Anarix® 1 mg

Anastrozole
Film coated tablets

Qualitative and quantitative composition

Each film coated tablet contains Anastrozole 1 mg.

Excipients: Lactose monohydrate, Povidone K-30, Purified water, Sodium starch Glycolate (Type A), Magnesium stearate, Hypromellose E-5, Macrogol 300, Titanium Dioxide (E171).

Pharmaceutical Form

Film-coated tablet.

Description

White to off white, round, biconvex, film coated tablets with "AHI" debossing on one side and plain on other side.

Indications

- Adjuvant treatment of post-menopausal women with hormone receptor positive early invasive breast cancer.
- Adjuvant treatment of early breast cancer in hormone receptor positive post-menopausal women who have received 2 to 3 years of adjuvant tamoxifen.
- Treatment of advanced breast cancer in post-menopausal women.

Efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen.

Posology and method of administration

- Adults including the elderly: One 1 mg tablet to be taken orally once a day.
- Children: Not recommended for use in children.
- 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.

Contraindications

Anastrozole is contraindicated in:

- Pre-menopausal 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 (see Interactions).

Warnings and precautions for use

Anastrozole is not recommended for use in children as safety and efficacy have not been established in this group of patients.
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 e.g. DEXA scanning 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.

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 (see Contraindications).

Pregnancy and lactation

Anastrozole is contraindicated in pregnant or lactating women.

Effects on 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.

Undesirable effects

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

Very common ≥10%)	Vascular:	Hot flushes, mainly mild or moderate in 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.
	Gastrointestinal:	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. Anaphylaticoid 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 (see warnings and precautions for use).

The table below presents the frequency of pre-specified adverse events 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	Arimidex (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%)	544 (17.6%)
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 post-menopausal 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.

Overdose

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 post-menopausal 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.

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 post-menopausal women.
Pharmacokinetics have not been studied in children.
Anastrozole is only 40% bound to plasma proteins.
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 extensively metabolised by post-menopausal 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.

Preclinical safety data

Acute toxicity

In acute toxicity studies in rodents the median lethal dose of anastrozole was greater than 100 mg/kg/day by the oral route and greater than 50 mg/kg/day by the intraperitoneal route. In an oral acute toxicity study in the dog the median lethal dose was greater than 45 mg/kg/day.

Chronic toxicity

Multiple dose toxicity studies utilised rats and dogs. No no-effect levels were established for anastrozole in the toxicity studies, but those effects that were observed at the low doses (1 mg/kg/day) and mid doses (dog 3 mg/kg/day; rat 5 mg/kg/day) were related to either the pharmacological or enzyme-inducing properties of anastrozole and were unaccompanied by significant toxic or degenerative changes.

Mutagenicity

Genetic toxicology studies with anastrozole show that it is not a mutagen or a clastogen.

Reproductive toxicology

Oral administration of anastrozole to female rats produced a high incidence of infertility at 1 mg/kg/day and increased pre-implantation loss at 0.02 mg/kg/day. These effects occurred at clinically relevant doses. An effect in man cannot be excluded. These effects were related to the pharmacology of the compound and were completely reversed after a 5-week compound withdrawal period.
Oral administration of anastrozole to pregnant rats and rabbits caused no teratogenic effects at doses up to 1.0 and 0.2 mg/kg/day respectively. Those effects that were seen (placental enlargement in rats and pregnancy failure in rabbits) were related to the pharmacology of the compound.
The survival of litters born to rats given anastrozole at 0.02 mg/kg/day and above (from day 17 of pregnancy to day 22 post-partum) was compromised. These effects were related to the pharmacological effects of the compound on parturition. There were no adverse effects on behaviour or reproductive performance of the first generation offspring attributable to maternal treatment with anastrozole.

Carcinogenicity

A two year rat oncogenicity study resulted in an increase in incidence of hepatic neoplasms and uterine stromal polyps in females and thyroid adenomas in males at the high dose (25 mg/kg/day) only. These changes occurred at a dose which represents 100-fold greater exposure than occurs at human therapeutic doses, and are considered not to be clinically relevant to the treatment of patients with anastrozole.
A two year mouse oncogenicity study resulted in the induction of benign ovarian tumours and a disturbance in the incidence of lymphoreticular neoplasms (fewer histiocytic sarcomas in females and more deaths as a result of lymphomas). These changes are considered to be mouse-specific effects of aromatase inhibition and not clinically relevant to the treatment of patients with anastrozole.

Incompatibilities

Not applicable

Shelf-life

Please refer to expiry date on the blister strip or outer carton.

Storage

Store below 30°C.

Pack size

28 film-coated tablets per pack.

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