Zortex®

Anastrozole 1 mg

FORMS AND PRESENTATION

Zortex®: Film coated tablets: Box of 30.

Composition:
Zortex®: Each film coated tablet contains Anastrozole 1mg.
Excipients: anhydrous lactose, starch, croscarmellose sodium, povidone, magnesium stearate, colloidal anhydrous silica, sodium starch glycollate, hypromellose, purified talc, yellow oxide of iron, titanium dioxide, triacetin.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties
Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. In postmenopausal women, estradiol is produced primarily from the conversion of androstenedione to estrone through the aromatase enzyme complex in peripheral tissues. Estrone is subsequently converted to estradiol. Reducing circulating estradiol levels has been shown to produce a beneficial effect in women with breast cancer. In postmenopausal women, Anastrozole at a daily dose of 1 mg produced estradiol suppression of greater than 80% using a highly sensitive assay.
Anastrozole does not possess any progestogenic, androgenic or oestrogenic activity.
Daily doses of Anastrozole up to 10 mg do not have any effect on cortisol or aldosterone secretion, measured before or after standard ACTH challenge testing. Corticoid supplements are therefore not needed.

Pharmacokinetic Properties
Absorption of Anastrozole is rapid and maximum plasma concentrations typically occur within two hours of dosing (under fasted conditions). Anastrozole is eliminated slowly with a plasma elimination half-life of 40 to 50 hours. Food slightly decreases the rate but not the extent of absorption. The small change in the rate of absorption is not expected to result in a clinically significant effect on steady-state plasma concentrations during once daily dosing of Anastrozole tablets. Approximately 90 to 95% of plasma Anastrozole steady-state concentrations are attained after 7 daily doses. There is no evidence of time or dose-dependency of Anastrozole pharmacokinetic parameters.
Anastrozole pharmacokinetics are independent of age in postmenopausal women.
In boys with pubertal gynaecomastia, Anastrozole was rapidly absorbed, was widely distributed, and was eliminated slowly with a half-life of approximately 2 days. Clearance of Anastrozole was lower in girls than in boys and exposure higher. Anastrozole in girls was widely distributed and slowly eliminated, with an estimated half-life of approximately 0.8 days.
Anastrozole is only 40% bound to plasma proteins.
Anastrozole is extensively metabolised by postmenopausal women with less than 10% of the dose excreted in the urine unchanged within 72 hours of dosing. Metabolism of Anastrozole occurs by N-dealkylation, hydroxylation and glucuronidation. The metabolites are excreted primarily via the urine. Triazole, the major metabolite in plasma, does not inhibit aromatase.
The apparent oral clearance of Anastrozole in volunteers with stable hepatic cirrhosis or renal impairment was in the range observed in healthy volunteers.

INDICATIONS

Treatment of advanced breast cancer in postmenopausal women. Efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen.
Adjuvant treatment of postmenopausal women with

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Zortex is indicated for the following:

Adjuvant treatment of hormone receptor positif early invasive breast cancer in post-menopausal women

Adjuvant treatment of early breast cancer in hormone receptor positif post-menopausal women who have received 2 to 3 years of adjuvant tamoxifen

Treatment of advanced breast cancer in post-menopausal women

Before prescribing please consult physicians' circular.

