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ARIMIDEX 1 mg Tablets
ASTRAZENECA

anastrozole

Tablet

Composition

Each tablet contains 1 mg anastrozole.
For excipients see List of excipients.

Pharmaceutical Form

Film-coated tablet

Therapeutic Indications

Adjuvant treatment of post-menopausal women with hormone receptor positive early invasive breast cancer.

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

Arimidex 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 as referenced in the List of excipients.

Oestrogen-containing therapies should not be co-administered with Arimidex as they would negate its pharmacological action.

Concurrent tamoxifen therapy (see Interaction).

Special warnings and precautions for use

Arimidex 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 Arimidex 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 Arimidex lowers circulating oestrogen levels it may cause a reduction in bone mineral density. Adequate data to show the effect of bisphosphonates on bone mineral density loss caused by anastrozole, or their utility when used prophylactically, are not currently available.

Interaction

Antipyrine and cimetidine clinical interaction studies indicate that the co-administration of Arimidex 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 Arimidex who also received other commonly prescribed drugs.

Oestrogen-containing therapies should not be co-administered with Arimidex as they would negate its pharmacological action.

Tamoxifen should not be co-administered with Arimidex, as this may diminish its pharmacological action (see Contraindications).

Pregnancy and lactation

Arimidex is contraindicated in pregnant or lactating women.

Effects on ability to drive and use machines

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

Undesirable effects

Very common (≥10%)	Vascular:	Hot flushes, mainly mild or moderate in nature.
Common (≥1% and <10%)	General:	Asthenia, mainly mild or moderate in nature.
	Musculoskeletal, connective tissue and bone:	Joint pain/stiffness, mainly mild or moderate in nature.
	Reproductive system and breast:	Vaginal dryness, mainly mild or moderate in nature.
	Skin and subcutaneous tissue:	Hair thinning, mainly mild or moderate in nature.
		Rash, mainly mild or moderate in nature.
	Gastrointestinal:	Nausea, mainly mild or moderate in nature.
		Diarrhoea, mainly mild or moderate in nature.
	Nervous system:	Headache, mainly mild or moderate in nature.
Uncommon (≥0.1% and <1%)	Reproductive system and breast:	Vaginal bleeding, mainly mild or moderate in nature*.
	Metabolism and nutrition:	Anorexia, mainly mild in nature.
		Hypercholesterolaemia, mainly mild or moderate in nature.
	Gastrointestinal:	Vomiting, mainly mild or moderate in nature.
	Nervous system:	Somnolence, mainly mild or moderate in nature.
Very rare (<0.01%)	Skin and subcutaneous tissue:	Erythema multiforme Stevens-Johnson syndrome Allergic reactions including angioedema, urticaria and anaphylaxis.

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

As Arimidex lowers circulating oestrogen levels, it may cause a reduction in bone mineral density placing some patients at a higher risk of fracture (see Special warnings and precautions for use).

Elevated gamma-GT and alkaline phosphatase have been reported uncommonly (≥0.1% and <1%). A causal relationship for these changes has not been established.

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 Arimidex and tamoxifen groups, respectively, after a median follow up of 68 months. The observed fracture rate for Arimidex 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 Arimidex 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 Arimidex, 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 Arimidex 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 Arimidex is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

Pharmacodynamic properties

ATC Code: L02B G03 (Enzyme inhibitors)

Arimidex is a potent and highly selective non-steroidal aromatase inhibitor. In post-menopausal women, oestradiol is produced primarily from the conversion of androstenedione to oestrone through the aromatase enzyme complex in peripheral tissues. Oestrone is subsequently converted to oestradiol. Reducing circulating oestradiol levels has been shown to produce a beneficial effect in women with breast cancer. In post-menopausal women, Arimidex at a daily dose of 1 mg produced oestradiol suppression of greater than 80% using a highly sensitive assay.

Arimidex does not possess any progestogenic, androgenic or oestrogenic activity.

Daily doses of Arimidex 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.

