Drug Monograph

A - Drug Name

**exemestane**

**SYNONYM(S):**  PNU 155971

**COMMON TRADE NAME(S):**  Aromasin® (Pfizer)

B - Mechanism of Action and Pharmacokinetics

Aromatase (estrogen synthetase) is an enzyme that catalyses various steps in the conversion of androgen to estrogen in peripheral tissues; it is the principal source of circulating estrogens in post-menopausal women. 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. Unlike the non-steroidal inhibitors, exemestane acts as a false substrate for the aromatase enzyme and is processed to an intermediate that binds irreversibly to the active site of the enzyme, causing its inactivation. Exemestane does not affect the synthesis of adrenal corticosteroid, aldosterone, or thyroid hormone.

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Bioavailability</th>
<th>Oral: at least 42%. Plasma level is increased (approximately by 40%) with high fat meals.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Exemestane is distributed extensively into tissue. At a dose of 25mg, maximal estrogen suppression occurs by 2 to 3 days. With daily repeated administration, steady state is reached within 7 days.</td>
<td></td>
</tr>
<tr>
<td>Cross blood brain barrier? PPB</td>
<td>no information found</td>
<td>90% (albumin and α1 acid glycoprotein)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Exemestane is extensively (90%) metabolized in the liver by cytochrome P450 isoenzyme 3A4 and aldoketoreductases. Does not inhibit or induce CYP isoenzymes.</td>
<td></td>
</tr>
</tbody>
</table>
### Elimination

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Active metabolites</td>
<td>no</td>
</tr>
<tr>
<td>Inactive metabolites</td>
<td>yes</td>
</tr>
</tbody>
</table>

Metabolites are excreted equally in the urine and feces (42% via each pathway over 1 week.)

<table>
<thead>
<tr>
<th>Org</th>
<th>SID Effect* (%)</th>
<th>Onset**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Arterial thromboembolism (rare)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Cardiotoxicity (1%)</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>Hypertension (10%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Venous thromboembolism (rare)</td>
<td>E</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Alopecia (15%)</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>Rash (7%) (may be severe)</td>
<td>E</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain (6%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Diarrhea (4%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>GI ulcer (&lt;1%)</td>
<td>E D</td>
</tr>
<tr>
<td></td>
<td>Nausea (9%)</td>
<td>I E</td>
</tr>
</tbody>
</table>

**Back to top**
**General**
- Fatigue (16%)

**Hematological**
- Myelosuppression (mild)

**Hepatobiliary**
- ↑ LFTs (up to 16%; may be severe)
- Hepatitis (rare)

**Hypersensitivity**
- Hypersensitivity (rare, has occurred up to 4 weeks after starting treatment; see rash)

**Metabolic / Endocrine**
- ↑ Cholesterol (4%)

**Musculoskeletal**
- Fracture (5%)
- Musculoskeletal pain (18%)
- Osteoporosis (5%)
- Other (3%) (carpal tunnel syndrome)

**Neoplastic**
- Secondary malignancy (4%)

**Nervous System**
- Anxiety (4%)
- Depression (6%)
- Dizziness (10%)
- Headache (14%)
- Insomnia (13%)
- Paresthesia (3%)

**Renal**
- Creatinine increased (6%)

**Reproductive and breast disorders**
- Estrogen deprivation symptoms (up to 22%)
- Vaginal bleeding (4%)

* "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. 
Dose-limiting side effects are underlined.

**I = immediate** (onset in hours to days)  
**E = early** (days to weeks)  
**D = delayed** (weeks to months)  
**L = late** (months to years)

Exemestane is generally well tolerated. The most common adverse reactions include hot flashes, musculoskeletal pain, nausea, fatigue, headache, dizziness, and insomnia.

**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. For more information about bone health via dietary and lifestyle measures, see pamphlet on “Bone Health in Post Menopausal Women”. Patients should be carefully monitored and treated appropriately.

E - Dosing

Refer to protocol by which patient is being treated.

