ARIANNA®

Anastrozole film-coated tablets

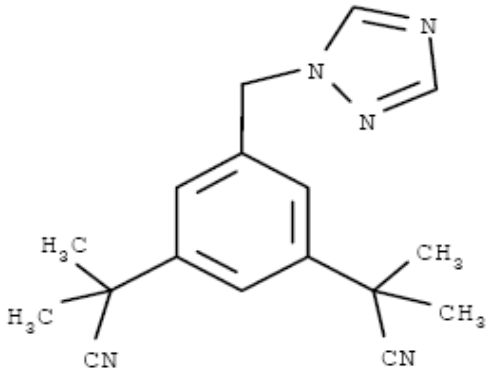
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient: Anastrozole

Chemical name: α,α,α′,α ′,-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-benzene-diacetonitrile

Structural formula:



Molecular Formula: $C_{17}H_{19}N_5$ Molecular Weight: 293.37

CAS Registry No.: 120511-73-1

DESCRIPTION

Anastrozole is a fine white to off-white powder. It is very slightly soluble in water (0.78 mg/mL at 25°C) and is independent of pH in the physiological range.

ARIANNA 1 mg is a round, white, biconvex, beveled edge film-coated tablet containing 1 mg anastrozole and includes the following excipients: lactose anhydrous, hypromellose, water – purified, sodium starch glycollate, magnesium stearate, titanium dioxide, polydextrose, glycerol triacetate and polyethylene glycol 8000.

PHARMACOLOGY

Pharmacodynamics

Anastrozole 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, anastrozole at a daily dose of 1 mg produced oestradiol suppression of greater than 80% using a highly sensitive assay.

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

Daily doses of anastrozole up to 10 mg do not have any effect on cortisol or aldosterone secretion, measured before or after standard ACTH challenge testing. Corticoid supplements are therefore not needed.

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

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 anastrozole 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 approximately 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 post-menopausal women. Clearance of anastrozole was lower in girls than in boys, resulting in longer exposure. Anastrozole in girls was widely distributed and slowly eliminated, with an estimated half-life of approximately 0.8 days.

CLINICAL TRIALS

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:

	Trial 0027	**Trial 0030**	**Pooled Trials**
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 1**.

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 1**. 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 1 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)**
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				
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: anastrozole [hazard ratios > 1.00 indicate that anastrozole is associated with a longer TTP than tamoxifen]; [2]Anastrozole 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 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 ($p < 0.025$).

INDICATIONS

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 anastrozole.

CONTRAINDICATIONS

ARIANNA must not be administered during pregnancy or lactation.

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

PRECAUTIONS

Paediatric use and use in pre-menopausal women

ARIANNA 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. Anastrozole 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 ARIANNA.

Bone mineral density

As anastrozole 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 post-menopausal 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.

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 (Risk Category: C)

Australian Pregnancy Categorisation Definition of Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

ARIANNA 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

ARIANNA 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.

Carcinogenesis

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*.

Effects on ability to drive and use machinery

ARIANNA 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.

INTERACTIONS WITH OTHER MEDICINES

Anastrozole inhibited reactions catalysed 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 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 ARIANNA 1 mg with other drugs will result in clinically significant inhibition of cytochrome P450-mediated metabolism.

Other drugs 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 ARIANNA 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 medicines. There were no clinically significant interactions with bisphosphonates (see **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.

ADVERSE 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 post-menopausal 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 the 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)
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 anastrozole. If bleeding persists, further evaluation should be considered.

[^] 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.

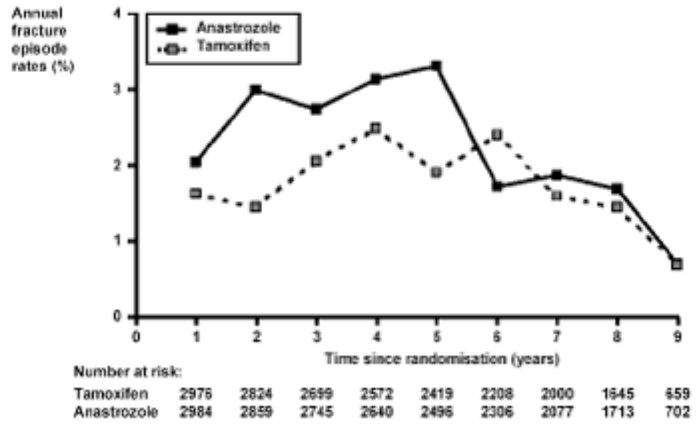
Compared to tamoxifen, anastrozole was associated with an increased incidence of lipid disorders and gastrointestinal events, but with a reduced incidence of gynaecological events.

In a large phase III study conducted in 9366 postmenopausal women with operable breast cancer treated for 5 years, ischemic 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). 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. Compared with tamoxifen, anastrozole treatment was associated with a reduced incidence of thromboses (3 vs. 12 cases; OR=0.25 (95% CI: 0.04 – 0.92; p=0.034).

In studies in the adjuvant setting, anastrozole has been associated with an increased incidence of fractures compared to tamoxifen treatment during the active treatment phase. 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). Patients receiving anastrozole also had an increase in joint disorders (including arthritis, arthrosis and arthralgia).

A plot of the 100 month analysis of a large phase III 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 to **Figure 1**).

Figure 1: Fracture episode rates at the 100 month analysis



The fracture rate for anastrozole whilst on treatment falls within the broad range of fracture rates reported in an age-matched post-menopausal population.

DOSAGE AND ADMINISTRATION

Adults including the elderly

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

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 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 ARIANNA is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

In cases of overdosage, it is advisable to contact the Poisons Information Centre (13 11 26 - Australia) for recommendation on the management and treatment of overdosage.

PRESENTATION AND STORAGE CONDITIONS

ARIANNA 1 mg tablet	A white film-coated, round, biconvex, beveled edge tablet debossed with ‘M’ on one side and ‘34’ on the other side, available in blister packs and bottles* of 30 tablets.

* Not marketed in Australia.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

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ABN 93 002 359 739

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POISON SCHEDULE OF MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

17/05/2010

DATE OF MOST RECENT AMENDMENT

11 June 2014

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