

## 1 NAME OF THE MEDICINE

Anastrozole

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg of anastrozole as the active ingredient.

Excipients with known effect: lactose

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

## 3 PHARMACEUTICAL FORM

ARIANNA 1 tablets are white to off white, round, biconvex, film-coated tablets debossed with “AHP” on one side and plain on other side.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

#### **Early breast cancer**

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

#### **Advanced breast cancer**

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

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

### 4.2 DOSE AND METHOD OF 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 anastrozole 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.

### 4.3 CONTRAINDICATIONS

Anastrozole must not be administered during pregnancy or lactation.

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

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

#### 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<sup>2</sup>) was in the range observed in healthy volunteers. Dosage adjustment is therefore not necessary. Anastrozole have 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 anastrozole.

#### Bone mineral density

As anastrozole lowers circulating estrogen 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 anastrozole 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 anastrozole alone, those in the moderate group were randomised to anastrozole plus bisphosphonate or anastrozole plus placebo and those in the high risk group received anastrozole 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 anastrozole 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.

#### Tendon disorders

The use of third generation aromatase inhibitors, including anastrozole, was found to be associated with tendonitis and tenosynovitis in randomised controlled trials. Tendon rupture was found to be a potential risk. Tendonitis and tenosynovitis were estimated to be of uncommon occurrence, and tendon rupture of rare occurrence. Monitor patients for signs and symptoms of tendon disorders during treatment with anastrozole.

#### 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.

#### 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.

#### Paediatric Use

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

## Use in pre-menopausal women

Anastrozole is not recommended for use in pre-menopausal women as safety and efficacy have not been established in this group of patients.

## Effects on Laboratory Tests

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Anastrozole inhibited reactions catalysed by cytochrome P450 1A2, 2C8/9, and 3A4 *in vitro* with  $K_i$  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 catalysed 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 anastrozole 1 mg with other drugs will result in clinically significant inhibition of cytochrome P450-mediated metabolism.

### Other medicines that affect 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*

Estrogen-containing therapies should not be co-administered with anastrozole 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 anastrozole who also received commonly prescribed drugs. There were no clinically significant interactions with bisphosphonates (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – 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.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### 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)

Anastrozole 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 fetal 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 estrogen 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 postpartum) 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

Anastrozole is contraindicated in breast-feeding women.

## 4.7 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.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Anastrozole 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.

**Table 1**

Frequency	System Organ Class	Event
Very common (≥10%)	Vascular	Hot flushes <sup>#</sup>
	General	Asthenia <sup>#</sup>
	Musculoskeletal, connective tissue & bone	Arthralgia/joint stiffness, arthritis <sup>#</sup> , osteoporosis
	Nervous system	Headache <sup>#</sup>

	Gastrointestinal	Nausea <sup>#</sup>
	Skin & subcutaneous tissue	Rash <sup>#</sup>
	Psychiatric disorders	Depression
<b>Common</b> (≥1% - <10%)	Reproductive system & breast	Vaginal dryness <sup>#</sup> , vaginal bleeding <sup>#+</sup>
	Skin & subcutaneous tissue	Hair thinning (alopecia) <sup>#</sup> , allergic reactions <sup>#</sup>
	Gastrointestinal	Vomiting <sup>#</sup> , diarrhoea <sup>#</sup>
	Nervous system	Somnolence <sup>#</sup> , Carpal Tunnel Syndrome <sup>^</sup> , sensory disturbances (including paraesthesia, taste loss and taste perversion)
	Hepatobiliary disorders	Increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase
	Metabolism & nutrition	Anorexia <sup>#</sup> , hypercholesterolaemia <sup>#</sup>
	Musculoskeletal, connective tissue & bone	Bone pain, myalgia
<b>Uncommon</b> (≥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
<b>Rare</b> (≥0.01% - <0.1%)	Skin & subcutaneous tissue	Erythema multiformae, anaphylactoid reaction, cutaneous vasculitis (including some reports of Henoch-Schönlein purpura)
<b>Very rare</b> (<0.01%)	Skin & subcutaneous tissue	Stevens-Johnson syndrome, angioedema

<sup>#</sup> mainly mild or moderate in nature.

