# ARIMIDEX®

anastrozole

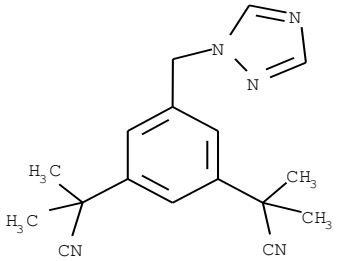
**PRODUCT INFORMATION**

## NAME OF THE MEDICINE

Anastrozole

Chemical name: 2,2'-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]bis(2-methylpropiononitrile).

Structural formula:




CAS number: 120511-73-1.

## DESCRIPTION

Anastrozole is a fine white to off-white powder. It has moderate aqueous solubility (0.53 mg/mL at 25°C) which is dependent on pH from pH 1 to 4 but independent of pH thereafter.

ARIMIDEX 1 mg is a round, white, biconvex film-coated tablet containing 1 mg anastrozole and includes the following excipients: lactose monohydrate, povidone, sodium starch glycollate, magnesium stearate, hypromellose, macrogol 300 and titanium dioxide.

## PHARMACOLOGY

### Pharmacodynamic properties

ARIMIDEX is a potent and highly selective non-steroidal aromatase inhibitor. It significantly lowers serum oestradiol concentrations and has no detectable effect on formation of adrenal corticosteroids or aldosterone.

Many breast cancers have oestrogen receptors and growth of these tumours can be stimulated by oestrogen. In postmenopausal 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. Many breast cancers also contain aromatase; the importance of tumour-generated oestrogens is uncertain

Reducing circulating oestradiol levels has been shown to produce a beneficial effect in women with breast cancer. In postmenopausal 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 phase III/IV study there was a neutral effect on plasma lipids in those patients treated with ARIMIDEX.

## Pharmacokinetics

### *Absorption*

Absorption of anastrozole is rapid and maximum plasma concentrations typically occur within two hours of dosing (under fasted conditions). 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.

### *Distribution*

Anastrozole is only 40% bound to plasma proteins. The pharmacokinetics of anastrozole are linear over the dose range of 1 mg to 20 mg and do not change with repeated dosing.

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.

### *Metabolism*

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, a major metabolite in plasma and urine, does not inhibit aromatase.

### *Elimination*

Anastrozole is eliminated slowly with a plasma elimination half-life of 40 to 50 hours.

### Paediatric pharmacokinetics

In boys with pubertal gynecomastia, anastrozole was rapidly absorbed, was widely distributed, and was eliminated slowly with a half-life of approximately 2 days. Pharmacokinetic parameters in boys were comparable to those of postmenopausal women. 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.

## CLINICAL TRIALS

### Switching in treatment of early breast cancer

A prospectively planned, combined analysis of 2 multicentre, open-label, randomised controlled trials (ABCSG trial 8 and ARNO 95) was conducted to examine the efficacy of switching postmenopausal patients with hormone-receptor positive early breast cancer receiving tamoxifen (20 or 30 mg daily), to ARIMIDEX (1 mg daily). A total of 3224 patients who had completed 2 years adjuvant treatment with tamoxifen and had remained disease-free, were randomised to receive ARIMIDEX for 3 years (n=1618) or to continue on tamoxifen for 3 years (20 to 30 mg daily; n=1606). The total duration of hormonal therapy was 5 years. Patients did not receive adjuvant chemotherapy. 74% of patients had lymph-node negative disease at commencement of hormonal therapy.

The primary endpoint was event-free survival, with an event being defined as loco-regional or distant recurrence or the development of contralateral breast cancer. Overall survival was a secondary end-point. Median follow-up after randomisation was 28 months, and 55% of patients in each group had completed the planned 5 years of hormonal therapy. Results are presented in **Table 1**.

**Table 1**

| | Arimidex | Tamoxifen | Hazard Ratio | p-value |
|---|---|---|---|---|
| No of events | 67 | 110 | 0.60 (95% CI: 0.44 - 0.81) | 0.0009 |
| Event-free survival at 3 years* | 95.8% | 92.7% | - | - |
| Overall survival | 97.2% | 96.3% | - | ns |

*Kaplan –Meier estimate
ns = non-significant

Compared with tamoxifen, anastrozole treatment was associated with a significantly increased incidence of fractures – 34 cases vs. 16 cases; Odds ratio (OR)=2.14 (95% CI 1.14 – 4.17; p=0.015), but with a reduced incidence of thromboses (3 vs. 12 cases; OR=0.25 (95% CI: 0.04 – 0.92; p=0.034)

Another open-label, randomised controlled trial (the ITA study) enrolled 448 postmenopausal patients with oestrogen–receptor positive early breast cancer. All

patients had lymph node involvement. Patients who remained disease-free after receiving 2 to 3 years of tamoxifen therapy were randomly assigned to receive ARIMIDEX (1 mg daily; n=233) or to continue therapy with tamoxifen (20 mg daily, n=225) for a total of 5 years hormonal therapy in each arm. 67% of patients in each arm received adjuvant chemotherapy.

