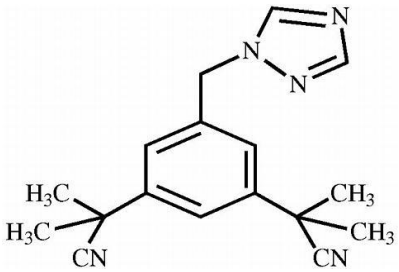
PRODUCT INFORMATION
ANASTROZOLE SANDOZ® 1 MG TABLETS

NAME OF THE MEDICINE

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

Chemical structure:



CAS : [120511-73-1]
Empirical formula : $C_{17}H_{19}N_5$
MW: 293.4

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.

Excipients – Lactose, –microcrystalline cellulose, sodium starch glycollate type A, magnesium stearate, colloidal anhydrous silica, hydroxypropylcellulose and Opadry II complete film coating system OY-L-28900 White [Lactose, hypromellose, titanium dioxide and Macrogol 4000].

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 1mg 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.

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 seven daily doses. There is no evidence of time or dose dependency of anastrozole pharmacokinetic parameters.

Anastrozole pharmacokinetics are independent of age in postmenopausal women.

Pharmacokinetics have not been studied in children.

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.

CLINICAL TRIALS

Switching in treatment of early breast cancer. A prospectively planned, combined analysis of two 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 anastrozole (1 mg daily). A total of 3,224 patients who had completed two years of adjuvant treatment with tamoxifen and had remained disease free were randomised to receive anastrozole for three years (n = 1,618) or to continue on tamoxifen for three years (20 to 30 mg daily; n = 1,606). The total duration of hormonal therapy was five 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 locoregional or distant recurrence or the development of contralateral breast cancer. Overall survival was a secondary endpoint. Median follow-up after randomisation was 28 months and 55% of patients in each group had completed the planned five years of hormonal therapy (see Table 1).

Table 1

	Anastrozole	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 versus 16 cases; odds ratio (OR) = 2.14 (95% CI: 1.14 to 4.17; p = 0.015)) but with a reduced incidence of thromboses (three versus 12 cases; OR = 0.25 (95% confidence interval (CI): 0.04 to 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 two to three 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 five 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 locoregional or distant recurrence. Event free survival was a secondary endpoint with an event being defined as locoregional 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 endpoint. Median follow-up after randomisation was 36 months (see Table 2).

Table 2

	Anastrozole	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

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.

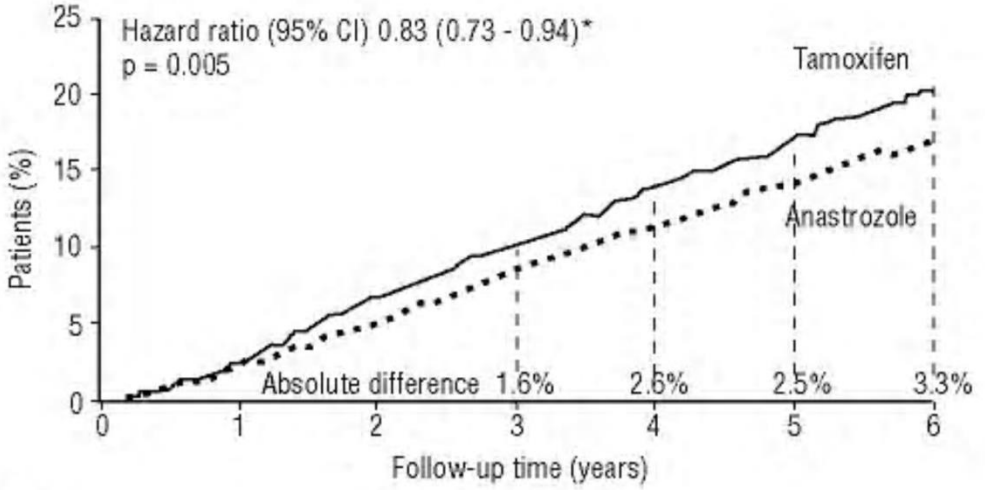
Demographic and other baseline characteristics were similar among the two treatment arms, with approximately 84% of patients with hormone receptor positive disease. The median follow-up was 68 months.