<sup>+</sup>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 anastrozole. If bleeding persists, further evaluation should be considered.

<sup>^</sup> Events of Carpal Tunnel Syndrome have been reported in patients receiving anastrozole 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 anastrozole 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, anastrozole have 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 anastrozole and tamoxifen treatment arms (see Section 5.1 PHARMACODYNAMIC PROPERTIES – CLINICAL TRIALS).

## Post-marketing experience

Musculoskeletal and connective tissue disorders: tendonitis, tenosynovitis and tendon rupture (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

## Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## 4.9 OVERDOSE

There is limited clinical experience of overdose of anastrozole. 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 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 are not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

### Mechanism of Action

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

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

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 estrogenic 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.

In a phase III/IV study there was a neutral effect on plasma lipids in those patients treated with anastrozole.

## Clinical Trials

### *Switching in treatment of early breast cancer*

A prospectively planned, combined analysis of 2 multicentre, open-label, randomised controlled trials (ABCSC 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 anastrozole (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 anastrozole 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 2**.

**Table 2**

	<b>Anastrozole</b>	<b>Tamoxifen</b>	<b>Hazard Ratio</b>	<b>p-value</b>
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 estrogen–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 anastrozole (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 3**.

**Table 3**

	<b>Anastrozole</b>	<b>Tamoxifen</b>	<b>Hazard Ratio</b>	<b>p-value</b>
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

Anastrozole 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 anastrozole 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 anastrozole 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 4**). In the clinically relevant hormone-receptor-positive sub-group, statistically significant benefits of anastrozole 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 4**). The absolute benefit in recurrence rates of anastrozole 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

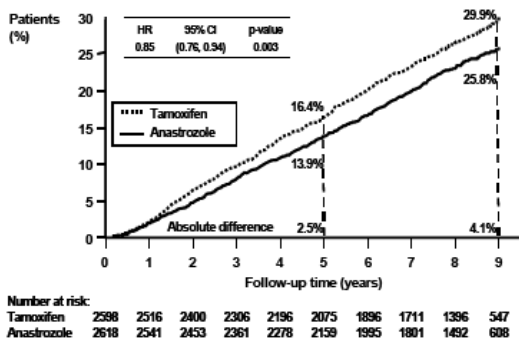


Figure 2 Time to recurrence in patients with hormone-receptor-positive tumours

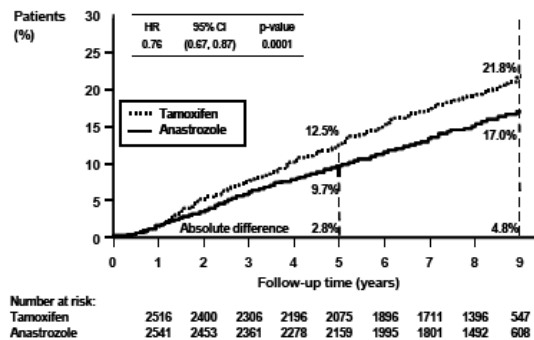


Figure 3 Time to distant recurrence in patients with hormone-receptor-positive tumours

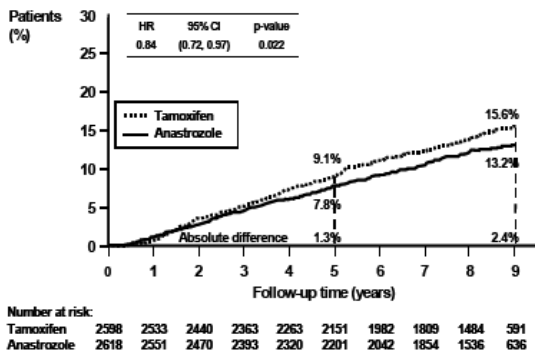
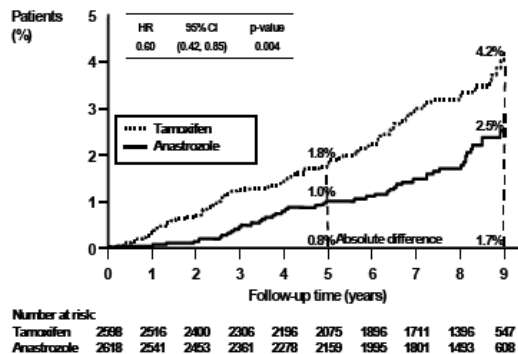


