I
	Nasal irritation (13%) (nasal route)	I

* "*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)

The most common side effects are expected pharmacologic effects such as **androgen withdrawal** symptoms, fatigue and injection site reactions. The reactions at the **injection site** include pain, irritation, swelling and urticaria. None of these reactions required discontinuation of therapy.

In non-orchidectomized patients, the initial stimulation of the pituitary caused by buserelin 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 buserelin 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 buserelin in prostate cancer patients. Since the danger of a flare reaction abates in the second week following buserelin administration, there is no strong reason for continuing antiandrogens much beyond this time.

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

Bone loss may occur during the hypoandrogenic state caused by long-term use of buserelin. 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 buserelin 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.

Hypertensive crises have been reported in patients with hypertension.

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. Patients who experience anaphylaxis or anaphylactoid shock while on the depot formulation may require surgical removal of the implant.

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E - Dosing

Refer to protocol by which patient is being treated.

Adults:

Prostate Cancer:

Induction:

Subcutaneous: 500 mcg q8h x 7 days

Maintenance:
Subcutaneous: 200 mcg Daily

Maintenance:
Intranasal: 400 mcg (200 mcg in each nostril) q8h (TID)

Maintenance:
Subcutaneous: 6.3 mg (depot injection) Every 2 months

Maintenance:
Subcutaneous: 9.45 mg (depot injection) Every 3 months

Dosage with Toxicity:

Dosage in myelosuppression: No adjustment required

Dosage with Hepatic Impairment:

No adjustment required; no studies conducted.

Dosage with Renal Impairment:

No adjustment required; no studies conducted.

Children:

Safety and efficacy have not been established.

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F - Administration Guidelines

- Subcutaneous injection of depot at Cancer Centre or physician's office; supplied by outpatient prescription.
- Subcutaneous: Rotate injection sites
- Solution for SC injection: Store at room temperature. May be kept up to 14 days after the first opening when stored at room temperature. Protect from light.
- Intranasal solution: Store at room temperature. May be kept up to 5 weeks after the first opening when stored at room temperature. Protect from light.
- DEPOT formulation for SC injection:
  - Store at room temperature. Protect from light.
  - Applicator containing implant rods should be kept horizontal before injection.
  - Before the injection, a local anesthetic may be used if needed.
  - Inject SC into the lateral abdominal wall.

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G - Special Precautions

Contraindications:

- patients who have a hypersensitivity to this drug or any of its components
- in patients who have undergone orchiectomy or who have non-hormone dependent prostate cancer

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

Other Drug Properties:

- Carcinogenicity:
  Very rare cases of pituitary tumours have been observed in humans with buserelin use.

Pregnancy and Lactation:

- Mutagenicity: No
- Fetotoxicity: Yes
- Pregnancy:
  Buserelin is **contraindicated** for use in pregnancy. Adequate non-hormonal contraception should be used by patients and their partners during treatment, and for at least **6 months** after the last dose (general recommendation).
- Breastfeeding: Contraindicated
  Buserelin is secreted into breast milk.
- Fertility effects: Probable
  Documented in animal studies

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Antidiabetic agents	↓ effect	Unknown	Caution
Drugs that may prolong QT (i.e. Amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	QTc prolongation, 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 pressure monitoring in patients with hypertension	regular
Blood glucose/HbA1c levels	baseline and periodic, especially in diabetic patients
EKG, Electrolytes, (including K, Ca, Mg)	baseline, also regular for at risk patients
PSA	baseline and periodic
Clinical assessment of disease flare, local reactions, thromboembolism, cardiovascular effects, osteoporosis, psychiatric effects, hot flashes	regular

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
ECG for patients at risk of QTc prolongation	baseline and as clinically indicated

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

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K - References

Product Monograph: Suprefact® (buserelin). Sanofi-aventis Canada, August 10, 2010.

Product Monograph: Suprefact® Depot (buserelin). Sanofi-aventis Canada, August 10, 2010.

Product Monograph: Suprefact®. Sanofi-aventis (New Zealand), October 2012.

November 2024 Updated Indications and Pregnancy and Lactation 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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