DRUG NAME: Exemestane

SYNONYM(S): PNU 155971

COMMON TRADE NAME(S): AROMASIN®

CLASSIFICATION: Aromatase inhibitor

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

MECHANISM OF ACTION:

Exemestane is an irreversible (Type 1), steroidal aromatase inhibitor. Aromatase catalyzes the final and rate-limiting step in the conversion of androgens to estrogens in peripheral tissues. This occurs mainly in adipose tissue, but also in normal and malignant breast tissues, and provides the main source of estrogen in postmenopausal women. The goal of hormone therapy in breast cancer is to deprive tumour cells of estrogens, which are implicated in the development or progression of tumours. Maximal estrogen suppression is produced by a 25 mg dose.[1] It occurs after 2-3 days and returns to baseline in 10-14 days. Exemestane does not have estrogenic activity.[1] Highly selective blockade of aromatase does not interfere with the production of other steroids (eg, adrenal corticosteroids[1], aldosterone[2], androgens).[3] Evidence suggests that tumour progression is not due to a loss of estrogen suppression but to newly developed tumour resistance, including acquired hypersensitivity of some tumour cells to estrogens.[2] Differences in the mechanism of action may contribute to the apparent lack of cross-resistance between steroidal (eg, exemestane) and nonsteroidal (eg, anastrozole, letrozole) aromatase inhibitors.[3]

PHARMACOKINETICS:

Interpatient variability	Moderate to high interpatient variability which is not clinically significant.[4]	
Oral Absorption	42% bioavailability; plasma levels increase by 40% after high-fat breakfast but maximum estrogen suppression is achieved under fasting conditions.	
	time to peak plasma concentration	1.2 h
Distribution	Distributed extensively into tissues. Distribution into blood cells is negligible.	
	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	90%
Metabolism	> 90% metabolized, by cytochrome P450 3A4 oxidation and aldoketoreductases reduction	
	active metabolite(s)	none
	inactive metabolite(s)	many
Excretion	mainly nonrenal, with less than 1% excreted unchanged in urine	
	urine	42%, over 7 days[5]
	feces	42%, over 7 days[5]
	terminal half life	24 h
	clearance	no information found
Gender	no clinically significant difference	
Elderly	no clinically significant difference over ages 43-68 y	
Children	no information found	
Ethnicity	no information found	

Adapted from reference[2] unless specified otherwise.

USES:

Primary uses:

* Breast cancer[6]

*Health Canada Therapeutic Products Programme approved indication

No pediatric indications.

SPECIAL PRECAUTIONS:

Carcinogenicity: No information found.

Mutagenicity: Not mutagenic in Ames test or in mammalian mutation test, or clastogenic in mammalian chromosome test. Exemestane was clastogenic in human lymphocytes *in vitro* at a concentration approximately 700 times the peak plasma level in humans after a single 25 mg dose.[2]

Fertility: No information found.

Pregnancy: FDA Pregnancy Category D.[5] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, 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.[2]

