DRUG NAME: Leuprolide

SYNONYM: Leuprorelin acetate[1]

COMMON TRADE NAME(S): ELIGARD®, LUPRON®, LUPRON DEPOT®

CLASSIFICATION: hormonal agent

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

MECHANISM OF ACTION:

Leuprolide is a luteinizing hormone releasing hormone (LHRH) agonist. It is a synthetic analog of LHRH (also known as gonadotropin releasing hormone [GnRH]).[2] 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,[3] leading to inhibition of estrogen-dependent cancers. In men, LHRHa can reduce serum androgen to castrate level. Similarly, in pre-menopausal women, serum estradiol level is reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and are maintained as long as treatment continues. LHRHa are 50-100 times more potent than LHRH.[4] 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[5]	
Distribution	high concentrations in kidney, liver, pineal, pituitary tissue[1]; low concentrations in hypothalamus, cerebral cortex, and muscle	
	cross blood brain barrier?	yes
	volume of distribution	males[6]: 27 L
	plasma protein binding	43-49%[6]
Metabolism	liver, kidney, hypothalamus, pituitary gland[7]: enzymatic degradation by pyroglutamate aminopeptidase, endopeptidase, and post-proline-cleaving enzymes[5]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	renal[6]	
	urine[6]	<5%
	feces	no information found
	terminal half life[6]	3 h
	clearance	7.6 L/h

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
Breast cancer[8]
*Prostate cancer

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to leuprolide, benzyl alcohol, other LHRH agonists, or LHRH[1,9]
- undiagnosed abnormal vaginal bleeding[6]

Caution:
- history of ***heart disease*** or previous heart attack or stroke, cardiovascular risk factors (i.e., hypertension, high cholesterol, smoking), or diabetes[10-13]
- leuporolide has the potential to ***prolong QT/QTc interval;*** patients at risk include those with long ***QT syndrome***, electrolyte abnormalities, CHF, and/or receiving other QT prolonging drugs concurrently[11-13]
- leuprolide may cause a ***drug-induced disease flare*** (a worsening of the symptoms of prostate or breast cancer) during the initial weeks of treatment[1]. Cases of spinal cord compression and/or urethral obstruction have been reported in men with prostate cancer receiving LHRH agonists; therefore, use with caution in patients at risk for developing these conditions (e.g., patients with vertebral metastases).[14] These conditions require mandatory use of ketoconazole (NIZORAL®) (high dose) or anti-androgens with LHRHa.[15]
- ***decreased bone mineral density*** may occur with leuprolide[2]; use with caution in patients at risk for fractures
- ***transient hypercalcemia*** may develop after initiation of LHRH agonists in patients with bone metastases.[9]
- at time of writing, use of LHRH agonists in ***male breast cancer*** is considered experimental.[16,17]

Carcinogenicity: Animal studies have shown an increased incidence of benign pituitary gland hyperplasia and adenomas.[2] In rats, there was a significant, but not dose-related, increase in pancreatic islet-cell adenomas in females and testicular interstitial cell adenomas in males.

Mutagenicity: Not mutagenic in mammalian *in vitro* mutation test.[2] No information found for clastogenicity.

Fertility: Ovulation is suppressed during treatment with leuprolide.[6] Leuprolide can reversibly suppress fertility in males and females.[1] Continuous leuprolide therapy in males may impair fertility.

Pregnancy: FDA Pregnancy Category X.[6] Contraindicated in pregnancy. Studies in animals or humans, or investigational or postmarketing reports have shown fetal risk which clearly outweighs any possible benefit to the patient. A nonhormonal contraceptive should be used.[6]

Breastfeeding is not recommended due to the potential secretion into breast milk.[2]

