DRUG NAME: Anastrozole

SYNONYM(S): IUPAC; ZD1033; ICI D1033

COMMON TRADE NAME(S): ARIMIDEX®

CLASSIFICATION: Aromatase inhibitor

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

MECHANISM OF ACTION:

Anastrozole is a reversible (Type II), nonsteroidal 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.[1,2] Maximal estrogen suppression is produced by a 1mg dose.[3] Estrogen suppression is maintained for up to 6 days after discontinuing anastrozole.[4] Differences in the mechanism of action may contribute to the apparent lack of cross-resistance between steroidal (e.g., exemestane) and nonsteroidal (e.g., anastrozole and letrozole) aromatase inhibitors.[5] Highly selective blockade of aromatase does not interfere with the production of other steroids (e.g., adrenal corticosteroids, aldosterone)[4] or thyroid stimulating hormone.[6] Anastrozole does not have progestogenic, androgenic or estrogenic activity.[4,6]

PHARMACOKINETICS:

Interpatient variability	no information found	
Oral Absorption	rapidly and almost completely absorbed[7]; food reduces absorption rate	
	time to peak plasma concentration	within 2 h
Distribution	steady-state plasma level is 3-4 times higher than the level after a single dose and achieved after 7-9 days of once daily oral dosing[4]	
	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	40%
Metabolism	primarily in the liver via N-dealkylation, hydroxylation and glucuronidation	
	active metabolite(s)	none
	inactive metabolite(s)	triazole, glucuronides, hydroxy-anastrozole
Excretion	biliary and renal excretion	
	biliary	85%
	urine	11%
	terminal half life	50 h (range, 30-60 h)[8]
	clearance	no information found
Gender	no information found	
Elderly	no clinically significant differences	
Children	no information found	
Ethnicity	no clinically significant differences in pharmacodynamics and pharmacokinetics between Asian and white postmenopausal women[9]	

Adapted from reference[6] unless specified otherwise.

USES:

Primary uses:

∗Breast cancer[10-14]

*Health Canada approved indication

No pediatric indications.

SPECIAL PRECAUTIONS:

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test and in mammalian *in vitro* mutation test. Anastrozole is clastogenic in *in vitro* and *in vivo* chromosome tests.[15]

Fertility: no information found

Pregnancy: FDA pregnancy category D[15] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., 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 potential secretion into breast milk.[6]

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.[16]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiovascular (general)	hypertension (3-9%)[17]
	ischemic cardiovascular disease (3-4%)[18-20]
	peripheral edema (8-10%)
	thromboembolism (2-4%)[18-20]
	vasodilatation (25-35%)[17]
constitutional symptoms	asthenia (16-18%)
	fatigue/tiredness (19%)[18-20]
	sweating (2-4%)[17]
	weight gain (13%)[12]
dermatology/skin	hair thinning (rare)
	rash (6-10%)[17]
endocrine	***hot flashes*** (13-35%)[18-20]
gastrointestinal	*emetogenic potential*: nonemetogenic[12]
	anorexia (5-7%)
	constipation (9%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	diarrhea (8%)
	dry mouth (6%)
	nausea (11-19%)[18-20]
	vomiting (8-13%)[18-20]
hemorrhage	vaginal bleeding (1-5%)[18-20]
hepatic	elevated liver function tests (infrequent)[16]
lymphatics	lymphoedema (9%)[17]
metabolic/laboratory	***hypercholesterolemia*** (7%)[17]
musculoskeletal	arthritis (14%)[17,21]
	arthrosis (6%)[21]
	fractures (6-11%)[17-20]
	hypertonia (3%)
	osteoporosis (7%)[20,21]
neurology	anxiety (5%)[17]
	depression (5-11%)[17]
	dizziness (6%)
	insomnia (6-9%)[17]
	ischemic cerebrovascular events (1-2%)[18-20]
	neuropathy, sensory (5%)
ocular/visual	cataracts (4-6%)[18-20]
pain	abdominal pain (8%)
	arthralgia/myalgia (5-36%)[17,20-22]
	back pain (10-12%)
	bone pain (5-11%)[21]
	breast tenderness (7%)[17]
	chest pain (5-7%)
	headache (9-14%)
	pelvic pain (5%)
pulmonary	cough (8-11%)
	dyspnea (10%)
	pharyngitis (6-12%)[17]
renal/genitourinary	vaginal discharge (2-3%)[18-20]
	vulvovaginitis (6%)[17]
sexual/reproductive function	vaginal bleeding (see under “hemorrhage”)
	vaginal dryness (3%)
syndromes	flu-like symptoms (7%)
	tumour flare (3%)

Adapted from reference[6] unless specified otherwise.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
antipyrine	no significant effects on antipyrine pharmacokinetics		
cimetidine	no significant effects on anastrozole pharmacokinetics		
estrogen (estrogen replacement therapy, Premarin, C.E.S., Estracomb, Estraderm)	may interfere with therapeutic effect of anastrozole	estrogen can counter the estrogen suppression effect of anastrozole	see below
warfarin	no significant effects on warfarin pharmacokinetics and pharmacodynamics		
tamoxifen[23]	no significant effects on tamoxifen pharmacokinetics; tamoxifen does not appear to affect estrogen suppressant effect of anastrozole		

Adapted from reference[17] unless specified otherwise.

Anastrozole is a weak inhibitor of cytochrome P450 *in vitro* and not expected to have clinically significant interactions with drugs metabolized by cytochrome P450.[24]

Estrogen use with anastrozole: 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.[25] 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.[26]

SUPPLY AND STORAGE:

Tablet*:* 1 mg; inactive ingredient includes lactose. Store at room temperature.[6]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral: ***1 mg PO once daily.***
Administer with food or on empty stomach.[6]

Dosage in renal failure: no adjustment required[6]

Dosage in hepatic failure: No dose adjustment is required in mild to moderate hepatic dysfunction. Dosing studies have not been done in patients with severe hepatic dysfunction.[6]

Dosage in dialysis: no information found

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