In a large phase III study conducted in 9366 postmenopausal women with operable breast cancer treated for 5 years, Arimidex was shown to be statistically superior to tamoxifen in disease free survival. A greater magnitude of benefit was observed for disease free survival in favour of Arimidex versus tamoxifen for the prospectively defined hormone receptor positive population. Arimidex was statistically superior to tamoxifen in time to recurrence. The difference was of even greater magnitude than in disease free survival for both the Intention To Treat (ITT) population and hormone receptor positive population. Arimidex was statistically superior to tamoxifen in terms of time to distant recurrence. The incidence of contralateral breast cancer was statistically reduced for Arimidex compared to tamoxifen. Following 5 years of therapy, anastrozole is at least as effective as tamoxifen in terms of overall survival. However, due to low death rates, additional follow-up is required to determine more precisely the long-term survival for anastrozole relative to tamoxifen. With 68 months median follow-up, patients in the ATAC study have not been followed up for sufficient time after 5 years of treatment, to enable a comparison of long-term post treatment effects of Arimidex relative to tamoxifen.

ATAC endpoint summary: 5-year treatment completion analysis

Efficacy endpoints	Number of events (frequency)			
	Intention-to-treat population		Hormone-receptor-positive tumour status	
	Arimidex (N=3125)	Tamoxifen (N=3116)	Arimidex (N=2618)	Tamoxifen (N=2598)
Disease-free survival[a]	575 (18.4)	651 (20.9)	424 (16.2)	497 (19.1)
Hazard ratio	0.87		0.83	
2-sided 95% CI	0.78 to 0.97		0.73 to 0.94	
p-value	0.0127		0.0049	
Distant disease-free survival[b]	500 (16.0)	530 (17.0)	370 (14.1)	394 (15.2)
Hazard ratio	0.94		0.93	

ATAC endpoint summary: 5-year treatment completion analysis				
Efficacy endpoints	**Number of events (frequency)**			
	Intention-to-treat population		**Hormone-receptor-positive tumour status**	
	Arimidex (N=3125)	**Tamoxifen (N=3116)**	**Arimidex (N=2618)**	**Tamoxifen (N=2598)**
2-sided 95% CI	0.83 to 1.06		0.80 to 1.07	
p-value	0.2850		0.2838	
Time to recurrence[c]	402 (12.9)	498 (16.0)	282 (10.8)	370 (14.2)
Hazard ratio	0.79		0.74	
2-sided 95% CI	0.70 to 0.90		0.64 to 0.87	
p-value	0.0005		0.0002	
Time to distant recurrence[d]	324 (10.4)	375 (12.0)	226 (8.6)	265 (10.2)
Hazard ratio	0.86		0.84	
2-sided 95% CI	0.74 to 0.99		0.70 to 1.00	
p-value	0.0427		0.0559	
Contra-lateral breast primary	35 (1.1)	59 (1.9)	26 (1.0)	54 (2.1)
Odds ratio	0.59		0.47	
2-sided 95% CI	0.39 to 0.89		0.30 to 0.76	
p-value	0.0131		0.0018	
Overall survival[e]	411 (13.2)	420 (13.5)	296 (11.3)	301 (11.6)
Hazard ratio	0.97		0.97	
2-sided 95% CI	0.85 to 1.12		0.83 to 1.14	
p-value	0.7142		0.7339	

[a] Disease-free survival includes all recurrence events and is defined as the first occurrence of loco-regional recurrence, contralateral new breast cancer, distant recurrence or death (for any reason).
[b] Distant disease-free survival is defined as the first occurrence of distant recurrence or death (for any reason).
[c] Time to recurrence is defined as the first occurrence of loco-regional recurrence, contralateral new breast cancer, distant recurrence or death due to breast cancer.
[d] Time to distant recurrence is defined as the first occurrence of distant recurrence or death due to breast cancer.
[e] Number (%) of patients who had died.

As with all treatment decisions, women with breast cancer and their physician should assess the relative benefits and risks of the treatment.

When Arimidex and tamoxifen were co-administered, the efficacy and safety were similar to tamoxifen when given alone, irrespective of hormone receptor status. The exact mechanism of this is not yet clear. It is not believed to be due to a reduction in the degree of oestradiol suppression produced by Arimidex.

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 Arimidex 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.

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 relevant to the prescriber

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 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 anastrazole.

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.

List of excipients
Lactose Monohydrate Ph. Eur.
Povidone Ph. Eur.
Sodium Starch Glycollate B.P.
Magnesium Stearate Ph. Eur.
Hypromellose Ph. Eur.
Macrogol 300 Ph. Eur.
Titanium Dioxide Ph. Eur.

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

Special precautions for storage
Do not store above 30ºC.

Pack size
Please refer to the outer carton for pack size.

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