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 13 and 21%, respectively (see Table 3). In the clinically relevant hormone receptor positive subgroup, statistically significant benefits of anastrozole compared to tamoxifen were also observed for disease-free survival and time to recurrence, with risk reductions of 17 and 26%, respectively (see Figures 1 and 2, and Table 3). The absolute difference in recurrence rates increased over time, even beyond the five years of scheduled treatment (see Figure 2).

Figure 1

Disease-free survival in patients with hormone receptor positive tumours

Hormone receptor positive population

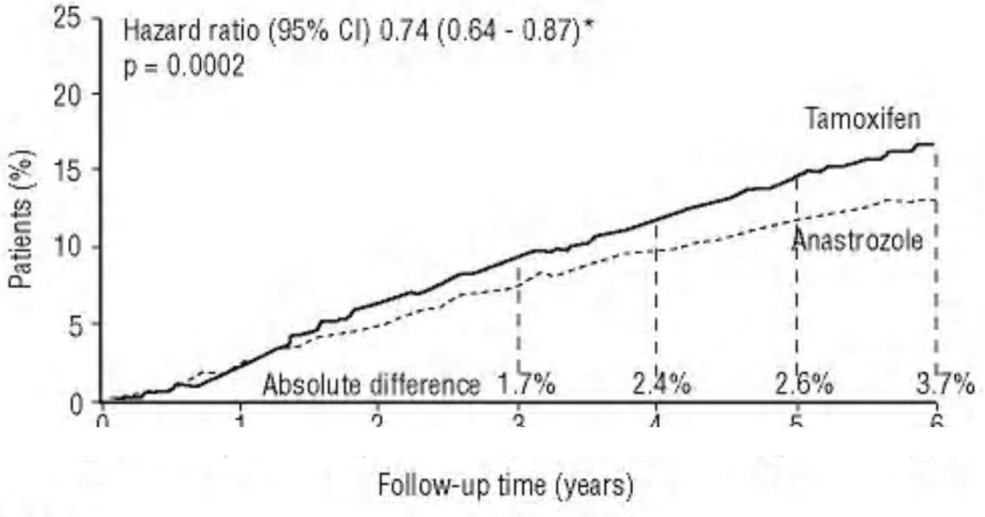


At risk:							
Anastrozole	2618	2540	2448	2355	2268	2014	830
Tamoxifen	2598	2516	2398	2304	2189	1932	774

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

Figure 2

Time to recurrence in patients with hormone receptor positive tumours



At risk:							
Anastrozole	2618	2540	2448	2355	2268	2014	830
Tamoxifen	2598	2516	2398	2304	2189	1932	774

[*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 68 months

Endpoint	Hazard ratio (95% confidence interval); p-Value	
	ITT group	HR-positive sub-group
Disease free survival	0.87 (0.78 - 0.97); p = 0.0127	0.83 (0.73 - 0.94); p = 0.0049
Time to recurrence	0.79 (0.70 - 0.90); p = 0.0005	0.74 (0.64 - 0.87); p = 0.0002
Time to distant recurrence	0.86 (0.74 - 0.99); p = 0.0427	0.84 (0.70 - 1.00); p = 0.0559
Overall survival	0.97 (0.85 - 1.12); p = 0.7142	0.97 (0.83 - 1.14); p = 0.7339
Time to death following recurrence	0.88 (0.74 - 1.05); p = 0.1676	0.87 (0.70 - 1.09); p = 0.2249
Contralateral breast cancer*	0.59 (0.39 - 0.89); p = 0.0131	0.47 (0.30 - 0.76); p = 0.0018

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

The primary survival analysis was for noninferiority. The overall survival benefit of tamoxifen was maintained with anastrozole. Similar overall survival was observed for both the ITT group and hormone receptor positive subgroup (see Table 3). The absence of a statistically significant survival benefit at this point in the study was anticipated and could be predicted from previous experience in a similar population.