The primary endpoint was disease recurrence, with a recurrence being defined as loco-regional or distant recurrence. Event-free survival was a secondary end-point with an event being defined as loco-regional or distant recurrence, the development of contralateral breast cancer, the development of a second primary cancer, or death occurring without disease recurrence. Overall survival was also a secondary end-point. Median follow-up after randomisation was 36 months. Results are presented in **Table 2**.

**Table 2**

| | **Arimidex** | **Tamoxifen** | **Hazard Ratio** | **p-value** |
|---|---|---|---|---|
| No of recurrences | 12 | 32 | 0.35 (95% CI: 0.18 – 0.68) | 0.001 |
| No of events | 17 | 45 | 0.35 (95% CI: 0.20 – 0.63) | 0.0002 |
| Overall survival | 98.2% | 95.6% | - | ns |

ns = non-significant

ARIMIDEX was associated with an increased incidence of lipid disorders and gastrointestinal events, but with a reduced incidence of gynaecological events, when compared with tamoxifen.

### Adjuvant treatment of early breast cancer in postmenopausal women

In a multicentre, double-blind trial (ATAC; trial 0029) 9,366 postmenopausal women aged 33 to 95 years old with early breast cancer were randomised to receive adjuvant treatment with ARIMIDEX 1 mg daily, tamoxifen 20 mg daily, or a combination of the two treatments for five years or until recurrence of disease.

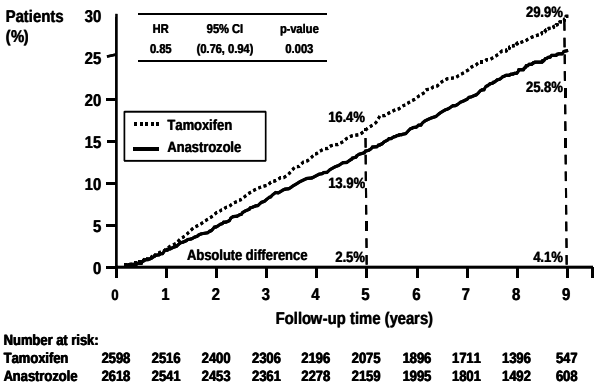
The primary endpoint was disease-free survival (i.e. time to occurrence of a distant or local recurrence, new contralateral breast cancer or death from any cause). Secondary and additional prospectively defined endpoints included time to distant recurrence, the incidence of contralateral breast cancer, overall survival, time to recurrence and time to death following recurrence.

Demographic and other baseline characteristics were similar among the two treatment arms, with approximately 84% of patients with hormone receptor positive disease. The median follow-up was 100 months.

Treatment with ARIMIDEX was superior to tamoxifen in the Intention-To-Treat (ITT) group, with statistically significant risk reductions in disease-free survival and time to recurrence of 10% and 19% respectively (refer **Table 3**). In the clinically relevant hormone-receptor-positive sub-group, statistically significant benefits of ARIMIDEX compared to tamoxifen were also observed for disease-free survival

and time to recurrence, with risk reductions of 15% and 24% respectively (refer **Figures 1**, **2** and **Table 3**). The absolute benefit in recurrence rates of ARIMIDEX over tamoxifen increased over the entire 100 month follow up period. The gain in absolute benefit during the off-treatment period demonstrates a superior carryover effect to that already demonstrated with 5 years of tamoxifen treatment (refer **Figure 2**).

