DRUG NAME: Buserelin

SYNONYM(S):

COMMON TRADE NAME(S): SUPREFACT®, SUPREFACT® DEPOT

CLASSIFICATION: hormonal agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Buserelin is a luteinizing hormone releasing hormone (LHRH) agonist. It is a synthetic analog of LHRH (also known as gonadotropin releasing hormone [GnRH]).[1] LHRH agonists (LHRHa) initially stimulate the release of luteinizing hormone (LH, gonadotropin), resulting in a transient elevation in serum androgen in men and serum estradiol in women. However, chronic administration can cause down-regulation of the LHRH receptors, thus inhibiting the secretion of LH and ultimately the sex hormones (androgen, estradiol). By decreasing the testicular production of androgen in men, LHRHa can inhibit the growth of androgen-dependent prostate cancer. Similarly, LHRHa reduce the ovarian secretion of estradiol and progesterone in women,[2] leading to inhibition of estrogen-dependent cancers. In men, LHRHa can reduce serum androgen to castrate level about 21 days after initiation of therapy. Similarly, serum estradiol level is suppressed in women around 4 weeks after initiation of treatment. LHRHa are 50-100 times more potent than LHRH.[3] In addition, they have a longer duration of action due to increased receptor affinity and greater biological stability.

PHARMACOKINETICS:

Oral Absorption	low, due to proteolysis in the GI tract[4]	
Distribution	high concentrations in liver; low concentrations in kidney, pituitary, thyroid	
	cross blood brain barrier?	yes
	volume of distribution	no information found
	plasma protein binding	15%[5]
Metabolism	liver, kidney, hypothalamus, pituitary gland[6]: enzymatic degradation by pyroglutamate aminopeptidase, endopeptidase, and post-proline-cleaving enzymes[4]	
	active metabolite(s)	no information found
	inactive metabolite(s)	buserelin-(5-9)-pentapeptide
Excretion	renal	
	urine	13-30%: 67% as buserelin, 32% as buserelin-(5-9)-pentapeptide
	feces[7]	bile: unchanged drug and metabolites
	terminal half life	72-80 min
	clearance	no information found

Adapted from standard reference[5] unless specified otherwise.

USES:

Primary uses:
Breast Cancer[8]
*Prostate cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to buserelin or any of its components,[1] other LHRHa, or LHRH[9]
- undiagnosed abnormal vaginal bleeding[10]

Caution:
- history of ***heart disease*** or previous heart attack or stroke, cardiovascular risk factors (i.e., hypertension, high cholesterol, smoking), or diabetes[11-14]; see paragraph after **Side Effects** table
- long QT syndrome, electrolyte abnormalities, CHF, or concurrent administration with other QT prolonging drugs[12-14]; see paragraph after **Side Effects** table

Drug-induced disease flare: During the initial weeks of treatment, LHRHa may cause a worsening (flare) of the symptoms of prostate or breast cancer.[9] Cases of spinal cord compression and/or ureteral obstruction have occurred in men with prostate cancer receiving LHRHa. These conditions require mandatory use of ketoconazole (NIZORAL®) (high dose) or anti-androgens, with LHRHa.[15] Administer with caution to patients at risk for developing these conditions; e.g., patients with vertebral metastases.[16] For more information, see paragraph following **Side Effects** table.

Changes in bone density: Decreased bone mineral density (BMD) may occur with buserelin therapy.[1,16] Use with caution in patients with risk factors. For more information, see paragraph following **Side Effects** table.

Transient hypercalcemia may develop after initiation of LHRHa in patients with bone metastases.[9]

Male breast cancer: At time of writing, use of LHRHa in male breast cancer is considered experimental.[17,18]

Carcinogenicity: Found to increase pituitary adenomas in rats treated with high doses of buserelin for durations >6 months.[1]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test.[1] No information found for clastogenicity.

Fertility: Ovulation is suppressed during treatment with buserelin.[10] Animal studies have shown decreased fertility in both males and females while receiving buserelin.

Pregnancy: Not available in the United States, therefore FDA Pregnancy Category has not been assigned. Buserelin is contraindicated in women who are pregnant, as it is not known if it can cause fetal abnormalities in humans.[10] Non-hormonal methods of birth control should be used during therapy.