® Registered trade name

Zortex® manufactured by BPI

CE GMP

Benta Pharma Industries - Dbayeh, Lebanon

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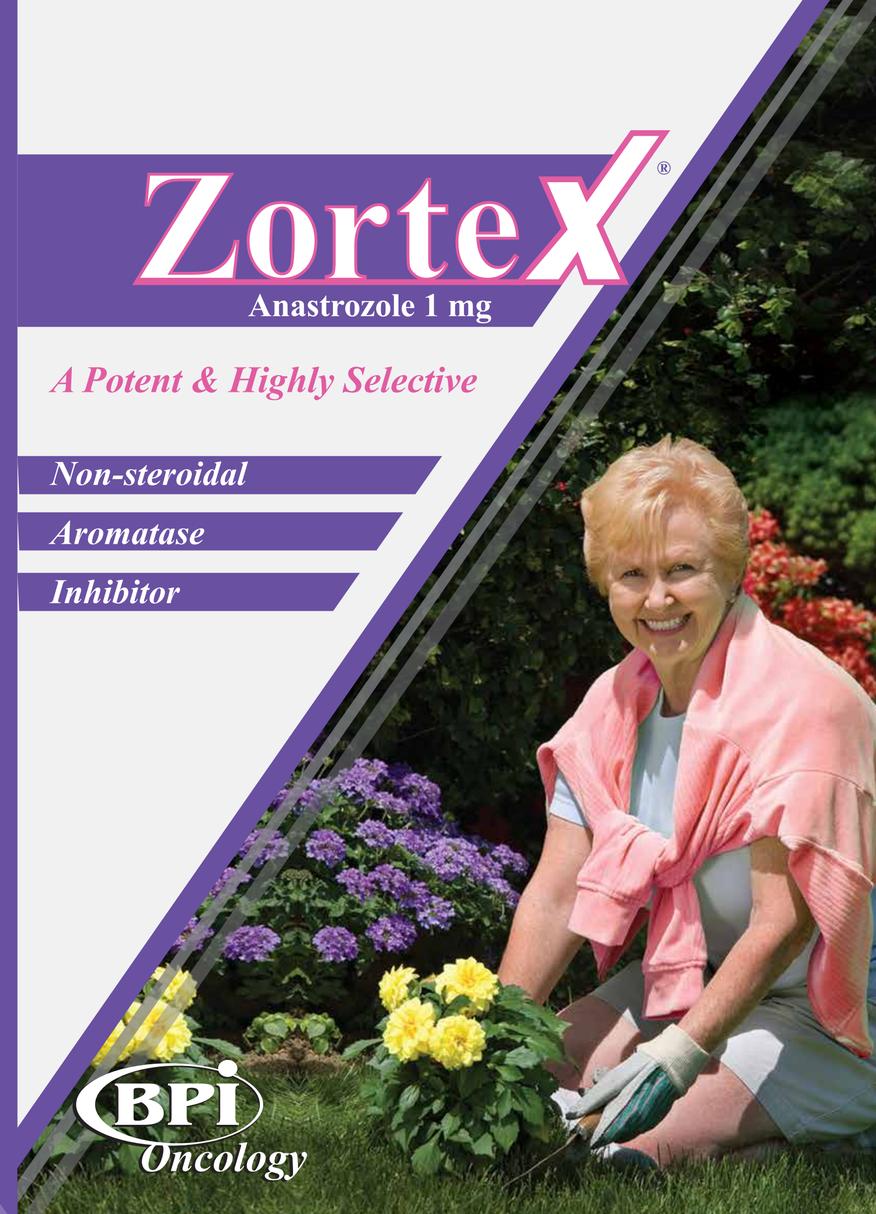
Anastrozole 1 mg

A Potent & Highly Selective

Non-steroidal

Aromatase

Inhibitor



BPi Oncology

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hormone receptor positive early invasive breast cancer.
Adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.

CONTRAINDICATIONS

Anastrozole is contraindicated in:
- premenopausal women.
- pregnant or lactating women.
- patients with severe renal impairment (creatinine clearance less than 20 ml/min).
- patients with moderate or severe hepatic disease.
- patients with known hypersensitivity to Anastrozole or to any of the excipients.

Oestrogen-containing therapies should not be co-administered with Anastrozole as they would negate its pharmacological action.
Concurrent tamoxifen therapy: tamoxifen should not be co-administered with Anastrozole, as this may diminish its pharmacological action.

