NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Aremed tablet 1mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1mg of anastrozole.

Excipients with known effect:

Tablets contain lactose and maize starch.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Aremed tablets are white, round, film coated tablets. Each tablet contains 1 mg of anastrozole and typically weighs 100 mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aremed is indicated for the:

- Treatment of early breast cancer in hormone receptor positive post-menopausal women.
- Adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.
- Reduction in the incidence of contralateral breast cancers in post-menopausal women receiving Aremed as adjuvant treatment for early breast cancer.
- Treatment of advanced breast cancer in post-menopausal women

4.2 Dose and method of administration

Adults including the elderly:

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

Special populations

Paediatric population

Aremed tablets is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 5.1 and 5.2).

Renal impairment

No dose change is recommended. Caution is recommended in patients with severe renal impairment (see section 4.4. and 5.2).

Hepatic impairment

No dose change is recommended. Caution is recommended in patients with severe hepatic impairment (see section 4.4. and 5.2).

4.3 Contraindications

Aremed is contraindicated in:

• Pregnant or lactating women

• Hypersensitivity to any of the ingredients in this product

4.4 Special warnings and precautions for use

Anastrozole 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 (See sections 5.1 and 5.2).

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 anastrozole.

As anastrozole lowers circulating oestrogen levels it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture. This possible increased risk should be managed according to treatment guidelines for managing bone health in postmenopausal women.

Tenosynovitis and tendonitis have been reported in association with the use of third generation aromatase inhibitors. Cases of tendon rupture have also been reported.

4.5 Interaction with other medicines and other forms of interaction

Antipyrine and cimetidine clinical interaction studies indicate that the coadministration of anastrozole with other medicines is unlikely to result in clinically significant medicine interactions mediated by cytochrome P450.

A review of the clinical trial safety database did not reveal evidence of clinically significant interaction in patients treated with anastrozole who also received other commonly prescribed medicines. There were no clinically significant interactions with bisphosphonates (See section 5.1).

Tamoxifen and/or other therapies containing oestrogen should not be co-administered with anastrozole as they may diminish its pharmacological action.

4.6 Fertility, pregnancy, and lactation

Pregnancy

Category C

Aremed is contraindicated in pregnant women.

Breast-feeding

Aremed is contraindicated in breast-feeding women.

4.7 Effects on ability to drive and use machines

Aremed is unlikely to impair the ability of patients to drive or 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 occur.

4.8 Undesirable effects

Unless specified, the following frequency categories were calculated from the number of adverse events reported in a large phase III study conducted in 9366 postmenopausal women with operable breast cancer treated for 5 years and unless specified, no account was taken of the frequency within the comparative treatment group or whether the investigator considered it to be related to study medication.

Frequency	**System Organ Class**	**Adverse Reaction**
Very common (≥ 10%)	*Vascular:*	• Hot flushes, mainly mild or moderate in nature
	General	• Asthenia, mainly mild or moderate in nature
	Musculoskeletal and connective tissue disorders:	• Arthralgia/Joint stiffness • Arthritis • Osteoporosis
	Nervous system:	• Headache, mainly mild or moderate in nature
	Gastrointestinal	• Nausea, mainly mild or moderate in nature
	Skin and subcutaneous tissue:	• Rash, mainly mild or moderate in nature
	Psychiatric disorders:	• Depression
Common (≥1% and <10%)	*Skin and subcutaneous tissue:*	• Hair thinning (Alopecia), mainly mild or moderate in nature • Allergic Reactions
	Gastrointestinal:	• Diarrhoea, mainly mild or moderate in nature • Vomiting, mainly mild or moderate in nature
	Nervous system:	• Somnolence, mainly mild or moderate in nature • Carpal Tunnel Syndrome* • Sensory disturbances (including paraesthesia, taste loss and taste perversion)
	Hepatobiliary disorders:	• Increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase
	Reproductive system and breast:	• Vaginal dryness, mainly mild or moderate in nature • Vaginal bleeding, mainly mild or moderate in nature**
	Musculoskeletal and connective tissue disorders:	• Bone pain • Myalgia
	Metabolism and nutrition	• Anorexia, mainly mild in nature • Hypercholesterolaemia mainly mild or moderate in nature
Uncommon (≥ 0.1% and <1%)	*Metabolism and nutrition:*	• Hypercalcaemia (with or without an increase in parathyroid hormone)
	Hepatobiliary disorders:	• Increases in gamma-GT and bilirubin • Hepatitis

	Skin and subcutaneous tissue: *Musculoskeletal and connective tissue disorders:*	• Urticaria • Trigger finger
Rare (>0.01% and < 0.1%)	*Skin and subcutaneous tissue:*	• Erythema multiforme • Anaphylactoid reaction • Cutaneous vasculitis (including some reports of Henoch-Schönlein purpura)
Very rare (<0.01%)	*Skin and subcutaneous tissue:*	• Stevens-Johnson syndrome • Angioedema

*Clinical trials with anastrozole have reported a higher incidence of Carpel Tunnel Syndrome than with Tamoxifen. Many of the patients affected had risk factors predisposing them to this syndrome.

