

**DRUG NAME: Fulvestrant****SYNONYM(S):****COMMON TRADE NAME(S):** FASLODEX®**CLASSIFICATION:** hormonal agent, cytotoxic<sup>1</sup>*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Fulvestrant acts as an estrogen receptor (ER) antagonist, by competitively binding to estrogen receptors on tumour and other tissue targets, producing a nuclear complex that decreases DNA synthesis.<sup>2,3</sup> Fulvestrant has no ER agonist activity.<sup>3</sup>

Fulvestrant significantly downregulates ER expression in ER positive tumours and also produces a significant decrease in progesterone receptor expression.<sup>3</sup> Fulvestrant has demonstrated activity against tamoxifen-resistant breast cancers.<sup>4</sup> Fulvestrant-resistant tumours may be cross-resistant to tamoxifen.<sup>3</sup>

**PHARMACOKINETICS:**

Oral Absorption	poor <sup>2</sup>	
Distribution	extensive and rapid; peak plasma levels achieved after 7-9 days <sup>4</sup> ; steady-state concentrations achieved within 3-6 months <sup>4</sup> ; plasma levels maintained for at least 1 month <sup>2,4</sup>	
	cross blood brain barrier?	no information found
	volume of distribution	3-5 L/kg; suggests extravascular distribution
	plasma protein binding	99%; primarily to VLDL, LDL and HDL lipoprotein fractions
Metabolism	extensive hepatic; several biotransformation pathways including oxidation, aromatic hydroxylation, and conjugation, similar to endogenous steroids	
	active metabolite(s)	yes
	inactive metabolite(s)	yes
Excretion	rapid hepatic clearance; exposure and elimination primarily determined by rate of release from injection site	
	urine	<1%
	feces	90%
	terminal half life <sup>2,4</sup>	~40 d
	clearance	rate approximates hepatic blood flow (10.5 mL plasma/min/kg); mean clearance reduced 1.3 and 2.2-fold in patients with mild and moderate hepatic impairment respectively <sup>3</sup>
Sex	no significant difference	
Elderly	no significant difference	
Ethnicity	no significant difference	

Adapted from standard reference<sup>3</sup> unless specified otherwise.

**USES:****Primary uses:**

\*Breast cancer

\*Health Canada approved indication

**Other uses:****SPECIAL PRECAUTIONS:**

Contraindicated in patients with a history of hypersensitivity reaction to fulvestrant or any of the excipients, including benzyl alcohol.<sup>3,4</sup>

Efficacy in premenopausal women has not been established<sup>4</sup>

**Carcinogenicity:** Increased incidence of benign ovarian granulosa cell tumours and testicular Leydig cell tumours in male and female rats, at doses approximating 1 to 5-fold the systemic exposure achieved in women.<sup>3</sup>

**Mutagenicity:** Not mutagenic in Ames test and mammalian *in vitro* mutation test.<sup>3</sup> Fulvestrant is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.<sup>3</sup>

**Fertility:** Effects upon reproduction, including a reversible reduction in fertility, have been demonstrated in rats and rabbits at doses similar to, or lower than typical human doses, on a mg/m<sup>2</sup> basis.<sup>3</sup> No information found regarding fertility in male animals receiving fulvestrant.<sup>3</sup>

**Pregnancy:** FDA Pregnancy Category D.<sup>2,4</sup> There is positive evidence of human fetal risk,<sup>3</sup> 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).

**Breastfeeding** is not recommended due to the potential secretion into breast milk.<sup>3</sup> In rats, fulvestrant is distributed into milk at levels significantly higher than those in plasma.<sup>3</sup>