Breastfeeding is not recommended due to the potential secretion into breast milk.[10]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[19,20] When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	allergic reactions, anaphylaxis
auditory/hearing	hearing disorders, tinnitus

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood/bone marrow/ febrile neutropenia	***anemia; males at increased risk***[19]
	leukopenia
	thrombocytopenia
cardiovascular (arrhythmia)	tachycardia (<1%), palpitations (≤5%)
cardiovascular (general)	CHF (<1%)
	hypertension (≤9%)
	myocardial infarction (male 0.3%)[20,21]***, sudden cardiac death (male 0.4%)***
constitutional symptoms	appetite changes (≤5%)
	fatigue
	fever (<1%)
	sleep disorders, insomnia (≤5%)
	weight gain[21]
	weight loss (<1%)
dermatology/skin	*extravasation hazard: none*[22]
	alopecia, hair growth
	injection site reaction; may include pain, irritation, swelling, urticaria
	rash (male 3%)[5]
endocrine	diabetes,[21] exacerbation of pre-existing diabetes[1] (<1%)
	drug-induced disease flare; see paragraph following **Side Effects** table
	hot flashes (≤23%)
gastrointestinal	*emetogenic potential: rare*[23]
	anorexia
	constipation (3%)[5]
	diarrhea (1%)[5]
	dyspepsia (1%)[5]
	nausea (≤5%)
	thirst, dry mouth/nose
	vomiting (male 1%[5], female frequency unknown)
hemorrhage	vaginal (1-10%)[5]; during early treatment; see paragraph following **Side Effects** table
lymphatics	edema (≤1%)
metabolic/laboratory	hypercalcemia[9]
	hypercholesterolemia, hyperlipidemia
	hyperglycemia (<1%)
	liver function tests, increase
musculoskeletal	***decreased bone mineral density***; osteoporosis; see paragraph following **Side Effects** table

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	fracture,[24,25] ***increased risk***; duration-related
	loss of muscle mass; males at increased risk[19]
	shoulder pain/stiffness (female)
neurology	anxiety, emotional lability, mood changes
	depression (≤2%)
	dizziness (≤5%)
	memory loss, concentration disturbances
	neck rigidity (1-5%)
	suicide attempt (<1%)
ocular/visual	blindness in one eye (<1%); temporary
	ophthalmic disorders (<1%); may include dryness, irritation, feeling of pressure behind eyes, and impaired vision
pain	general (≤2%)
	headache[5]
	myalgia, arthralgia (≤5%)
pulmonary	dyspnea (<1%)
	pharyngitis (<1%)
renal/genitourinary	genitourinary effects, usually transient and may result from drug-induced disease flare; see paragraph following **Side Effects** table
	urinary retention
secondary malignancy	pituitary adenomas (<1%)
sexual/reproductive function	amenorrhea (100%)[26]
	gynecomastia (<1%)
	hirsutism
	impotence (90%)
	libido, decreased (male 100%,[20] female frequency unknown)
	ovulation, inhibition[10]
	vaginal dryness
vascular	thrombophlebitis (<1%)

Adapted from standard reference[1] unless specified otherwise.

***Bone density*:** Both androgen and estrogen are involved in bone formation by increasing osteoblast activity.[9,27] Estrogen plays a central role in the homeostasis of normal skeleton in both males and females.[28,29] Thus, the hypogonadic state produced by buserelin can result in decreased bone mineral density (BMD) and possible increased fracture risk.[24,25,30] Fractures can be severe, as they may occur in the spine and hip.

BMD should be monitored, and calcium and vitamin D supplementation should be initiated. Lifestyle modification including regular exercise, particularly weight-bearing exercise (e.g., walking), should be encouraged. If treatment is required, consult current national guidelines[31,32] for specific recommendations. Options may include bisphosphonate therapy.[25]

Drug-induced disease flare: New or worsening signs and symptoms of prostate or breast cancer may occur in the initial weeks of buserelin therapy.[9,33,34] The flare is a result of the buserelin-induced increase in androgen (in men) and estradiol (in women) during the initial weeks of therapy, prior to LHRH down-regulation.

In men, symptoms may include: acute exacerbation of bone pain, spinal cord compression[4], urinary retention, urethral obstruction[9], lymphedema.[35] Blockage of flare in men can be achieved using anti-androgens (e.g., flutamide, bicalutamide, nilutamide, cyproterone) concurrent with the first administration of buserelin.[9,35] Flare is experienced significantly less frequently today due to the use of anti-androgens and the initiation of LHRHa earlier in the treatment of prostate cancer.

In women, symptoms may include[34,36]: acute exacerbation of bone pain, skin erythema, increase in the size and/or number of metastatic skin nodules. There are currently no agents available to achieve blockage of flare in women.

Treatment of flare may include the use of analgesics for pain.

Vaginal bleeding, or breakthrough bleeding, may frequently occur during early buserelin therapy. The normal menstrual cycle consists of a follicular, or proliferative, phase and a luteal, or post-ovulatory, phase.[37,38] Increasing levels of estrogen in the follicular phase lead to maturation of the follicle and proliferation of the uterine mucosa, while decreasing levels of hormone in the luteal phase lead to sloughing of the endometrium (menses). At the initiation of therapy, menses may still occur as estrogen levels fall, particularly if treatment was started in the luteal phase of the menstrual cycle. It may also be possible that the initial buserelin-induced estrogen increase (flare) will induce the follicular phase of the menstrual cycle; again, menses will occur as estrogen levels fall. Therefore, one or two menses could be expected following the start of therapy. There is still potential for pregnancy to occur early after initiation.