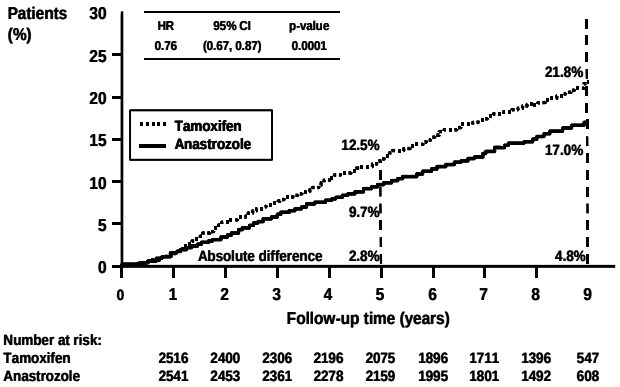
**Figure 1 Disease-free survival in patients with hormone-receptor-positive tumours**




Number at risk:

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Tamoxifen | 2598 | 2516 | 2400 | 2306 | 2196 | 2075 | 1896 | 1711 | 1396 | 547 |
| Anastrozole | 2618 | 2541 | 2453 | 2361 | 2278 | 2159 | 1995 | 1801 | 1492 | 608 |

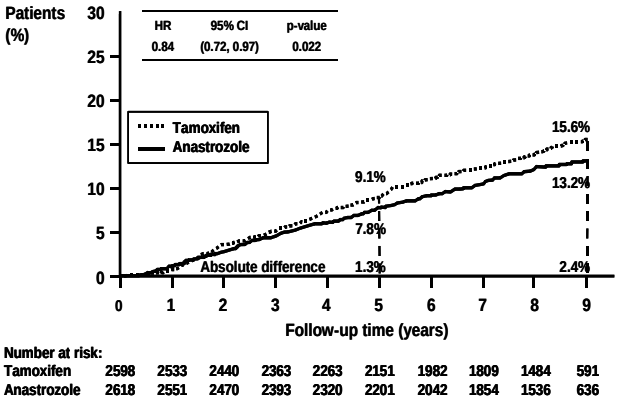
**Figure 2 Time to recurrence in patients with hormone-receptor-positive tumours**




Number at risk:

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Tamoxifen | 2516 | 2400 | 2306 | 2196 | 2075 | 1896 | 1711 | 1396 | 547 |
| Anastrozole | 2541 | 2453 | 2361 | 2278 | 2159 | 1995 | 1801 | 1492 | 608 |

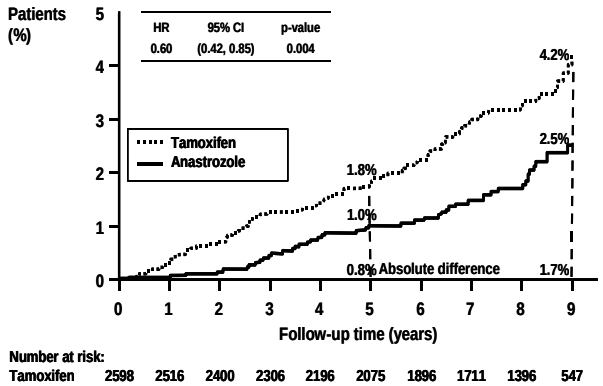
**Figure 3 Time to distant recurrence in patients with hormone-receptor-positive tumours**




Number at risk:

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Tamoxifen | 2598 | 2533 | 2440 | 2363 | 2263 | 2151 | 1982 | 1809 | 1484 | 591 |
| Anastrozole | 2618 | 2551 | 2470 | 2393 | 2320 | 2201 | 2042 | 1854 | 1536 | 636 |

**Figure 4 Contralateral breast cancer prevalence in patients with hormone-receptor-positive tumours**




Number at risk:

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Tamoxifen | 2598 | 2516 | 2400 | 2306 | 2196 | 2075 | 1896 | 1711 | 1396 | 547 |
| Anastrozole | 2618 | 2541 | 2453 | 2361 | 2278 | 2159 | 1995 | 1801 | 1493 | 608 |

Hazard ratios of <1.00 indicate that treatment with anastrozole is favourable relative to tamoxifen

**Table 3 Efficacy endpoint summary for Trial 0029 at a median follow-up of 100 months**

| | Hazard Ratio (95% Confidence Interval); p value | |
|---|---|---|
| **Endpoint** | **ITT group** | **HR-positive sub-group** |
| Disease free survival | 0.90 (0.82-0.99); p=0.025 | 0.85 (0.76-0.94); p=0.003 |
| Time to recurrence | 0.81 (0.73-0.91); p=0.0004 | 0.76 (0.67-0.87); p=0.0001 |
| Time to distant recurrence | 0.86 (0.75-0.98); p=0.022 | 0.84 (0.72-0.97); p=0.022 |
| Overall survival | 1.00 (0.89-1.12); p=0.99 | 0.97 (0.86-1.11); p=0.7 |
| Time to death following recurrence | 0.91 (0.79-1.05); p=0.2 | 0.90 (0.75-1.07); p=0.2 |
| Contralateral breast cancer* | 0.68 (0.49-0.94); p=0.020 | 0.60 (0.42-0.85); p=0.004 |