**Adults:**

- The recommended dose is 25mg orally once daily.
- Take with food, preferably after a meal.

**Dosage with Toxicity:**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Exemestane Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppression</td>
<td>No adjustment required</td>
</tr>
<tr>
<td>Severe cutaneous reactions or acute generalized exanthematus pustulosis (AGEP)</td>
<td>Discontinue permanently</td>
</tr>
</tbody>
</table>

**Dosage with Hepatic Impairment:**

Although AUC is tripled in the presence of liver impairment, 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 required.
**Children:**

Safety and efficacy not established.

**F - Administration Guidelines**

- Oral self-administration; drug available by outpatient prescription.
- Swallow whole tablet with a glass of water after a meal (to enhance absorption)
- Store tablets at room temperature (15-30°C)

**G - Special Precautions**

**Contraindications:**

- Patients with known hypersensitivity to exemestane or any of its components
- Pre-menopausal women
- Co-administration with estrogen-containing agents as this could interfere with its pharmacological action

**Other Warnings/Precautions:**

- Patients with pre-existing severe osteoporosis or hepatic impairment
- Patients with cardiovascular disease (excluded from clinical trials)
- Patients receiving warfarin and switching from tamoxifen to exemestane; warfarin dosage adjustment may be required (see Drug Interactions)

**Other Drug Properties:**

- Carcinogenicity: Probable
Pregnancy and Lactation:

- Fetotoxicity: Yes
- Abortifacient effects: Yes
  There are no well-controlled studies for use in pregnant or breast-feeding women.
- Fertility effects: Probable

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.

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John’s Wort, etc)</td>
<td>↓ effect of exemestane (theoretical)</td>
<td>↑ metabolism of exemestane</td>
<td>Caution; but dose adjustment not needed</td>
</tr>
<tr>
<td>Estrogenic agents</td>
<td>↓ effect of exemestane</td>
<td>antagonistic effects</td>
<td>Avoid concomitant use</td>
</tr>
<tr>
<td>CYP3A4 inhibitors (i.e. ketoconazole, voriconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges, starfruit or pomegranate)</td>
<td>↑ effect of exemestane (theoretical)</td>
<td>↓ metabolism of exemestane (no significant PK change observed with ketoconazole)</td>
<td>Caution, but dose adjustment not needed</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>May ↑ risk of gastric ulcers</td>
<td>Unknown</td>
<td>monitor</td>
</tr>
<tr>
<td>warfarin</td>
<td>possible INR level changes when switched from tamoxifen to exemestane</td>
<td>possible interaction between tamoxifen and warfarin (exemestane not expected to interact with warfarin)</td>
<td>Monitor PT/INR, especially at switch from tamoxifen to exemestane</td>
</tr>
</tbody>
</table>
I - Recommended Clinical Monitoring

### Recommended Clinical Monitoring

- Cholesterol and lipids evaluation; baseline and regular
- Bone mineral density; baseline and regular
- Clinical assessment of estrogen withdrawal symptoms, fatigue, cardiovascular, musculoskeletal, thromboembolism, hypersensitivity, skin, GI effects, etc.; regular
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

### Suggested Clinical Monitoring

- 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

back to top

J - Supplementary Public Funding

### ODB Limited Use (ODB Formulary)

- Hormonal treatment of metastatic breast cancer in hormone receptor positive postmenopausal women who have disease progression following tamoxifen therapy
- In combination with everolimus, for the treatment of hormone-receptor positive HER2 negative advanced breast cancer, in postmenopausal women with ECOG performance status less than or equal to 2 after recurrence or progression following a non-steroidal aromatase inhibitor (NSAI)
- **Sequential treatment of postmenopausal women with estrogen receptor-positive early breast cancer who have received 2-3 years of initial adjuvant tamoxifen therapy**

back to top

K - References


Any use of the information is subject, at all times, to CCO’s Terms and Conditions.
May 2014: updated side effects, dose modifications and clinical monitoring based on updated product monograph

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.