Drug Monograph

A - Drug Name

fulvestrant

COMMON TRADE NAME(S): Faslodex®

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B - Mechanism of Action and Pharmacokinetics

Fulvestrant is a competitive estrogen receptor antagonist that blocks the trophic action of estrogen without any partial agonist activity. Fulvestrant inhibits the growth of tamoxifen-resistant breast cancer cells; however, fulvestrant-resistant breast tumors may be cross-resistant to tamoxifen.

Absorption	After a long-acting intramuscular injection, plasma concentrations are maintained over a period of at least one month, with trough concentration about one-third of Cmax.	
	Time to reach steady state	Within 1st month of 500mg loading doses on days 1, 15, and 29
Distribution	Fulvestrant is subject to extensive and rapid distribution, which is largely extravascular.	
	Cross blood brain barrier?	No information
	PPB	99% (lipoproteins)
Metabolism	Metabolism of fulvestrant appears similar to those of endogenous steroids, including oxidation, aromatic hydroxylation, and conjugation. Cytochrome P-450 3A4 (CYP 3A4) is the only P-450 isoenzyme involved in the oxidation of fulvestrant.	

	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Fulvestrant is rapidly cleared by the hepatobiliary route. Excretion is primarily via the feces. Renal elimination is negligible.	
	Feces	~ 90%
	Urine	< 1%
	Half-life	40 days (apparent)

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C - Indications and Status

Health Canada Approvals:

- Breast cancer

Refer to the product monograph for a full list of approved indications.

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D - Adverse Effects

Emetogenic Potential: Not applicable

Extravasation Potential: None

The following side effects are from the fulvestrant 500mg arms of randomized controlled trials in patients with prior anti-estrogen therapy. It also includes severe, life-threatening or post-marketing adverse events from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial/venous thromboembolism (1%)	E
	Hypertension (4%)	E

Gastrointestinal	Anorexia (6%)	I E
	Diarrhea (5%)	I E
	Nausea, vomiting (10%)	I E
General	Fatigue (10%)	E
Hematological	Myelosuppression ± infection, bleeding (<10%) (mostly thrombocytopenia)	D
Hepatobiliary	↑ LFTs (14%) (may be severe)	E
Hypersensitivity	Hypersensitivity (rare)	I E
Injection site	Injection site reaction (14%) (may be severe)	I E
Musculoskeletal	Musculoskeletal pain (7%)	E
	Osteoporosis (<1%)	D
	Other (19%) (joint disorder)	D
Nervous System	Headache (8%)	E
Reproductive and breast disorders	Estrogen deprivation symptoms (9%)	E
Respiratory	Cough (6%)	E

* "*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 for fulvestrant include joint disorders, ↑ LFTs, injection site reaction, fatigue, nausea and vomiting.

Injection site reactions with mild transient pain and inflammation were seen with fulvestrant. They may occur even after previous uneventful injections; systemic allergic response (e.g. widespread urticaria) has been reported to develop with time. More severe injection site reactions, including sciatica, neuralgia and peripheral neuropathy have also been reported when using dorsogluteal injections.

Hypersensitivity may occur shortly after injection; a case of angioedema has been reported several days after injection.

Increases in LFTs and bilirubin have been commonly reported with fulvestrant, and may rarely be fatal. Discontinuation of treatment resulted in improvements in some cases. In a retrospective analysis, 1% of cases met the criteria for Hy's Law.

Due to fulvestrant's mechanism of action, there is a risk of **osteoporosis**; however, this data was not collected in the long-term follow-up of the CONFIRM trial.

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E - Dosing

Refer to protocol by which patient is being treated.

Adults:

Intramuscular: 500 mg on day 1, 15, 29 and then every 28 days

Dosage with Toxicity:

Toxicity	Action
Hypersensitivity	Consider discontinuing if severe.
Mild hepatotoxicity	Hold until recovery and then restart.
Moderate to severe hepatotoxicity	Discontinue.

Dosage with Hepatic Impairment:

Fulvestrant is metabolized primarily in the liver. There are no efficacy and safety data in patients with breast cancer and hepatic impairment. Decreased clearance (by 2.2 fold) and changes in exposure (↑ 70%) were observed in women with moderate hepatic impairment compared to patients with normal hepatic function.

Hepatic Impairment	Fulvestrant Dose
Mild to Moderate (Child-Pugh Class A or B)	Use with caution. No dose adjustment required.
Severe (Child-Pugh Class C)	Not studied. Use not recommended.

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Fulvestrant Dose
≥ 30	No dosage adjustment required.
< 30	Use with caution; no data.

Dosage in the elderly:

No dosage adjustment required.

Children:

Not recommended for use in children or adolescents as safety and effectiveness have not been established in this age group.

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F - Administration Guidelines

- Each dose consists of 2 pre-filled syringes (250 mg/5mL). Administer each pre-filled syringe as SLOW intramuscular injection (1-2 minutes per injection) into EACH buttock.
- Caution should be taken due to proximity of the sciatic nerve and large blood vessels.
- Administer according to local guidelines at the Cancer Centre or physician's office.
- Store refrigerated at 2 to 8°C in original package.

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G - Special Precautions

Contraindications:

- Patients with known hypersensitivity to the drug or to any of the formulation or container
- Pregnant and breastfeeding women

Other Warnings/Precautions:

- Due to the route of administration, use with caution in patients with bleeding disorders or on anticoagulants.
- Exercise caution when driving or operating machinery due to fatigue.
- There is a potential osteoporosis risk due to fulvestrant's mechanism of action.

Pregnancy and Lactation:

- Mutagenicity: No
- Teratogenicity: Yes
- Fetotoxicity: Yes
  Fulvestrant is **contraindicated** in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **2 years** after the last dose.
- Breastfeeding: Contraindicated
- Fertility effects: Probable
  In animals, fulvestrant caused reversible reduction in female fertility and in embryonic survival, dystocia, fetal abnormalities and loss of sperm.

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H - Interactions

Fulvestrant does not significantly inhibit any of the major cytochrome P450 (CYP) isoenzymes and has no inhibitory effects on CYP3A4. Although CYP3A4 is involved in the metabolism of fulvestrant, clinical trials have shown that dosage adjustment is not necessary in patients co-prescribed CYP3A4 inhibitors or inducers.

Fulvestrant may interfere with estradiol immunoassay measurements (falsely elevated estradiol levels) due to its structural similarity with estradiol.

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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
Liver function tests	Baseline and as clinically indicated
Clinical assessment of injection site reactions, hypersensitivity, estrogen deprivation symptoms, fatigue, thromboembolism and musculoskeletal effects	At each visit

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Renal function tests	Baseline and repeat as clinically indicated

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- fulvestrant

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K - References

Di Leo A, Jerusalem G, Petruzelka L, et al. Final analysis of overall survival for the Phase III CONFIRM trial: fulvestrant 500 mg versus 250 mg. San Antonio Breast Cancer Symposium 2012, Oral presentation # S1-4.

Di Leo A, Jerusalem G, Petruzelka L et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor–positive advanced breast cancer. J Clin Oncol 2010;28(30):4594-600.

Product Monograph: Faslodex® (fulvestrant). AstraZeneca Canada, June 18, 2020.

January 2024 Modified Indications and Dosing 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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