* Odds ratio computed instead of Hazard Ratio; ITT - intent-to-treat; HR – hormone receptor; Hazard ratios of <1.00 indicate that treatment with anastrozole is favourable relative to tamoxifen

Overall survival was a secondary endpoint in the ATAC study. The 100 month analysis of this study demonstrated that overall survival in the ARIMIDEX arm and the tamoxifen arm were not significantly different. Similar overall survival was observed for both the ITT group and hormone-receptor-positive sub-group (refer **Table 3**). At the 100 month follow up the mean age of the surviving population was 72 years, with non-breast cancer deaths accounting for 42 and 46% of total mortality in the ITT and hormone-receptor positive subgroup respectively.

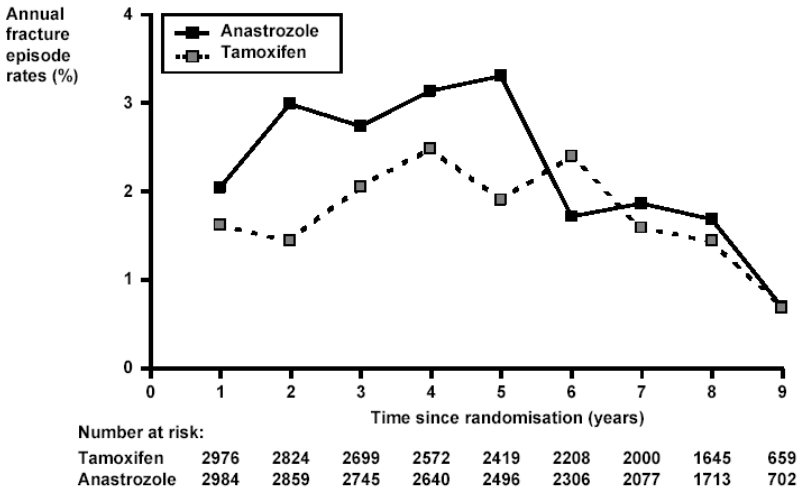
Other secondary and additional outcome variables were all either significantly in favour of ARIMIDEX or with trends evident in favour of ARIMIDEX when compared to tamoxifen (refer **Table 3**).

Overall, ARIMIDEX was well tolerated. Withdrawals due to drug-related adverse events were less common with ARIMIDEX compared to tamoxifen (6.5% vs 8.9%; Odds Ratio 0.71, 95% CI 0.59 - 0.86; p=0.0004). The following adverse events were reported regardless of causality. Patients receiving ARIMIDEX had a significant decrease in hot flushes, vaginal bleeding, vaginal discharge, endometrial cancer, venous thromboembolic events and ischaemic cerebrovascular events compared to patients receiving tamoxifen. Patients receiving ARIMIDEX also had an increase in joint disorders (including arthritis, arthrosis and arthralgia) and total number of fractures compared with patients receiving tamoxifen. Although the incidences of fractures (both serious and non-serious, occurring either during or after treatment) were higher in the ARIMIDEX compared to the tamoxifen treatment group, the incidences of hip fractures were similar between the groups. The fracture rate for ARIMIDEX whilst on treatment

falls within the broad range of fracture rates reported in an age-matched postmenopausal population.

A plot of the annual first fracture rates, throughout the study, shows that following the end of treatment the annual first event rates were similar in the ARIMIDEX and tamoxifen treatment groups and the increased first fracture rate seen during treatment was not continued in the post-treatment follow-up period (refer Fig 5).

**Figure 5: Fracture episode rates at the 100 month analysis**




Serious adverse events continued to be collected during the off-treatment follow-up. Overall the number of treatment-related serious adverse events remained lower with anastrozole than with tamoxifen for the active follow-up period, and was significantly lower during treatment and similar after treatment completion. The incidence of cardiovascular events reported was similar in the ARIMIDEX and tamoxifen arms (3.9% vs. 3.7%, respectively) in the 100 month analysis.

Ischaemic cardiovascular events (consisting mainly of angina pectoris) in the on-treatment period were reported more frequently in patients treated with ARIMIDEX compared to those treated with tamoxifen (mainly associated with patients with pre-existing ischaemic heart disease), although the difference was not statistically significant (p=0.1224).