PRECAUTIONS

Anastrozole is not recommended for use in children as safety and efficacy have not been established in this group of patients.
Anastrozole should not be used in boys with growth hormone deficiency in addition to growth hormone treatment. In the pivotal clinical trial, efficacy was not demonstrated and safety was not established.
Since Anastrozole reduces estradiol levels, Anastrozole must not be used in girls with growth hormone deficiency in addition to growth hormone treatment.
Long-term safety data in children and adolescents are not available.
The menopause should be defined biochemically in any patient where there is doubt about hormonal status.
There are no data to support the safe use of Anastrozole in patients with moderate or severe hepatic impairment, or patients with severe impairment of renal function (creatinine clearance less than 20 ml/min).
Women with osteoporosis or at risk of osteoporosis, should have their bone mineral density formally assessed by bone densitometry at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored.
There are no data available for the use of Anastrozole with LHRH analogues. This combination should not be used outside clinical trials.
As Anastrozole lowers circulating oestrogen levels it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture. The use of bisphosphonates may stop further bone mineral loss caused by Anastrozole in postmenopausal women and could be considered.
This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ability to drive and use machines:

Anastrozole is unlikely to impair the ability of patients to drive and operate machinery. However, asthenia and somnolence have been reported with the use of Anastrozole and caution should be observed when driving or operating machinery while such symptoms persist.

PREGNANCY AND LACTATION

Anastrozole is contraindicated in pregnant or lactating women.

DRUG INTERACTIONS

Antipyrine and cimetidine clinical interaction studies indicate that the co-administration of Anastrozole with other drugs is unlikely to result in clinically significant drug interactions mediated by cytochrome P450.
A review of the clinical trial safety database did not reveal evidence of clinically significant interaction in patients treated with Anastrozole who also received other commonly prescribed drugs. There were no clinically significant interactions with bisphosphonates.
Oestrogen-containing therapies should not be co-administered with Anastrozole as they would negate its pharmacological action.
Tamoxifen should not be co-administered with Anastrozole, as this may diminish its pharmacological action.

ADVERSE EFFECTS

Unless specified, the following frequency categories were calculated from the number of adverse effects reported in a large phase III study conducted in 9366 postmenopausal women with operable breast cancer treated for five years (ATAC study: Anastrozole, Tamoxifen Alone or in Combination).

Frequency	System Organ Class	Adverse reaction
Very common (≥10%)	*Vascular*	Hot flushes, mainly mild or mo nature
	General	Asthenia, mainly mild or moderate in nature
	Musculoskeletal, connective tissue and bone	Joint pain/stiffness, mainly mild or moderate in nature
	Nervous system	Headache, mainly mild or moderate in nature
	Gastroin	Nausea, mainly mild or moderate in nature
	Skin and subcutaneous tissue	Rash, mainly mild or moderate in nature
Common (≥ 1% and <10%)	*Skin and subcutaneous tissue*	Hair thinning (Alopecia), mainly mild or moderate in nature Allergic reactions
	Gastrointestinal	Diarrhoea, mainly mild or moderate in nature Vomiting, mainly mild or moderate in nature
	Nervous system	Somnolence, mainly mild or moderate in nature Carpal Tunnel Syndrome
	Hepatobiliary disorders	Increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase
	Reproductive system and breast	Vaginal dryness, mainly mild or moderate in nature Vaginal bleeding, mainly mild or moderate in nature*
	Metabolism and nutrition	Anorexia, mainly mild in nature Hypercholesterolaemia, mainly mild or moderate in nature
Uncommon (≥0.1% and <1%)	*Hepatobiliary disorders*	Increases in gamma-GT and bilirubin Hepatitis
	Skin and subcutaneous tissue	Urticaria
	Musculoskeletal, connective tissue and bone	Trigger finger
Rare (≥0.01% and <0.1%)	*Skin and subcutaneous tissue*	Erythema multiforme Anaphylactoid reaction
Not known	*Skin and subcutaneous tissue*	Stevens-Johnson syndrome** Angioedema**

*Vaginal bleeding has been reported commonly, mainly in patients with advanced breast cancer during the first few weeks after changing from existing hormonal therapy to treatment with Anastrozole. If bleeding persists, further evaluation should be considered.