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 (see Table 3).

Overall, anastrozole was well tolerated. Withdrawals due to medicine related adverse events were less common with anastrozole compared to tamoxifen (6.5 versus 8.9%, odds ratio 0.71, 95% CI 0.59 to 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 hip fractures (generally associated with greater morbidity) was similar for the two treatment groups. A fracture rate for all fractures (both on treatment and off treatment events) of 22 per 1,000 patient years was observed with anastrozole and 15 per 1,000 patient years with tamoxifen with a median follow-up of 68 months. The fracture rate for anastrozole falls within the broad range of fracture rates reported in an age matched postmenopausal population. Ischaemic cardiovascular events (consisting mainly of angina pectoris) 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 subgroup. 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), 1,021 postmenopausal women between the ages of 30 and 92 years old with advanced breast cancer (stage IV (metastatic disease) and stage III (locally advanced disease)) were randomised to receive anastrozole 1 mg daily (n = 511) or tamoxifen 20 mg once daily (n = 510) as first line therapy.

The primary endpoints 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 in trial 0030, respectively. The number of patients still on trial treatment at the end of the follow-up period was as follows.

Anastrozole 1 mg. Trial 0027: 101 out of 340 (29.7%); trial 0030: 48 out of 171 (28.1%); pooled trials: 149 out of 511 (29.2%).
Tamoxifen 20 mg. Trial 0027: 88 out of 328 (26.8%); trial 0030: 40 out of 182 (22.0%); pooled trials: 128 out of 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.

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 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 – 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% confidential interval also satisfied these criteria; response rate is the sum of complete responders plus partial responders based on modified UICC criteria; LCL = lower confidence limit.

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 or 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 oestrogen receptor positive or unknown status (with about 5% being oestrogen receptor 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 two 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

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 anastrozole.

CONTRAINDICATIONS

Administration during pregnancy (see PRECAUTIONS, Use in pregnancy) or lactation.

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

PRECAUTIONS

Use with caution in the following circumstances
Paediatric use and use in premenopausal women. Anastrozole is not recommended for use in children or in premenopausal women as safety and efficacy have not been established in these groups of patients. The menopause should be defined biochemically (luteinizing-hormone (LH), follicle stimulating hormone (FSH), and/or estradiol levels) in any patient where there is doubt about menopausal status.

Co-administration of tamoxifen or estrogen-containing therapies with anastrozole should be avoided as this may diminish its pharmacological action.

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. The use of specific treatments, e.g., bisphosphonates, may stop further bone mineral loss caused by anastrozole in postmenopausal women and could be considered.

Combination with luteinising hormone releasing hormone (LHRH). There are no data available for the use of anastrozole with LHRH analogues. This combination should not be used outside clinical trials.

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

Impaired hepatic function. The apparent oral clearance of anastrozole in volunteers with stable hepatic cirrhosis was in the range observed in healthy volunteers. Dosage adjustment is, therefore, not necessary. Anastrozole has not been investigated in patients with severe hepatic impairment. The potential risk/ benefit to such patients should be carefully considered before administration of anastrozole.

Use in pregnancy [Category C]
Anastrozole is contraindicated in pregnant women.

After oral administration of anastrozole to pregnant rats and rabbits, the medicine was shown to cross the placenta and was detectable in foetal tissues at concentrations approximately 40% of corresponding maternal plasma medicine 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 (nine and three 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 medicine of this class.

In a perinatal/ 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 breastfeeding women.

Use in paediatrics
See Paediatric use and use in premenopausal women, above.

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

Anastrozole should not be used in boys with growth hormone deficiency in addition to growth hormone treatment. Since anastrozole reduces estradiol levels, anastrozole must not be used in girls with growth hormone deficiency in addition to growth hormone treatment. Long-term safety data in children and adolescents are not available.