At a median follow-up of 33 months, the combination arm did not demonstrate any efficacy benefit when compared with tamoxifen in either the ITT group or the hormone-receptor-positive sub-group. This treatment arm was discontinued from the trial.

### First line therapy in postmenopausal women with advanced breast cancer

In two similar controlled trials (Trials 0027 and 0030), 1021 postmenopausal women aged 30 to 92 years old, with advanced breast cancer [stage IV (metastatic disease) and stage III (locally advanced disease)] were randomised to receive ARIMIDEX 1 mg (n=511) or tamoxifen 20 mg (n=510) once daily as first line therapy.

The primary end points for both trials were time to progression, objective response rate and safety. The trials were designed to allow data to be pooled. The median duration of follow-up was 18.8 and 17.7 months in Trial 0027 and Trial 0030 respectively. The number of patients still on trial treatment at the end of the follow-up period was as follows:

| | Trial 0027 | Trial 0030 | Pooled trials |
|---|---|---|---|
| ARIMIDEX 1 mg | 101/340 (29.7%) | 48/171 (28.1%) | 149/511 (29.2%) |
| Tamoxifen 20 mg | 88/328 (26.8%) | 40/182 (22.0%) | 128/510 (25.1%) |

Demographics and other baseline characteristics were similar for the two treatment groups for both trials. The hormone receptor status at entry for all randomised patients in trials 0027 and 0030 is summarised in **Table 4**.

ARIMIDEX was at least as effective as tamoxifen for the primary endpoints of time to progression and objective-response rate. A comparison of the results for the primary endpoints, for both trials, is provided in **Table 4**. Positive oestrogen/progesterone receptor status had an impact on the primary efficacy parameters and this may partly explain the difference in results between the two trials.

**Table 4 Hormone receptor status and primary efficacy results in Trials 0027 and 0030 - ARIMIDEX 1 mg compared to tamoxifen 20 mg**

| | Trial 0027 | | Trial 0030 | |
|---|---|---|---|---|
| | ARIMIDEX (n=340) | Tamoxifen (n=328) | ARIMIDEX (n=171) | Tamoxifen (n=182) |
| RECEPTOR STATUS | | | | |
| ER-positive and/or PR-positive | 154 (45.3%) | 144 (43.9%) | 151 (88.3%) | 162 (89.0%) |
| ER and PR unknown | 185 (54.4%) | 183 (55.8%) | 19 (11.1%) | 20 (11.0%) |
| ER-negative, PR-negative | 1 (0.3%) | 1 (0.3 %) | 1 (0.6%) | 0 |
| ENDPOINTS | | | | |

| | Trial 0027 | | Trial 0030 | |
|---|---|---|---|---|
| | **ARIMIDEX (n=340)** | **Tamoxifen (n=328)** | **ARIMIDEX (n=171)** | **Tamoxifen (n=182)** |
| Median time to progression [TTP] (mths) | 8.2 | 8.3 | 11.1* | 5.6 |
| % Subjects who progressed | 73% | 75% | 67% | 76% |
| HAZARD RATIO[1] [LCL] | 0.99 [0.86] | | 1.44 [1.16] | |
| % Response rate | 32.9% | 32.6% | 21.1% | 17.0% |
| Difference in response rate [w/LCL][2] | -1.0% [-6.7%] | | +5.0% [-1.9%] | |

ER = Oestrogen receptor; PR = Progesterone receptor; *p = 0.005; [1]Tamoxifen: ARIMIDEX [hazard ratios > 1.00 indicate that ARIMIDEX is associated with a longer TTP than tamoxifen]; [2]ARIMIDEX minus Tamoxifen; The criteria for non-inferiority were that the lower one-sided 95% confidence bound for the hazard ratio was ≥ 0.80 and the difference in response rate ≥ -10%. These criteria were met. The lower limit of the 2-sided 95% confidence interval also satisfied these criteria; Response rate is the sum of complete responders plus partial responders based on modified UICC criteria.

### Second line therapy in postmenopausal women with advanced breast cancer who had disease progression following tamoxifen therapy

In two similar controlled trials (Trials 0004 and 0005), 764 postmenopausal women with advanced breast cancer who had disease progression following tamoxifen therapy for either early or advanced breast cancer were randomised to receive ARIMIDEX 1 mg daily, ARIMIDEX 10 mg daily or megestrol acetate 40 mg four times daily. Some of the patients had also received previous cytotoxic treatment. Patients were either ER-positive or unknown status (with about 5% being ER-negative) and had responded to previous treatment with tamoxifen.