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.[18,19] 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 reaction (<5%), anaphylaxis[6,20]
auditory/hearing	hearing disorders, tinnitus (<5%)
blood/bone marrow/ febrile neutropenia	***anemia*** (<5%)[2,20]; males at increased risk[18]
	leukopenia (≤5%)[2,20]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	increased eosinophils (≥5%)[20]
	thrombocytopenia (>5%)
cardiovascular (arrhythmia)	arrhythmias (<5%)
cardiovascular (general)	CHF (<5%), angina (<5%)
	heart murmurs (<5%)
	hypertension (<5%)
	hypotension (<5%)[2,20]
	myocardial infarction (male 0.3%)[19,21], ***sudden cardiac death*** (male 0.4%)
constitutional symptoms	***fatigue***[2,20] (<5%)
	fever, chills (<5%)
	sleep disorders, insomnia (≥5%)
	weight gain[21]
	weight loss[1] (≥5%)
dermatology/skin	*extravasation hazard:* none[22]
	alopecia (<5%)[2,20]
	dermatitis (<5%)
	dry skin (<5%)
	hair growth (<5%)[2,20]
	injection site reaction[2,20]; may include pain, irritation, swelling, urticaria
	photosensitivity
	pigmentation (<5%)
	pruritus (<5%)[2,20]
	rash (<1%)
endocrine	diabetes[21] (<5%)[2]
	drug-induced disease flare; see paragraph following **Side Effects** table
	hot flashes (40-77%)
	thyroid enlargement (<5%), hard nodule in throat (male)
gastrointestinal	*emetogenic potential:* rare[23]
	anorexia (≥5%)
	appetite changes (<5%)
	constipation (≥5%)
	diarrhea (<5%)
	dysphagia (<5%)
	glossitis (<5%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	nausea and/or vomiting (≥5%)
	rectal polyps (<5%)
	taste perversion (<5%)
	thirst (<5%), dehydration (<5%), dry mouth (<5%)
	ulcer (<5%)
hemorrhage	epistaxis
	GI (<5%)
	vaginal; during early treatment, see paragraph following **Side Effects** table
infection	infection, inflammation (<5%)
	vaginitis
lymphatics	edema (<5%), lymphedema (<5%), peripheral edema (≤12%)
metabolic/laboratory	hypercalcemia (<5%)
	hypercholesterolemia (≥5%)[20]
	hyperglycemia (<5%)
	hypoglycemia (<5%)
	hypoproteinemia (<5%)
	hyperuricemia[6] (<5%)
	liver function test elevations (≥5%)
	PT increase (≥5%)
musculoskeletal	***bone mineral density decrease;*** see paragraph following **Side Effects** table
	fracture[24,25] (<3%); spinal fractures, paralysis
	loss of muscle mass; males at increased risk[18]
	joint changes, ankylosing spondylosis (<5%)
	pelvic fibrosis (<5%)
	weakness[20] (<4%)
neurology	anxiety (<5%), emotional lability (≥5%), confusion (<5%), mood swings (<5%), delusions (<5%)
	depression
	dizziness (≥5%)
	memory loss (<5%)
	numbness (<5%), paresthesia (<5%), hypoesthesia (<5%)
	peripheral neuropathy (<5%)
	syncope, blackouts (<5%)
	vertigo (≥5%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
ocular/visual	ophthalmic disorders(<5%); e.g., blurred vision,[1] ambylopia, abnormal vision, dry eyes, conjunctivitis
pain	breast pain, tenderness (<2%)[20]
	general (≥5%)
	headache (≥5%)
	myalgia (<5%)
	prostate (<5%), testicular (<5%)
pulmonary	cough (<5%)
	dyspnea (<5%)
	hemoptysis (<5%)
	pharyngitis (<5%)
	pleural effusion (<5%), pleural rub (<5%), pulmonary infiltrates (<5%)
	pneumonia (<5%)
renal/genitourinary	bladder spasms (<5%)
	genitourinary effects; usually transient and may result from drug-induced disease flare; see paragraph following **Side Effects** table
	urinary disorders (10-15%); e.g., dysuria (<5%), frequency/urgency/incontinence (<5%), nocturia[20] (1-2%)
secondary malignancy	bladder cancer (<5%)
	skin cancer (<5%)
sexual/reproductive function	abortion, spontaneous
	amenorrhea (100%)[26]
	breast reduction (<5%)
	gynecomastia (<5%)
	libido, decrease (male 100%,[19] female frequency unknown)
	libido, increase (<5%)
	impotence (90%)[19]
	ovulation, inhibition[6]
	penile disorder (<5%); testicular atrophy (5-20%)
	vaginal dryness
syndromes	pituitary apoplexy (<1%)
vascular	phlebitis, thrombosis (<5%)
	pulmonary embolus (<5%)

