DRUG NAME: Goserelin

SYNONYM: Decapeptide I[1]

COMMON TRADE NAME(S): ZOLADEX®, ZOLADEX® LA

CLASSIFICATION: hormonal agent

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

MECHANISM OF ACTION:

Goserelin is a luteinizing hormone releasing hormone (LHRH) agonist.[2] It is a synthetic analog of LHRH (also known as gonadotropin releasing hormone [GnRH]). 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 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.[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	cross blood brain barrier?	yes
	volume of distribution	male[6]: 44.1 L female[6]: 20.3 L
	plasma protein binding	27.3%[7]
Metabolism	liver, kidney, hypothalamus, pituitary gland[8]: 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[7]	
	urine[7]	>90%
	feces	no information found
	terminal half life[5]	4.9 h
	clearance[8]	8 L/h

Adapted from standard reference[2,9] unless specified otherwise.

USES:

Primary uses:
*Breast cancer
*Prostate cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to goserelin or any of its components,[9] other LHRHa, or LHRH[1]
- undiagnosed abnormal vaginal bleeding[2]

Caution:
- history of ***heart disease*** or previous heart attack or stroke, cardiovascular risk factors (i.e., hypertension, high cholesterol, smoking), or diabetes[10-13]; see paragraph after **Side Effects** table
- long QT syndrome, electrolyte abnormalities, CHF, or concurrent administration with other QT prolonging drugs[11-13]; 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.[1] Cases of spinal cord compression and/or urethral 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.[14] Administer with caution to patients at risk to developing these conditions; e.g., patients with vertebral metastases.[2] For more information, see paragraph following **Side Effects** table.

Changes in bone density: Decreased bone mineral density (BMD) may occur with goserelin therapy.[2] 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.[1]

Male breast cancer: At time of writing, use of LHRHa in male breast cancer is considered experimental.[15,16]

Carcinogenicity: Animal studies have shown an increased incidence of benign pituitary gland adenomas.[9]

Mutagenicity: Not mutagenic in mammalian *in vitro* mutation test.[9] Goserelin is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.

Fertility: Ovulation is suppressed during treatment with goserelin.[2] Animal studies have shown that fertility and general reproductive performance is reduced in rats that became pregnant after goserelin was discontinued.[9] Studies in rats and rabbits confirm that goserelin will increase pregnancy loss in a dose-related manner. There is no evidence of impaired conception following goserelin therapy continued for a period of 6 months.

Pregnancy: FDA Pregnancy Category D.[6] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Non-hormonal methods of birth control should be used during therapy[9], and following discontinuation, until return of menses (or for at least 12 weeks).[6]

Breastfeeding is contraindicated as goserelin is detected in human breast milk.[1]