At a median follow-up of approximately 30 months and with approximately 60% of patients having died, the data from both studies combined demonstrated significant prolongation of survival with ARIMIDEX 1 mg compared to megestrol acetate. The median time to death for ARIMIDEX 1 mg was 26.7 months compared to 22.5 months for megestrol acetate, with a 2 year survival rate for ARIMIDEX 1 mg of 56.1% compared to 46.3% for megestrol acetate. The hazard ratio of risk of death of patients on ARIMIDEX 1 mg compared to megestrol acetate was 0.78, and there was a statistically significant difference in time to death ($p < 0.025$).

## INDICATIONS

### Early breast cancer

Adjuvant treatment of early breast cancer in postmenopausal women with oestrogen/progesterone-receptor-positive disease.

### Advanced breast cancer

First line treatment of advanced breast cancer in postmenopausal women with oestrogen/progesterone-receptor-positive disease.

Treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. Patients with oestrogen-receptor-negative disease and patients who have not responded to previous tamoxifen therapy rarely respond to ARIMIDEX.

## CONTRAINDICATIONS

ARIMIDEX must not be administered during pregnancy or lactation.

Known hypersensitivity to the active substance or to any of the excipients of this product.

## PRECAUTIONS

### Paediatric use and use in pre-menopausal women

ARIMIDEX is not recommended for use in children or in pre-menopausal women as safety and efficacy have not been established in these groups of patients.

### Use in renal and hepatic impairment

The apparent oral clearance of anastrozole in volunteers with stable hepatic cirrhosis or renal impairment (creatinine clearance less than 30 mL/min/1.73m$^2$) was in the range observed in healthy volunteers. Dosage adjustment is therefore not necessary. ARIMIDEX has not been investigated in patients with severe hepatic or severe renal impairment. The potential risk/benefit to such patients should be carefully considered before administration of ARIMIDEX.

### Bone mineral density

As ARIMIDEX lowers circulating oestrogen levels it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture. 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 and monitored as appropriate.

In the phase III/IV SABRE study, 234 postmenopausal women with hormone receptor positive early breast cancer scheduled for treatment with ARIMIDEX were stratified to low, moderate and high-risk groups according to their existing risk of fragility fracture. All patients received treatment with vitamin D and calcium. Patients in the low risk group received ARIMIDEX alone, those in the moderate group were randomised to ARIMIDEX plus bisphosphonate or ARIMIDEX plus placebo and those in the high risk group received ARIMIDEX plus bisphosphonate.

The 12-month main analysis has shown that patients already at moderate to high risk of fragility fracture had their bone health (assessed by bone mineral density and bone formation and resorption markers) successfully managed by using ARIMIDEX in combination with a bisphosphonate. These findings were mirrored in the secondary efficacy variable of change from baseline in total hip BMD at 12 months.

### Combination with LHRH agonists

There are no data available for the use of anastrozole with LHRH agonists. This combination should not be used outside clinical trials.

### Effects on fertility

In female rats treated orally with anastrozole for 14 days prior to mating up to day 7 of gestation, the fertility index (pregnancies/matings) was reduced after oral doses of 1 mg/kg and above [9 times the maximum recommended clinical dose, based on body surface area (BSA)]. Pre-implantation loss was increased, and the number of implantations decreased, at doses of 0.02 mg/kg and above (0.2 times the maximum recommended clinical dose, based on BSA). It is not known whether anastrozole impairs fertility in humans.

### Use in pregnancy (Category C)

ARIMIDEX is contraindicated in pregnant women.

After oral administration of anastrozole to pregnant rats and rabbits, the drug was shown to cross the placenta and was detectable in foetal tissues at concentrations approximately 40% of corresponding maternal plasma drug concentrations. Anastrozole showed no evidence for teratogenic activity and had no effects on pregnancy parameters at oral doses of up to 1 mg/kg/day in rats and up to 0.2 mg/kg/day in rabbits (9 and 3 times the maximum recommended clinical dose, based on BSA, respectively). However, enlargement of the placenta was seen in rats and treatment of rabbits with anastrozole at doses greater than 0.2 mg/kg/day caused abortion in 100% of animals. These effects are consistent with disruption of oestrogen dependent events during pregnancy and are not unexpected with a drug of this class.