A possible increased risk of ***myocardial infarction, sudden cardiac death, and stroke*** has been associated with androgen deprivation therapy in men, possibly due to effects on traditional cardiovascular risk factors, including serum lipoproteins, insulin sensitivity, and obesity. Monitor for signs and symptoms suggestive of cardiovascular disease and manage according to current clinical practice. Risk of treatment should be weighed against risk of disease. Androgen deprivation therapy also has the potential to ***prolong QT/QTc interval*** on ECG; therefore, concurrent therapy with other QT prolonging drugs may increase the risk of potentially fatal arrhythmias. Assess patients with long QT syndrome, electrolyte abnormalities, or CHF for increased cardiovascular risk.[11-14] Cardiovascular risk in women is unknown.

INTERACTIONS:

No documented drug interactions.[1]

SUPPLY AND STORAGE:

Nasal solution[10]: sanofi-aventis Canada Inc. supplies 1 mg/mL solution in a 10 mL bottle for intranasal administration and includes a metered-dose pump or nebulizer. Each pump action delivers 100 mcg buserelin or 0.1 mL solution. Store at room temperature in the original container; do not freeze; protect from light.

Injection: sanofi-aventis Canada Inc. supplies 3 products[1,10]:

- 1 mg/mL in 5.5 mL multi-dose vials for **subcutaneous** administration. Selected non-medicinal ingredients: benzyl alcohol. Store at room temperature in the original container; do not freeze; protect from light.
- 6.3 mg (2-month) depot and 9.45 mg (3-month) depot for **subcutaneous** administration.[1] The 2-month depot contains 1 implantable dose consisting of 2 identical cylindrical rods. The 3-month depot contains 1 implantable dose consisting of 3 identical cylindrical rods. Both are available as a pre-filled syringe. Store at room temperature in the original container; protect from heat.

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	• non-depot injection[10] • ***depot injection into the lateral abdominal wall***[2]
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	no information found
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Subcutaneous:	daily[10]:	• initial therapy: 500 mcg (0.5 mL) SC every 8 hours for 7 consecutive days starting on day 1 • maintenance therapy: 200 mcg (0.2 mL) SC as a single daily dose
	n/a[8]:	***6.3 mg depot injection SC every 6 weeks for 2 treatments, then every 8 weeks*** ***Once clinical response has been established, may substitute 9.45 mg depot injection SC every 12 weeks.***
	8 weeks[39]:	***6.3 mg depot injection SC for one dose on day 1 (total dose per cycle 6.3 mg)***
	12 weeks[39]:	***9.45 mg depot injection SC for one dose on day 1 (total dose per cycle 9.45 mg)***
Intranasal:	daily[10]:	• initial therapy: use subcutaneous route, as above • maintenance therapy: 400 mcg (200 mcg into each nostril) three times daily using metered-dose pump (nebulizer)

Concurrent radiation: no dosing adjustment required[20]

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure: no information found

BCCA usual dose noted in ***bold, italics***

	Cycle Length:
Dosage in hepatic failure:	no information found
Dosage in dialysis:	no information found

Children: no information found for the use of buserelin in oncology

REFERENCES:

1. sanofi-aventis Canada Inc. SUPREFACT® DEPOT 2 months and SUPREFACT® DEPOT 3 months product monograph. Laval, Quebec; 26 April 2006.
2. Tyrrell JB, Findling JW, Aron DC. Hypothalamus and pituitary. Basic and Clinical Endocrinology. 4th ed. Norwalk, Connecticut: Appleton and Lange; 1994. p. 81-82.
3. Engel JB, Schally AV, Engel JB, et al. Drug Insight: clinical use of agonists and antagonists of luteinizing-hormone-releasing hormone. Nat Clin Pract Endocrinol Metab 2007;3(2):157-67.
4. Chabner BA, Longo DL. Cancer Chemotherapy and Biotherapy. 3rd ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2001. p. 95-97.
5. DRUGDEX Evaluations [database on the Internet]. Buserelin. Thomson MICROMEDEX®, 2007. Available at: http://www.micromedex.com/, 2 April 2007.
6. DeVita VT, Hellman S, Rosenberg SA. Cancer Principles & Practice of Oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 483-484.
7. MARTINDALE- The Complete Drug Reference [database on the Internet]. Buserelin. Thomson MICROMEDEX®, 2007. Available at: http://www.micromedex.com/;. Accessed 2 April 2007.
8. BC Cancer Agency Breast Tumour Group. (BRAVLHRHT) BCCA Protocol Summary for Palliative Therapy for Breast Cancer Using LHRH agonist and Tamoxifen. Vancouver, British Columbia: BC Cancer Agency; 1 June 2006.
9. McEvoy GK, editor. AHFS 2006 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 1064-1066.
10. sanofi-aventis Canada Inc. SUPREFACT® product monograph; buserelin acetate injection; buserelin acetate nasal solution. Laval, Quebec; 8 May 2006.
11. Health Canada. MedEffect® e-Notice - GnRH agonists: Heart-related Risk in Men Treated for Prostate Cancer. 8 September 2011. Available at: http://www.hc-sc.qc.ca/ahc-asc/media/advisories-avis/.
12. sanofi-aventis Canada Inc. ELIGARD® product monograph. Laval, Quebec; 31 May 2011.
13. Abbott Laboratories Limited. LUPRON® and LUPRON DEPOT® product monograph. St-Laurent, Quebec; 2 September 2011.
14. sanofi-aventis Canada Inc. SUPREFACT® product monograph. Laval, Quebec; 10 August 2010.
15. Judy Sutherland MD. Personal communication. BC Cancer Agency Genitourinary Tumour Group.; 16 June 2007.
16. AstraZeneca Canada Inc. ZOLADEX® product monograph. Mississauga, Ontario; 8 June 2004.
17. Giordano SH, Hortobagyi GN. Leuprolide Acetate Plus Aromatase Inhibition for Male Breast Cancer. J Clin Oncol 2006;24(21):42e-43.
18. Susan Ellard MD. Personal communication. BC Cancer Agency Breast Tumour Group; 25 June 2007.
19. Susan Ellard MD. Personal communication. BC Cancer Agency Breast Tumour Group.; 10 May 2007.
20. Tom Pickles MD. Personal communication. BC Cancer Agency Genitourinary Tumour Group.; 24 April 2007.
21. Keating NL, O'Malley AJ, Smith MR, et al. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24(27):4448-56.
22. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and management of extravasation of chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 September 2006.
23. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 November 2005.
24. Smith MR, Lee WC, Brandman J, et al. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. J Clin Oncol 2005;23(31):7897-903.
25. Shahinian VB, Kuo YF, Freeman JL, et al. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352(2):154-64.
26. Chabner BA, Longo DL. Cancer Chemotherapy and Biotherapy. 3rd ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2001. p. 116-117.
27. Mottet N, Prayer-Galetti T, Hammerer P, et al. Optimizing outcomes and quality of life in the hormonal treatment of prostate cancer. BJU International 2006;98(1):20-7.
28. Theriault RL. Strategies to prevent chemotherapy-induced bone loss in women with breast cancer. Clin Breast Cancer 2005;5 Suppl(2):S63-70.
29. Smith MR. Therapy Insight: osteoporosis during hormone therapy for prostate cancer. Nat Clin Pract Urol 2005;2(12):608-615; quiz 28.

30. Smith MR. Diagnosis and management of treatment-related osteoporosis in men with prostate carcinoma. Cancer 2003;97(3 Suppl):789-95.
31. Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002;167(90100):1S-34.
32. BC Cancer Agency Genitourinary Tumour Group. Osteoporosis Screening Guidelines. Vancouver, British Columbia: BC Cancer Agency; 25 April 2007.
33. Emens LA, Davidson NE. Adjuvant Hormonal Therapy for Premenopausal Women with Breast Cancer. Clin Cancer Res 2003;9(1):486S-494.
34. Clarysse A. Hormone-induced Tumor Flare. Eur J Cancer Clin Oncol 1984;21(5):545-547.
35. Thompson I. Flare Associated with LHRH-Agonist Therapy. Rev Urol 2001;3(Suppl 3):S10-S14.
36. Rose BD editor. Endocrine Therapy of Metastatic Breast Cancer. UpToDate 15.1 ed. Waltham, Massachusetts: UpToDate®; 2007.
37. Underwood JCE, editor. General and Systemic Pathology. 3rd ed. Edinburgh, London, New York, Philadelphia, St Louis, Sydney, Toronto: Churchill Livingstone; 2000. p. 330-340.
38. Koda-Kimble MA, Young LY, editors. Applied Therapeutics. 7th ed. Baltimore Maryland: Lippincott Williams & Wilkins; 2001. p. 43-2,3,4.
39. BC Cancer Agency Genitourinary Tumour Group. (GUPLHRH) BCCA Protocol Summary for Therapy for Prostate Cancer Using LHRH Agonist (Goserelin, Leuprolide or Buserelin). Vancouver, British Columbia: BC Cancer Agency; 1 February 2007.