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.[17,18] When placebo-controlled trials are available, adverse events are included if the incidence is $\geq$5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	allergic reactions (1-10%)[6], anaphylaxis
blood/bone marrow/ febrile neutropenia	***anemia (1-10%)[6]; males at increased risk[17]***
	leukopenia
	thrombocytopenia
cardiovascular (arrhythmia)	arrhythmia (1-10%)[6], tachycardia (1-10%)[6]
cardiovascular (general)	CHF (male 5%)[6]
	myocardial infarction (male 0.3%)[19], sudden cardiac death (male 0.4%)
	transient changes in blood pressure[1]; hypertension (1-10%)[6] or hypotension
constitutional symptoms	***fatigue[6]***
	fever/chills (1-10%)[6]
	sleep disorders, insomnia (male 5%, female 11%)[6]
	weight gain[19] (1-10%)[6]
dermatology/skin	*extravasation hazard: none*[20]
	alopecia (1-10%)[6]
	injection site reaction; may include pain, irritation, swelling, urticaria
	pigmentation (1-10%)[6]
	rash, erythema, urticaria (male 6%, female >1%)[6], dry skin, seborrhea (female >5%)[1]
endocrine	diabetes[19]
	drug-induced disease flare; see paragraph following **Side Effects** table
	hot flashes (male 62%, female 96%)[6]
gastrointestinal	*emetogenic potential: rare*[21]
	anorexia (male 5%, female >1%)[6]
	constipation (1-10%)[6]
	diarrhea (1-10%)[6]
	dry mouth (1-10%)[6]
	dyspepsia (1-10%)[6]
	flatulence (1-10%)[6]
	nausea (male 5%,[6] females >5%[1])
	ulcer (1-10%)[6]
	vomiting (1-10%)[6]
hemorrhage	epistaxis (1-10%)[6]
	hemorrhage (1-10%)[6]
	vaginal (1-10%);[6] during early treatment[9], see paragraph following **Side Effects** table
infection	infection (female 13%)[6]
	sinusitis (1-10%)[6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	upper respiratory tract infection (male 7%)[6]
	urinary tract infection (1-10%)[6]
	vaginitis (75%)[6]
lymphatics	edema (1-10%)[6]
metabolic/laboratory	alkaline phosphatase, increase
	hypercalcemia[1]
	hypercholesterolemia, hyperlipidemia
	hyperuricemia, gout (1-10%)[6]
musculoskeletal	***decreased bone mineral density*** (male >5%,[1] female frequency unknown), osteoporosis (male >5%)[1]; see paragraph following **Side Effects** table
	fracture[22,23] (male >5%, female frequency unknown)[1]
	joint disorder (1-10%)[6]
	loss of muscle mass; males at increased risk[17]
neurology	anxiety (1-10%)[6], emotional lability[6]
	depression[6]
	dizziness (male 5%, female 6%)[6]
	memory loss
	paraesthesias (1-10%)[6]
ocular/visual	ophthalmic disorders; may include ambylopia (1-10%)[6], dryness (1-10%)[6]
pain	arthralgia (1-10%)[6]
	breast pain (female 7%)[6]
	dysmenorrhea (1-10%)[6]
	dyspareunia (14%)[6]
	general (male 8%, female 17%)[6]
	headache (male 1-5%, female 75%)[6]; migraine (1-10%)[6]
	pelvic pain (male 6%)
pulmonary	chronic obstructive pulmonary disease (male 5%)[6]
	cough (1-10%)[6]
	pharyngitis (female 5%)[6], bronchitis (1-10%)[6]
renal/genitourinary	genitourinary effects, usually transient and may result from drug-induced disease flare; see paragraph following **Side Effects** table
	lower urinary tract symptoms[1] (male 13%)[6]
secondary malignancy	pituitary adenomas (<1%)
sexual/reproductive function	amenorrhea (100%)[5]; menses usually resumed within 8 weeks following completion of therapy[2]
	breast enlargement (female 18%)[6]
	breast reduction (female >5%)[1]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	gynecomastia (1-5%)[6]
	hirsutism (>5%)[1]
	impotence (90%)[18]
	libido, decreased (male 100%[18] female 61%)[6]
	libido, increased (female >5%)[1]
	menorrhagia
	ovarian cyst formation
	ovulation, inhibition
	sexual dysfunction (21%)[6]
	vaginal dryness/soreness
vascular	deep vein thrombosis[7]
	peripheral vascular disorder (1-10%)[6]

Adapted from standard reference[2] unless specified otherwise.

***Bone density*:** Both androgen and estrogen are involved in bone formation by increasing osteoblast activity.[1,24] Estrogen plays a central role in the homeostasis of normal skeleton in both males and females.[25,26] Thus, the hypogonadic state produced by goserelin therapy can result in decreased bone mineral density (BMD) and possible increased fracture risk.[22,23,27] Fractures can be severe, as they may occur in the spine and hip.[24]

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[28,29] for specific recommendations. Options may include bisphosphate therapy.[22]

Drug-induced disease flare: New or worsening signs and symptoms of prostate or breast cancer may occur in the initial weeks of goserelin therapy.[1,30,31] The flare is a result of the goserelin-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[1], lymphedema.[32] Blockage of flare in men can be achieved using anti-androgens (e.g., flutamide, bicalutamide, nilutamide, cyproterone) concurrent with the first administration of goserelin.[1,32] 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.

In women, symptoms may include[31,33]: 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 goserelin therapy. The normal menstrual cycle consists of a follicular, or proliferative, phase and a luteal, or post-ovulatory, phase.[34,35] 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 goserelin-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.[10-13] Cardiovascular risk in women is unknown.

INTERACTIONS: No documented drug interactions.[36]

SUPPLY AND STORAGE:

Injection: AstraZeneca supplies 2 products[9]:

- 3.6 mg (1-month) depot and 10.8 mg (3-month) depot for **subcutaneous** administration. Both contain 1 implantable dose consisting of 1 cylindrical rod. Both are available as a pre-filled syringe. Store at room temperature in the original container; protect from light and moisture.

PARENTERAL ADMINISTRATION:

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

Subcutaneous	***into the anterior abdominal wall below the navel line***[37,38]
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:	***4 weeks***[39]***:***	***3.6 mg SC for one dose on day 1 (total dose per cycle 3.6 mg) Once clinical response has been established, may substitute 10.8 mg SC every 12 weeks.***

4 weeks[40]: ***3.6 mg SC for one dose on day 1 (total dose per cycle 3.6 mg)***

12 weeks[40]: ***10.8 mg SC for one dose on day 1 (total dose per cycle 10.8 mg)***

If required, the implant can be located using ultrasound and removed.[1]

Concurrent radiation: no dosing adjustment required[18]

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[2]: although half-life is increased with impaired renal function, this has minimal effects; no dosing adjustment required

Dosage in hepatic failure[2]: no dosing adjustment required

Dosage in dialysis: no information found

Children: safety and effectiveness of goserelin has not been established[9]

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