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.[7]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood/bone marrow	lymphocytopenia (20%[2], severe 6%[8])
cardiovascular (general)	***edema*** (2-5%)
	hypertension (5%)
	thromboembolic event (1%)[9]
constitutional symptoms	asthenia (6%)
	fatigue (22-24%)[2,9]
	fever (5%)
	hoarseness (5%)[10]
	sweating (6-19%)[2,9]
	weight gain (8%)
dermatology/skin	alopecia (2-5%)
	hypertrichosis and acne (2-5%)[10,11]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pruritus (2-5%)
	rash (2-5%)
endocrine	***hot flashes*** (13-42%)[2,9]
gastrointestinal	*emetogenic potential*: nonemetogenic
	anorexia (6%)
	constipation (5%)
	diarrhea (4%)[9]
	dyspepsia (2-5%)
	increased appetite (3%)
	nausea (11-18%)[2,9]
	vomiting (7%)
hemorrhage	vaginal bleeding (4%)[9]
infection	infection (2-5%)
	upper respiratory tract infection (2-5%)
	urinary tract infection (2-5%)
lymphatics	lymphedema (2-5%)
metabolic/laboratory	increased gamma glutamyl transferase 3%
musculoskeletal	***osteoporosis*** (7%)[9]
	pathological fracture (2-5%)[9]
neurology	anxiety (10%)
	confusion (2-5%)
	depression (5-13%)[2,9]
	dizziness (8-13%)[2,9]
	insomnia (11-20%)[2,9]
	neuropathy – sensory (2-5%)
ocular/visual	visual disturbances (7%)[9]
pain	abdominal pain (6%)
	arthralgia/myalgia (2-33%)[2,9]
	back pain (2-5%)
	chest pain (2-5%)
	cramps (3%)[9]
	headache (8-19%)[2,9]
	pain at tumour site (8%)
	skeletal pain (2-5%)
pulmonary	bronchitis (2-5%)
	cough (6%)
	dyspnea (10%)
	pharyngitis (2-5%)
	rhinitis (2-5%)
	sinusitis (2-5%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
sexual/reproductive function	***gynecologic symptoms*** (i.e., vaginal dryness/discharge/itching) (6%)[9]
syndromes	flu-like symptoms (6%)

Adapted from reference[2] unless specified otherwise.

Visual disturbances: There was a suggestion of an increased incidence of visual disturbances associated with exemestane compared to tamoxifen.[9]

Lymphocytopenia: A moderate transient decrease in lymphocytes was seen in about 20% of patients, most of whom had pre-existing lymphocytopenia. However, there was no significant change in the mean lymphocyte counts over time and patients did not experience any opportunistic infections or significant increase in viral infections.[2]

Androgenic symptoms: Alopecia (10%), hypertrichosis (5%), hoarseness (5%) and acne (4%) were seen in one study using high dose exemestane 200 mg daily.[10]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
estrogen (estrogen replacement therapy, Premarin, C.E.S., Estracomb, Estraderm)	may interfere with therapeutic effect of exemestane	estrogen can counter the estrogen suppression effect of exemestane	see below
ketoconazole[2]	no significant influence on exemestane pharmacokinetics		

Exemestane is metabolized by cytochrome P450 (CYP) 3A4 but its pharmacokinetics are not significantly affected by the CYP 3A4 inhibitor ketoconazole. Exemestane does not inhibit CYP isoenzymes. Significant CYP-mediated interactions appear unlikely, although a possible decrease in plasma exemestane level by CYP 3A4 inducers cannot be excluded.[2] Grapefruit or grapefruit juice may inhibit CYP 3A4 metabolism in the intestinal wall, and theoretically may increase the plasma level of exemestane,[12] however, the manufacturer does not recommend the avoidance of grapefruit or grapefruit juice during exemestane treatment.[13]

Estrogen use with exemestane: use other options for conditions in which estrogen is indicated. If estrogen is used, prescribe the lowest dose to relieve symptoms, monitor patient carefully and consider short term use.[14] For vaginal complaints such as dyspareunia, dryness and sexual dysfunction, topical estrogen may be considered. Estring produces a local effect with systemic levels measurable only for the first 24 hours of the three month ring. Premarin cream can be used but may have variable systemic levels related to the absorption through the vaginal tissues. The lowest dose to relieve symptoms should be used.[15]

SUPPLY AND STORAGE:

Oral: Pfizer Canada Inc supplies exemestane as 25 mg tablets. Store at room temperature.[13]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

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

Oral:	***25 mg PO once daily.*** May be taken with food or on an empty stomach (although the manufacturer recommends administration with food, after breakfast, maximal estrogen suppression is achieved also under fasting conditions).[2]
Dosage in renal failure:	no adjustment required[2]
Dosage in hepatic failure:	no adjustment required[2]
Dosage in dialysis:	no information found

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