**Cannot be estimated from the available data.
As Anastrozole lowers circulating oestrogen levels, it may cause a reduction in bone mineral density placing some patients at a higher risk of fracture. The table below presents the frequency of pre-specified adverse effects in the ATAC study, irrespective of causality, reported in patients receiving trial therapy and up to 14 days after cessation of trial therapy.

Adverse effects	Anastrozole (N=3092)	Tamoxifen (N=3094)
Hot flushes	1104 (35.7%)	1264 (40.9%)
Joint pain/stiffness	1100 (35.6%)	911 (29.4%)
Mood disturbances	597 (19.3%)	554 (17.9%)
Fatigue/asthenia	575 (18.6%)	
Nausea and vomiting	393 (12.7%)	384 (12.4%)
Fractures	315 (10.2%)	209 (6.8%)
Fractures of the spine, hip, or wrist/Colles	133 (4.3%)	91 (2.9%)
Wrist/Colles fractures	67 (2.2%)	50 (1.6%)
Spine fractures	43 (1.4%)	22 (0.7%)
Hip fractures	28 (0.9%)	26 (0.8%)
Cataracts	182 (5.9%)	213 (6.9%)
Vaginal bleeding	167 (5.4%)	317 (10.2%)
Ischaemic cardiovascular disease	127 (4.1%)	104 (3.4%)
Angina pectoris	71 (2.3%)	51 (1.6%)
Myocardial infarct	37 (1.2%)	34 (1.1%)
Coronary artery disorder	25 (0.8%)	23 (0.7%)
Myocardial ischaemia	22 (0.7%)	14 (0.5%)
Vaginal discharge	109 (3.5%)	408 (13.2%)
Any venous thromboembolic event	87 (2.8%)	140 (4.5%)
Deep venous thromboembolic events including PE	48 (1.6%)	74 (2.4%)
Ischaemic cerebrovascular events	62 (2.0%)	88 (2.8%)
Endometrial cancer	4 (0.2%)	13 (0.6%)

Fracture rates of 22 per 1000 patient-years and 15 per 1000 patient-years were observed for the Anastrozole and tamoxifen groups, respectively, after a median follow-up of 68 months. The observed fracture rate for Anastrozole is similar to the range reported in age-matched postmenopausal populations. It has not been determined whether the rates of fracture and osteoporosis seen in ATAC in patients on Anastrozole treatment reflect a protective effect of tamoxifen, a specific effect of Anastrozole, or both.
The incidence of osteoporosis was 10.5% in patients treated with Anastrozole and 7.3% in patients treated with tamoxifen.

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DOSAGE AND ADMINISTRATION

Adults including the elderly: 1 tablet to be taken orally once a day.
Children: Zortex® is not recommended for use in children due to insufficient data on safety and efficacy.
Renal impairment: No dose change is recommended in patients with mild or moderate renal impairment.
Hepatic impairment: No dose change is recommended in patients with mild hepatic disease.
For early disease, the recommended duration of treatment should be 5 years.

OVERDOSAGE

There is limited clinical experience of accidental overdosage. In animal studies, Anastrozole demonstrated low acute toxicity. Clinical trials have been conducted with various dosages of Anastrozole, up to 60 mg in a single dose given to healthy male volunteers and up to 10 mg daily given to postmenopausal women with advanced breast cancer; these dosages were well tolerated. A single dose of Anastrozole that results in life-threatening symptoms has not been established. There is no specific antidote to overdosage and treatment must be symptomatic.
In the management of an overdose, consideration should be given to the possibility that multiple agents may have been taken. Vomiting may be induced if the patient is alert. Dialysis may be helpful because Anastrozole is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

STORAGE CONDITIONS

Store below 25°C.
Keep in original pack in intact conditions.

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