Figure 4 Contralateral breast cancer prevalence in patients with hormone-receptor-positive tumours



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



**Table 4: Efficacy endpoint summary for Trial 0029 at a median follow-up of 100 months**

<b>Hazard Ratio (95% Confidence Interval); p value</b>		
<b>Endpoint</b>	<b>ITT group</b>	<b>HR-positive sub-group</b>
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

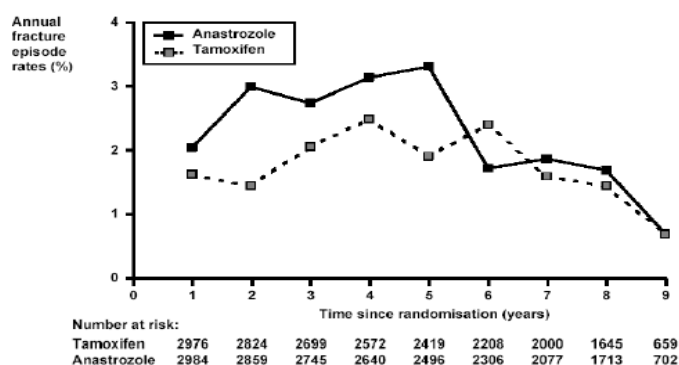
\*Odds ratio computed instead of Hazard Ratio; ITT - intent-to-treat; HR –hormone receptor Hazard ratios of <1.00 indicate that treatment with anastrozole is favourable relative to tamoxifen.

Overall survival was a secondary endpoint in the ATAC study. The 100 month analysis of this study demonstrated that overall survival in the anastrozole 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 4**). 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 anastrozole or with trends evident in favour of anastrozole when compared to tamoxifen (refer **Table 4**).

Overall, anastrozole was well tolerated. Withdrawals due to medicine-related adverse events were less common with anastrozole 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 anastrozole 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 anastrozole had an increase in joint disorders (including arthritis, arthrosis and arthralgia) and total number of fractures compared with patients receiving tamoxifen. Although the incidence of fractures (both serious and non-serious, occurring either during or after treatment) were higher in the anastrozole compared to the tamoxifen treatment group, the incidences of hip fractures were similar between the groups. The fracture rate for anastrozole 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 anastrozole and tamoxifen treatment groups and the increased first fracture rate seen during treatment was not continued in the post-treatment follow-up period (refer **Figure 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 anastrozole 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 anastrozole 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 anastrozole 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:

	<b>Trial 0027</b>	<b>Trial 0030</b>	<b>Pooled trials</b>
Anastrozole 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 5**.

Anastrozole 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 5**. Positive estrogen/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 5: Hormone receptor status and primary efficacy results in Trials 0027 and 0030 – anastrozole 1 mg compared to tamoxifen 20 mg**

	Trial 0027		Trial 0030	
	Anastrozole (n=340)	Tamoxifen (n=328)	Anastrozole (n=171)	Tamoxifen (n=182)
<b>RECEPTOR STATUS</b>				
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
<b>ENDPOINTS</b>				
Median time to progression [TTP] (mths)	8.2	8.3	11.1*	5.6
% Subjects who progressed	73%	75%	67%	76%
Hazard ratio <sup>1</sup> [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] <sup>2</sup>	-1.0% [-6.7%]		+5.0% [-1.9%]	