In a peri-postnatal study (administration from day 17 of gestation to day 21 post-partum) in rats, increased resorption was observed at 0.5 mg/kg/day. Increased stillbirths and evidence for dystocia (increased variability in the length of gestation and/or vaginal bleeding at birth) were reported at doses of 0.1 mg/kg/day or greater. Pup survival was reduced at all doses tested (0.02 mg/kg/day and above, 0.2 times the maximum recommended clinical dose, based on BSA). There was no evidence of adverse effects on behaviour or reproductive performance of the first generation offspring attributable to maternal treatment with anastrozole.

### Use in lactation

ARIMIDEX is contraindicated in breast-feeding women.

### Use in the elderly

Anastrozole pharmacokinetics have been investigated in postmenopausal female volunteers and patients with breast cancer. No age related effects were seen over the range < 50 to > 80 years.

### Preclinical chronic toxicity

Multiple dose toxicity studies utilized 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. Plasma levels of anastrozole at these doses in rats and dogs were at least 3 and 12 times greater, respectively, than those expected in human postmenopausal women during treatment with anastrozole. At higher doses of anastrozole, nephropathy was observed in rats, ECG changes were observed in dogs, and changes in cholesterol levels were observed in both animal species.

### Carcinogenicity

In a two year rat oncogenicity study, anastrozole caused an increase in incidence of hepatic adenomas and carcinomas and uterine stromal polyps in females and thyroid adenomas in males at the high dose (25 mg/kg/day), where exposure (AUC) was approximately 100-fold that which occurs at the maximum recommended clinical dose. At the no tumourigenic effect level (5 mg/kg/day), exposure (AUC) was approximately 20-fold that which occurs at the maximum recommended clinical dose.

In a two year mouse oncogenicity study, anastrozole induced 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). The benign tumourigenic effect on the ovary occurred at all doses including the lowest dose tested (5 mg/kg/day) [exposure (AUC) was approximately 1 to 2-fold that which occurs at the maximum recommended clinical dose]. The clinical relevance of these findings in the mouse are not clear.

### Genotoxicity

Anastrozole did not show evidence of genotoxicity in assays for gene mutations in vitro and chromosomal damage in vitro and in vivo.

### Interactions with other medicines

Anastrozole inhibited reactions catalyzed by cytochrome P450 1A2, 2C8/9, and 3A4 *in vitro* with Ki values which were approximately 30 times higher than the mean steady-state $C_{max}$ values observed following a 1 mg daily dose. Anastrozole had no inhibitory effect on reactions catalyzed by cytochrome P450 2A6 or 2D6 *in vitro*. Based on these *in vitro* and the *in vivo* results with antipyrine and cimetidine, it is unlikely that co-administration of ARIMIDEX 1 mg with other drugs will result in clinically significant inhibition of cytochrome P450-mediated metabolism.

### *Other medicines that effect anastrozole*

*Demonstrated interactions*

On the basis of clinical and pharmacokinetic data from the ATAC trial, tamoxifen must not be administered with anastrozole. Co-administration of anastrozole and tamoxifen resulted in a reduction of anastrozole plasma levels by 27% compared with those achieved with anastrozole alone.

*Theoretical interactions*

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

*Potential interactions that have been excluded*

A review of the clinical trial safety database did not reveal evidence of any clinically significant interaction in patients treated with ARIMIDEX who also received commonly prescribed drugs. There were no clinically significant interactions with bisphosphonates (refer **Precautions – Bone mineral density**).

### *Effects of anastrozole on other medicines*

*Potential interactions that have been excluded*

Antipyrine

Administration of a single 30 mg/kg or multiple 10 mg/kg doses of anastrozole to subjects had no effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites.

Cimetidine

Pre-treatment with cimetidine, at a dose of 300 mg every six hours for four days, in normal postmenopausal women had no effect on the single dose pharmacokinetics of anastrozole (10 mg).

Warfarin

An interaction study with warfarin showed no clinically significant effect of anastrozole on warfarin pharmacokinetics or anticoagulant activity.