**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.<sup>5</sup>

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
allergy/immunology	hypersensitivity reactions ( $\leq 1\%$ ); including angioedema and urticaria; typically occurs shortly after injection; angioedema occurring several days after injection has been reported in one case
blood/bone marrow/ febrile neutropenia	anemia (5%)
	leukopenia ( $< 1\%$ ) <sup>2</sup>
cardiovascular (general)	<b>vasodilation</b> (18%)
constitutional symptoms	<b>asthenia</b> ( $\leq 23\%$ ); typically mild or moderate
	fever (6%)
	<b>hot flashes</b> ( $\leq 24\%$ ) <sup>3,4,6</sup>
	sweating (5%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
dermatology/skin	<i>extravasation hazard: none</i> <sup>7</sup>
	<b>injection site reactions</b> ( $\leq 10\%$ ); increased frequency (27%) when dose is divided into 2 injections; reaction includes mild transient pain and inflammation; may occur after prior uneventful injection and has been reported to develop into a systemic allergic response
	rash ( $\leq 10\%$ ); typically mild
gastrointestinal	<i>emetogenic potential: rare</i> <sup>8</sup>
	anorexia ( $\leq 10\%$ ); typically mild
	constipation (13%)
	diarrhea ( $\leq 12\%$ ); typically mild
	<b>nausea</b> ( $\leq 26\%$ ); typically mild
	vomiting ( $\leq 13\%$ ); typically mild
hepatobiliary/pancreas	elevated liver enzymes ( $\leq 10\%$ ); typically $< 2 \times$ ULN
infection	urinary tract infections ( $\leq 10\%$ ); typically mild
lymphatics	peripheral edema (9%)
musculoskeletal	arthritis (3%)
neurology	anxiety (5%)
	depression (6%)
	dizziness (7%)
	insomnia (7%)
	paresthesia (6%)
pain	<b>abdominal pain</b> (12%)
	<b>back pain</b> (14%)
	<b>bone pain</b> (16%)
	chest pain (7%)
	<b>headache</b> ( $\leq 15\%$ ); typically mild
	injection site pain (11%)
	pain not otherwise specified (19%)
	pelvic pain (10%)
pulmonary	<b>dyspnea</b> (15%)
	increased cough (10%)
	pharyngitis (16%)
sexual/reproductive function	<b>vaginal bleeding</b> ( $< 1\%$ ) <sup>2,4</sup> ; typically occurs during the first 6 weeks of changing from existing hormonal therapy <sup>4</sup>
syndromes	flu-like syndrome (7%)
vascular	<b>thrombosis</b> ( $< 1\%$ ) <sup>2</sup>

Adapted from standard reference<sup>3</sup> unless specified otherwise.

**INTERACTIONS:**

Although fulvestrant may be a minor substrate of CYP 3A4,<sup>2,3</sup> dosage adjustment is not necessary when prescribed with CYP 3A4 inhibitors or inducers.<sup>3</sup> In small clinical studies, ketoconazole and rifampicin were tested with fulvestrant and no pharmacokinetic interactions were noted.<sup>3</sup> Fulvestrant does not significantly inhibit any of the major CYP P450 isoenzymes *in vitro*.<sup>3</sup>

**SUPPLY AND STORAGE:**

**Injection:** AstraZeneca Canada Inc. supplies fulvestrant as a 250 mg/5 mL long-acting, single-use, sterile solution in a pre-filled syringe. Selected non-medicinal ingredients: ethanol 96%, benzyl alcohol, benzyl benzoate, and castor oil. Store in original packaging, in the refrigerator.<sup>3</sup> May be removed from the refrigerator and kept at room temperature or rolled gently between the hands before administration to ensure patient comfort.<sup>4</sup>

**Additional information:** The manufacturer's prescribing information should be consulted for details on assembly and use of the safety needle.<sup>3,4</sup>

**PARENTERAL ADMINISTRATION:**

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

Subcutaneous	should not be used <sup>2</sup>
Intramuscular	<b><i>administer slowly into the gluteal muscle</i></b> <sup>3</sup>
Direct intravenous	should not be used <sup>2</sup>
Intermittent infusion	no information found
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	should not be used <sup>2</sup>
Intravesical	no information found

**DOSAGE GUIDELINES:**

Refer to protocol by which patient is being treated.

**Adults:**

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

<i>Intramuscular:</i>	Cycle Length: monthly:	250 mg IM for one dose on day 1 (total dose per cycle 250 mg) dose has been divided into two concurrent injections <sup>2-4</sup> which may be administered bilaterally <sup>4</sup> ; however, an increased incidence of injection site reactions have been reported <sup>3</sup>
<i>Concurrent radiation:</i>	has been used <sup>5</sup>	
<i>Dosage in myelosuppression:</i>	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<sup>3</sup>:*

Creatinine clearance (mL/min)	Dose
≥30	100%
<30	use with caution; safety and effectiveness have not been established; no dosing details found

Calculated creatinine clearance =  $N \times (140 - \text{Age}) \times \text{weight in kg}$   
 Serum Creatinine in  $\mu\text{mol/L}$

\* For males  $N=1.23$ ; for females  $N=1.04$

*Dosage in hepatic failure:*

- mild to moderate impairment (Child-Pugh A and B): no adjustment required<sup>3</sup>
- severe impairment (Child-Pugh C): use with caution; safety and effectiveness have not been established<sup>3</sup>; no dosing details found

*Dosage in dialysis:*

no information found

**Children:**

safety and effectiveness have not been established<sup>3</sup>

**REFERENCES:**

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4. McEvoy GK, editor. AHFS 2007 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 1049-1050.
5. Vanessa Bernstein MD. Personal communication. BC Cancer Agency Breast Tumour Group; 25 February 2008.
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