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.

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 tumorigenic 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 tumorigenic effect on the ovary occurred at all doses including the lowest dose tested (5 mg/kg/day) (exposure (AUC) was approximately one to twofold that which occurs at the maximum recommended clinical dose). The clinical relevance of these findings in the mouse are not clear.

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 (nine times the maximum recommended clinical dose, based on body surface area (BSA)). Preimplantation 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.

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 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

coadministration of Anastrozole 1 mg with other medicines will result in clinically significant inhibition of cytochrome P450 mediated metabolism.

Demonstrated interactions. On the basis of clinical and pharmacokinetic data from the ATAC trial, tamoxifen must not be administered with anastrozole. Coadministration 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 coadministered 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 biphosphonates or other commonly prescribed medicines.

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. Pretreatment 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 laboratory tests

Preclinical chronic toxicity. Multiple dose toxicity studies utilised rats and dogs. No no-effect levels were established for anastrozole in the toxicity studies, but those effects that were observed at the low doses (1 mg/kg/day) and mid doses (dogs 3 mg/kg/day; rats 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 species.

Effect on ability to drive or operate machinery.

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.

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. Adverse effects which have been associated with anastrozole are provided below.

Very common (greater than or equal to 10%).
Vascular. Hot flushes[#].
General. Asthenia[#].
Musculoskeletal, connective tissue and bone. Arthralgia/joint stiffness, arthritis[#].
Nervous system. Headache[#]
Gastrointestinal. Nausea[#]
Skin and subcutaneous tissue. Rash[#].

Common (greater than or equal to 1% and < 10%).
Reproductive system and breast. Vaginal dryness[#], vaginal bleeding[#]*.
Skin and 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 and nutrition. Anorexia[#], hypercholesterolaemia[#].
Musculoskeletal, connective tissue and bone. Bone pain, myalgia.

Uncommon (greater than or equal to 0.1% and < 1%).
Metabolism and nutrition. Hypercalcaemia (with or without an increase in parathyroid hormone)
Musculoskeletal, connective tissue and bone. Trigger finger.
Skin and subcutaneous tissue. Urticaria.
Hepatobiliary disorders. Increases in gamma-GT and bilirubin, hepatitis.

Rare (greater than or equal to 0.01% and < 0.1%).
Skin and subcutaneous tissue. Erythema multiformae, anaphylactoid reaction, cutaneous vasculitis (including some reports of Henoch-Schönlein purpura).

Very rare (< 0.01%).
Skin and 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.

In a large phase III study conducted in 9,366 postmenopausal women with operable breast cancer treated for five years, ischaemic cardiovascular events (consisting mainly of angina pectoris) 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 has been associated with an increased incidence of fractures compared to tamoxifen treatment (see CLINICAL TRIALS).

DOSAGE AND ADMINISTRATION

Adults (including the elderly).
One tablet (1 mg) to be taken orally once daily.

For early breast cancer, the recommended duration of treatment should be five years. For patients being switched to anastrozole from tamoxifen, the switch should occur after completion of two to three years of tamoxifen therapy. There are no data to support switching at earlier or later time points.

Infants and children
Not recommended for use in children.

Use in patients with hepatic or renal impairment
No dose change is recommended for patients with renal or hepatic impairment.

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.

Treatment
There is no specific antidote to overdosage and treatment must be symptomatic. In the management of an overdose, consideration should be given to the possibility that multiple agents may have been taken. Vomiting may be induced if the patient is alert.

Dialysis may be helpful because anastrozole is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

ANASTROZOLE SANDOZ® 1 mg: white, round, biconvex film coated tablet without breaking notch and embossment 'A1' on one side. Available in PVC/ Al blisters of 30 tablets.

Anastrozole Sandoz should be stored below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty. Ltd.
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 31/07/2008

Date of most recent amendment: 27 May 2015