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***Bone density*:** Both androgen and estrogen are involved in bone formation by increasing osteoblast activity.[1,27] Estrogen plays a central role in the homeostasis of normal skeleton in both males and females.[28,29] Thus, the hypogonadic state produced by leuprolide therapy 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.[27] 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 for specific recommendations.[31,32] Options may include bisphosphate therapy.[25]

Drug-induced disease flare: New or worsening signs and symptoms of prostate or breast cancer may occur in the initial weeks of leuprolide therapy.[9,33,34] The flare is a result of the leuprolide-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[5], urinary retention, ureteral 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 leuprolide.[9,35] Flare is experienced significantly less frequently today due to the use of anti-androgens and the initiation of LHRH agonists earlier in the treatment of prostate cancer. Treatment of flare may include the use of analgesics for pain. In women, symptoms may include acute exacerbation of bone pain, skin erythema, increase in the size and/or number of metastatic skin nodules.[34,36] There are currently no agents available to achieve blockage of flare in women.

Vaginal bleeding, or breakthrough bleeding, may frequently occur during early leuprolide therapy. The normal menstrual cycle consists of a follicular, or proliferative, phase and a luteal, or post-ovulatory, phase. 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 leuprolide-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.[37,38]

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.[10-13] Cardiovascular risk in women is unknown.

INTERACTIONS: None known[2]

SUPPLY AND STORAGE:

Injection:
AbbVie Corporation[39] supplies leuprolide acetate:

- LUPRON® as a sterile solution in a 14 mg/2.8 mL (5 mg/mL) multi-dose vial for **subcutaneous** administration. Vials contain benzyl alcohol as preservative. Refrigerate. Protect from light. Keep in original packaging.

AND

- LUPRON DEPOT® as a pre-filled dual chamber syringe containing lyophilized microspheres of leuprolide in a 7.5 mg (1-month) depot, 22.5 mg (3-month) depot, and 30 mg (4-month) depot injection for **intramuscular** administration. Store at room temperature. Once reconstituted, the suspension is stable for 24 hours.

sanofi-aventis Canada Inc.[40] supplies leuprolide acetate (ELIGARD®) in a 7.5 mg (1-month) depot, 22.5 mg (3-month) depot, 30 mg (4-month) depot, and 45 mg (6-month) depot injection for **subcutaneous** administration. Each kit contains two pre-filled syringes which must be combined prior to use: one syringe containing lyophilized leuprolide and the other containing a polymeric delivery system. Refrigerate. Allow product to reach room temperature before using. Complete administration within 30 minutes of mixing. ELIGARD® may be stored at room temperature in original packaging up to 8 weeks prior to administration.

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PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	• LUPRON® non-depot injection[39] • ***ELIGARD®**** depot injection[40]
Intramuscular	***LUPRON DEPOT®*** injection[39]
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

*ELIGARD® is currently only used in prostate cancer

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:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Parenteral:	daily[2]:	1 mg SC (LUPRON®) as a single daily dose
	4 weeks[8]:	***7.5 mg IM (LUPRON® DEPOT) for one dose on day 1;*** once response has been established may substitute 22.5 mg IM (LUPRON® DEPOT) every 12 weeks
	4 weeks[41]:	***7.5 mg IM (LUPRON® DEPOT)*** or ***SC (ELIGARD®)* for one dose on day 1*** (total dose per cycle 7.5 mg)
	12 weeks[41]:	***22.5 mg IM (LUPRON® DEPOT)*** or ***SC (ELIGARD®)* for one dose on day 1*** (total dose per cycle 22.5 mg)
	16 weeks[41]:	***30 mg IM (LUPRON® DEPOT)*** or ***SC (ELIGARD®)* for one dose on day 1*** (total dose per cycle 30 mg)
	24 weeks[41]:	***45 mg SC (ELIGARD®)* for one dose on day 1*** (total dose per cycle 45 mg)

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Because of different release characteristics, a fractional dose of the 22.5 mg or 30 mg depot is not equivalent to the same dose of the once-monthly formulation, and should not be used for monthly dosing.[1]

Concurrent radiation: no dosing adjustment required[19]

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BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:
Dosage in renal failure:	pharmacokinetics of the drug in patients with renal impairment have not been determined[2]
Dosage in hepatic failure:	pharmacokinetics of the drug in patients with hepatic impairment have not been determined[2]
Dosage in dialysis:	no information found

Children[1]: no information found

REFERENCES:

1. McEvoy GK, editor. AHFS 2006 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 1117-1125.
2. TAP Pharmaceuticals Inc. LUPRON® & LUPRON DEPOT® product monograph. Lake Forest, Illinois; 6 December 2006.
3. Tyrrell JB, Findling JW, Aron DC. Hypothalamus and pituitary. Basic and Clinical Endocrinology. 4th ed. Norwalk, Connecticut: Appleton and Lange; 1994. p. 81-82.
4. 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 Feb 2007;3(2):157-67.
5. Chabner BA, Longo DL. Cancer chemotherapy and biotherapy. 3rd ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2001. p. 95-97.
6. Rose BD editor. Leuprolide: Drug Information. UpToDate 15.1 ed. Waltham, Massachusetts: UpToDate®; accessed 7 March 2007.
7. DeVita VT, Hellman S, Rosenberg SA. Cancer Principles & Practice of Oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 483-484.
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. Health Canada. MedEffect® e-Notice - GnRH agonists: Heart-related Risk in Men Treated for Prostate Cancer. 8 September 2011. Available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html. Accessed 1 November 2011.
11. sanofi-aventis Canada Inc. ELIGARD® product monograph. Laval, Quebec; 31 May 2011.
12. Abbott Laboratories Limited. LUPRON® and LUPRON DEPOT® product monograph. St-Laurent, Quebec; 2 September 2011.
13. sanofi-aventis Canada Inc. SUPREFACT® product monograph. Laval, Quebec; 10 August 2010.
14. AstraZeneca Canada Inc. ZOLADEX® product monograph. Mississauga, Ontario; 8 June 2004.
15. Judy Sutherland MD and BC Cancer Agency Genitourinary Tumour Group. Personal communication. 16 June 2007.
16. Giordano SH, Hortobagyi GN. Leuprolide Acetate Plus Aromatase Inhibition for Male Breast Cancer. J Clin Oncol 20 July 2006;24(21):42e-43.
17. Susan Ellard MD. BC Cancer Agency Breast Tumour Group. Personal communication. 25 June 2007.
18. Susan Ellard MD. BC Cancer Agency Breast Tumour Group. Personal communication. 10 May 2007.
19. Tom Pickles MD.BC Cancer Agency Genitourinary Tumour Group. Personal communication. 24 April 2007.
20. sanofi-aventis Canada Inc. ELIGARD® product monograph. Laval, Quebec; 17 August 2006.
21. Keating NL, O'Malley AJ, Smith MR, et al. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol Sep 20, 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 Nov 1, 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 Jan 13, 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 Jul 2006;98(1):20-7.

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28. Theriault RL. Strategies to prevent chemotherapy-induced bone loss in women with breast cancer. Clin Breast Cancer Feb 2005;5 Suppl(2):S63-70.
29. Smith MR. Therapy Insight: osteoporosis during hormone therapy for prostate cancer. Nat Clin Pract Urol Dec 2005;2(12):608-15; quiz 28.
30. Smith MR. Diagnosis and management of treatment-related osteoporosis in men with prostate carcinoma. Cancer Feb 1, 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 November 12, 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 January 1, 2003;9(1):486S-494.
34. Clarysse A. Hormone-induced Tumor Flare. Eur J Cancer Clin Oncol 13 November 1984;21(5):545-547.
35. Thompson I. Flare Associated with LHRH-Agonist Therapy. Rev Urol 2001;3(Suppl 3):S10-S14.
36. Ellis M, Hayes DF, edited by Rose BD. Endocrine Therapy of Metastatic Breast Cancer. UpToDate® 15.1, Available at: www.uptodate.com. Accessed 11 April 2007.
37. Underwood JCE, editor. General and Systemic Pathology. 3rd ed. Edinburgh: Churchill Livingstone; 2000. p. 330-340.
38. Koda-Kimble MA, Young LY, editors. Applied Therapeutics. 7th ed. Baltimore, Maryland: Lippincott Williams & Wilkins; 2001. p. 43.2-43.4.
39. AbbVie Corporation. LUPRON® & LUPRON DEPOT® product monograph. St-Laurent, Quebec; 20 June 0219.
40. sanofi-aventis Canada Inc. ELIGARD® product monograph. Laval, Quebec; 7 December 2018.
41. 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.

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