Drug Monograph

A - Drug Name

exemestane

COMMON TRADE NAME(S): Aromasin®

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B - Mechanism of Action and Pharmacokinetics

Exemestane is a potent and irreversible steroidal aromatase inactivator. It inhibits the conversion of adrenally generated androstenedione to estrone by aromatase in peripheral tissues, such as adipose tissue as well as in tumours. Exemestane does not affect the synthesis of adrenal corticosteroid, aldosterone, or thyroid hormone.

Absorption	Bioavailability	≥ 42%
	Effects with food	Plasma level is increased (approximately by 40%) with high fat meals.
	Time to reach steady state	Within 7 days
Distribution	Exemestane is distributed extensively into tissue.	
	PPB	90% (albumin and α1 acid glycoprotein)
Metabolism	Exemestane is extensively (90%) metabolized in the liver by cytochrome P450 isoenzyme 3A4 and aldoketoreductases.	
	Active metabolites	No
	Inactive metabolites	Yes

Elimination	Metabolites are excreted equally in the urine and feces.	
	Feces	42%
	Urine	42% (< 1% unchanged)
	Half-life	24 hours (terminal)

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C - Indications and Status

Health Canada Approvals:

- Hormonal treatment of advanced breast cancer in women with natural or artificially induced post-menopausal status whose disease has progressed following anti-estrogen therapy.
- Sequential adjuvant treatment of postmenopausal women with estrogen receptor-positive early breast cancer who have received 2-3 years of initial adjuvant tamoxifen therapy.

Other Uses:

- Endometrial cancer

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D - Adverse Effects

Emetogenic Potential: Not applicable

The following table contains adverse effects reported in ≥ 5% of postmenopausal patients with early breast cancer in sequential adjuvant clinical trials. It also includes severe, life-threatening, or post-marketing adverse events from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (rare)	E
	Cardiotoxicity (1%)	D
	Hypertension (10%)	E
	Venous thromboembolism (2%)	E

Dermatological	Alopecia (15%)	D
	Rash (7%) (may be severe)	E
Gastrointestinal	Diarrhea (4%)	E
	GI ulcer (<1%)	E D
	Nausea (9%)	I E
General	Fatigue (16%)	E
Hematological	Myelosuppression (<1% severe)	E
Hepatobiliary	Hepatitis (rare)	E
	↑ LFTs (≤16%) (may be severe)	E
Hypersensitivity	Hypersensitivity (rare, has occurred up to 4 weeks after starting treatment; see rash)	I E
Metabolic / Endocrine	↑ Cholesterol (4%)	E D
Musculoskeletal	Fracture (5%)	D
	Musculoskeletal pain (18%)	E
	Osteoporosis (5%)	E
	Other (3%) (carpal tunnel syndrome)	E
Neoplastic	Secondary malignancy (4%)	D
Nervous System	Anxiety (4%)	E
	Depression (6%)	E D
	Dizziness (10%)	E
	Headache (14%)	E
	Insomnia (13%)	E
	Paresthesia (3%)	E
Renal	Creatinine increased (6%)	E
Reproductive and breast disorders	Estrogen deprivation symptoms (≤22%)	E D
	Vaginal bleeding (4%)	E D

* "*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 exemestane include estrogen deprivation symptoms, musculoskeletal pain, fatigue, ↑ LFTs, alopecia, headache, insomnia, hypertension and dizziness.

Severe rash, usually early, including erythema multiforme and acute generalized exanthematus pustulosis (AGEP) has been reported.

As compared with megestrol acetate in advanced breast cancer, exemestane produced fewer side effects, including less weight gain, but caused more **hot flashes, depression, insomnia, dizziness, anorexia, nausea,** and **vomiting**. As compared to tamoxifen in early breast cancer, exemestane had higher incidences of **fatigue, headache, hot flashes, musculoskeletal and nervous system disorders, osteoporosis, (± fractures), hypercholesterolemia, cardiovascular events,** ↑ **LFTs** and ↑ **creatinine.**

Patients treated with aromatase inhibitors may be at a higher risk for cardiovascular events as well as osteoporosis.