### 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.

## ADVERSE EFFECTS

ARIMIDEX has generally been well tolerated. Adverse events have usually been mild to moderate with only few withdrawals from treatment due to undesirable events. 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 5 years and unless specified, no account was taken of the frequency within the comparative treatment group or whether the investigator considered it to be related to study medication.

| Frequency | System Organ Class | Event |
|---|---|---|
| **Very common (≥10%)** | *Vascular* | Hot flushes[#] |
| | *General* | Asthenia[#] |
| | *Musculoskeletal, connective tissue & bone* | Arthralgia/joint stiffness, arthritis[#] |
| | *Nervous system* | Headache[#] |
| | *Gastrointestinal* | Nausea[#] |
| | *Skin & subcutaneous tissue* | Rash[#] |
| **Common (≥1% - <10%)** | *Reproductive system & breast* | Vaginal dryness[#], vaginal bleeding[#+] |
| | *Skin & subcutaneous tissue* | Hair thinning (alopecia)[#], allergic reactions[#] |
| | *Gastrointestinal* | Vomiting[#], diarrhoea[#] |
| | *Nervous system* | Somnolence[#], Carpal Tunnel Syndrome^, sensory disturbances (including paraesthesia, taste loss and taste perversion) |
| | *Hepatobiliary disorders* | Increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase |
| | *Metabolism & nutrition* | Anorexia[#], hypercholesterolaemia[#] |
| | *Musculoskeletal, connective tissue & bone* | Bone pain, myalgia |
| **Uncommon (≥0.1% - <1%)** | *Metabolism and nutrition* | Hypercalcaemia (with or without an increase in parathyroid hormone) |
| | *Musculoskeletal, connective tissue & bone* | Trigger finger |
| | *Skin & subcutaneous tissue* | Urticaria |
| | *Hepatobiliary disorders* | Increases in gamma-GT and bilirubin, hepatitis |
| **Rare (≥0.01% - <0.1%)** | *Skin & subcutaneous tissue* | Erythema multiformae, anaphylactoid reaction, cutaneous vasculitis (including some reports of Henoch-Schönlein purpura) |

| Frequency | System Organ Class | Event |
|---|---|---|
| **Very rare (<0.01%)** | *Skin & subcutaneous tissue* | Stevens-Johnson syndrome, angioedema |

[#] mainly mild or moderate in nature.

[+]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.

^ Events of Carpal Tunnel Syndrome have been reported in patients receiving ARIMIDEX treatment in clinical trials in greater numbers than those receiving treatment with tamoxifen. However, the majority of these events occurred in patients with identifiable risk factors for the development of the condition

In a large phase III study conducted in 9366 postmenopausal women with operable breast cancer treated for 5 years, ischaemic cardiovascular events (consisting mainly of angina pectoris) in the on-treatment period were reported more frequently in patients treated with ARIMIDEX compared to those treated with tamoxifen (mainly associated with patients with pre-existing ischaemic heart disease), although the difference was not statistically significant (p=0.1224).

In studies in the adjuvant setting, ARIMIDEX has been associated with an increased incidence of fractures compared to tamoxifen treatment during the active treatment phase. At the 100 month analysis of a large phase III study the off treatment fracture episode rate was no different between the ARIMIDEX and tamoxifen treatment arms (see **Clinical Trials**).

## DOSAGE AND ADMINISTRATION

### Adults including the elderly

One tablet (1 mg) to be taken orally once a day.

For early breast cancer, the recommended total duration of hormonal therapy is 5 years. For patients being switched to ARIMIDEX from tamoxifen, the switch should occur after completion of 2 to 3 years of tamoxifen therapy. There are no data to support switching at earlier or later time points.

### Children

Not recommended for use in children.

### Use in adults with renal impairment

No dose change is recommended.

### Use in adults with hepatic impairment

No dose change is recommended.

## OVERDOSAGE

There is limited clinical experience of overdose of ARIMIDEX. There are no reports where a patient has taken a dose exceeding 60 mg. No toxicity was observed and no clinically relevant adverse effects have been seen.

There is no 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 postmenopausal 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.

## PRESENTATION AND STORAGE CONDITIONS

ARIMIDEX is presented as a round, white, biconvex film-coated tablet containing 1 mg of anastrozole with the following markings impressed on tablet:

*Front:* 


*Back:* 


ARIMIDEX tablets are presented in a PVC blister/aluminium foil blister calendar pack containing 30 tablets.

### Storage conditions

Store below 30°C.

## NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
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MACQUARIE PARK NSW 2113

Telephone: 1800 805342

## POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine).

## DATE OF APPROVAL

Date of approval: 15 Jun 2009

Date of most recent amendment: 16 May 2017

ARIMIDEX® is a trademark of the AstraZeneca group of companies