ER = Estrogen receptor; PR = Progesterone receptor; \*p = 0.005; <sup>1</sup>Tamoxifen: Anastrozole [hazard ratios > 1.00 indicate that anastrozole is associated with a longer TTP than tamoxifen]; <sup>2</sup>Anastrozole minus Tamoxifen; The criteria for non-inferiority were that the lower one-sided 95% confidence bound for the hazard ratio was  $\geq 0.80$  and the difference in response rate  $\geq -10\%$ . 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 anastrozole 1 mg daily, anastrozole 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 anastrozole 1 mg compared to megestrol acetate. The median time to death for anastrozole 1 mg was 26.7 months compared to 22.5 months for megestrol acetate, with a 2 year survival rate for anastrozole 1 mg of 56.1% compared to 46.3% for megestrol acetate. The hazard ratio of risk of death of patients on anastrozole 1 mg compared to megestrol acetate was 0.78, and there was a statistically significant difference in time to death (p < 0.025).

An open label, balanced, randomized, two-treatment, two period, two-sequence, single dose, two-way crossover, comparative oral bioavailability study of two formulations of Anastrozole tablets 1 mg was conducted in 26 healthy, postmenopausal human female subjects under fasting conditions. The study compared Anastrozole Tablets 1 mg with reference product Arimidex® 1 mg tablets.

Statistical comparisons of geometric means for Test v's Reference for Anastrozole  $T_{max}$ ,  $C_{max}$  and  $AUC_{0-\infty}$  were as follows:

**Table 6**

Parameters (units)	Geometric Least Squares Mean (In-transformed)			90% Confidence Interval (Parametric)
	Test Product B	Reference Product A	Ratio B/A %	
C <sub>max</sub> (ng/mL)	24.550	24.374	100.7	95.50-106.23%
AUC <sub>0-∞</sub> (ng.h/mL)	1323.138	1369.162	96.6	93.15-100.26%

The median T<sub>max</sub> found was 2.000 hours for the reference (Arimidex<sup>®</sup> 1 mg) and 2.250 hours for the test product (Anastrozole Tablets 1 mg).

This comparison of test product with reference product Anastrozole met the predefined criteria for bioequivalence, as the calculated 90% CI for all ratios of pre-specified In-Transformed PK parameters fell within the range 80.00%-125.00%.

## 5.2 PHARMACOKINETIC PROPERTIES

### 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 anastrozole.

### Distribution

Anastrozole is 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.

### Excretion

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.

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

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

### 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.

### 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.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Lactose monohydrate, povidone, sodium starch glycollate type A, magnesium stearate, hypromellose, macrogol 300 and titanium dioxide.

### 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

### 6.5 NATURE AND CONTENTS OF CONTAINER

PVC/PVDC blister/aluminium foil blister containing 30 tablets.

### Australian Register of Therapeutic Goods (ARTG)

AUST R 259991 – ARIANNA 1 anastrozole 1 mg film-coated tablet blister pack

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

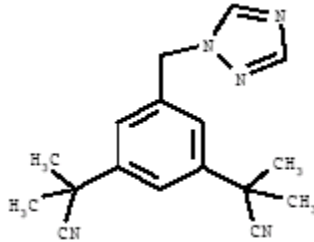
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical Structure

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

Structural formula :



Molecular formula : C<sub>17</sub>H<sub>19</sub>N<sub>5</sub>

Molecular weight : 293.4

Anastrozole is a fine white to off-white powder. Anastrozole 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.

Solubility of anastrozole is independent of pH in the physiological range. Anastrozole is freely soluble in methanol, acetone, ethanol and tetrahydrofuran and very soluble in acetonitrile. It is also very soluble in chloroform and dimethylformamide, freely soluble in benzene and ethyl acetate and soluble in isopropyl alcohol and toluene.

### CAS Number

120511-73-1

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

## 8 SPONSOR

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## 9 DATE OF FIRST APPROVAL

04/12/2015

## 10 DATE OF REVISION

05/08/2024

**Summary Table of Changes**

<b>Section Changed</b>	<b>Summary of New Information</b>
<b>All</b>	Minor editorial changes
<b>4.4</b>	Subsection added for tendon disorders
<b>4.8</b>	Post-marketing experience added for musculoskeletal and connective tissue disorders

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