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E - Dosing

Refer to protocol by which patient is being treated.

Assess patient's risk factors for osteoporosis and consider calcium and vitamin D supplements and bisphosphonates where appropriate. Refer patients to the Bone Health During Cancer Treatment pamphlet for more information.

Adults:

Oral: 25 mg Daily

Dosage with Toxicity:

Toxicity	Exemestane Dose
Myelosuppression	No adjustment required.
Severe cutaneous reactions or acute generalized exanthematus pustulosis (AGEP)	Discontinue permanently.

Dosage with Hepatic Impairment:

Although AUC is tripled in the presence of liver impairment (Child-Pugh C), adverse effects are not increased. No dosage adjustment is required.

Dosage with Renal Impairment:

Although AUC is tripled in the presence of severe renal impairment (CrCl < 30 mL/min), adverse effects are not increased. No dosage adjustment is required.

Dosage in the elderly:

No dosage adjustment is required.

Children:

Safety and efficacy not established.

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F - Administration Guidelines

- Tablets should be swallowed whole with a glass of water after a meal (to enhance absorption).
- Store tablets at room temperature (15-30°C).

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G - Special Precautions

Contraindications:

- Patients with known hypersensitivity to exemestane or any of its components

Other Warnings/Precautions:

- Use is not recommended in pre-menopausal women*.
- Patients with pre-existing severe osteoporosis, a history of osteoporotic fracture or significant cardiac disorders were excluded from clinical trials in early breast cancer.
- Exemestane may increase risk of gastric ulcers especially in patients on NSAIDs and/or with a prior history.

**not receiving ovarian suppression*

Other Drug Properties:

- Carcinogenicity: Probable

Pregnancy and Lactation:

- Fetotoxicity: Yes
  In animal studies, exemestane caused placental enlargement, dystocia, and prolonged gestation.
- Abortifacient effects: Yes
  Exemestane is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** (general recommendation) after the last dose.
- Excretion into breast milk: Yes
  Breastfeeding is not recommended during treatment. Exemestane is excreted into breast milk in animal studies.
- Fertility effects: Probable

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H - Interactions

Exemestane is metabolized by cytochrome P450 CYP 3A4 and aldoketoreductases. It does not inhibit any of the major CYP isoenzymes, including CYP1A2, 2C9, 2D6, 2E1, and 3A.

CYP3A4 inhibition (e.g. ketoconazole) showed no significant effect on exemestane pharmacokinetics.

CYP3A4 induction (e.g. rifampin) produced pharmacokinetic effects but did not affect the suppression of plasma estrogen concentrations. No dose adjustment is required.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Estrogen-containing or estrogenic agents	↓ effect of exemestane	Antagonistic effects	Avoid concomitant use
NSAIDS	May ↑ risk of gastric ulcers	Unknown	Caution; monitor
Warfarin	Possible INR level changes when switched from tamoxifen to exemestane	Possible interaction between tamoxifen and warfarin (exemestane not expected to interact with warfarin)	Monitor PT/INR, especially at switch from tamoxifen to exemestane

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Cholesterol and lipids evaluation	Baseline and as clinically indicated
Bone mineral density	Baseline and as clinically indicated
Clinical assessment of estrogen deprivation symptoms, fatigue, cardiovascular, musculoskeletal, thromboembolism, hypersensitivity, skin and GI 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
CBC	Baseline and as clinically indicated
Liver and renal function tests	Baseline and as clinically indicated
INR for patients on warfarin (when switching from tamoxifen to exemestane)	As clinically indicated

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- exemestane

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K - References

Clemett D, Lamb H. Exemestane: a review of its use in postmenopausal women with advanced breast cancer. Drugs 2000 Jun; 59(6): 1279-96.

Prescribing Information: Aromasin® (exemestane). Pfizer Inc (USA). May 2018.

Product Monograph: Aromasin® (exemestane). Pfizer Canada Inc. March 6, 2018.

November 2020 Updated mechanism of action/pharmacokinetics, indications, special precautions and interactions 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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