^Vaginal bleeding has been reported 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.

A large study of post-menopausal women with operable breast cancer identified an increased risk of ischaemic cardiovascular events in patients taking anastrozole compared with those taking tamoxifen. The difference was not statistically significant and was mainly due to more reports of angina pectoris associated with a sub-group of patients with pre-existing ischaemic heart disease.

Post-market adverse reactions:

System Organ Class	**Adverse Reaction**
Musculoskeletal and connective tissue disorders	• Tenosynovitis • Tendonitis • Tendon rupture

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

There is limited clinical experience of overdose with anastrozole. There are no reports where a dose in excess of 60 mg has been taken. No toxicity has been observed and no clinically adverse effects have been seen at this dose.

Acute toxicity was seen in animals at a dose >45 mg/kg (equivalent to 2.7 g). 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 post-menopausal women with advanced breast cancer; these doses were well tolerated. A single dose of anastrozole that results in life-threatening symptoms has not been established.

There is no specific antidote to overdose, and treatment should 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

In clinical trials treatment with anastrozole at a dose of 1mg has demonstrated significant prolongation of survival time.

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.

Extensive phase III clinical study programmes showed that anastrozole is an effective treatment of early breast cancer and advanced breast cancer in postmenopausal women suitable for endocrine therapy.

CLINICAL EFFICACY AND SAFETY

Primary Adjuvant treatment of early breast cancer

In a large phase III study conducted in 9366 post-menopausal women with operable breast cancer, anastrozole was shown to be statistically superior to tamoxifen in recurrence-free survival. The incidence of contralateral breast cancer was statically significantly reduced for anastrozole compared with tamoxifen. Time to distant recurrence was also numerically superior for anastrozole. The combination of anastrozole and tamoxifen did not demonstrate any efficacy benefits in comparison to tamoxifen.

For the prospectively defined receptor positive population, even greater statistical superiority was observed for recurrence-free survival; in favour of anastrozole versus tamoxifen. Again, the comnination of anastrozole and tamoxifen did not demonstrate any efficacy benefits in comparison with tamoxifen in this group of patients.

Adjuvant treatment of early breast cancer for patients being treated with adjuvant tamoxifen

In a phase III trial (ABCSG 8) conducted in 2579 post-menopausal women with hormone receptor positive early breast cancer being treated with adjuvant tamoxifen, patient had a superior disease-free survival in patients switched to anastrozole compared with those continuing on tamoxifen.

Time to any recurrence, time to local or distant recurrence and time to distant recurrence confirmed a statistical advantage on anastrozole, consistent with the results of disease free survival. The incidence of contralateral breast cancer was very low in the two treatment arms, with a numerical advantage for anastrozole. Overall survival was similar for the two treatment groups.

Two further trials (GABG/ARNO 95 and ITA) with anastrozole, as well as a combined analysis of ABCGSG 8 and GABG/ARNO 95, supported these results.

The anastrozole safety profile in these 3 studies was consistent with the known safety profile established in post-menopausal women with hormone-receptor positive early breast cancer.

Study of anastrozole with the bisphosphonate risedronate (SABRE)

BMD

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. Patient 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 received anastrozole plus bisphosphonate.

The12-months 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 anastrozole in combination with bisphosphonate. In addition, no changes in BMD were seen in the low-risk group treated with anastrozole alone and given vitamin D and calcium. These findings were mirrored in the secondary efficacy variable of change from baseline in total hip BMD at 12 months.

Lipids

In the SABRE study there was a neutral effect on plasma lipids both in those patients treated with anastrozole alone and in those treated with anastrozole plus a bisphosphonate.

Paediatrics

Three clinical trials were conducted in paediatric patients (two in pubertal boys with gynaecomastia and one in paediatric girls with Mccune Albright Syndrome).

Gynaecomastia Study

Trial 0006 was a randomised, double-blind, multi-centre study, of 80 pubertal boys with gynaecomastia of greater than 12 months duration (aged 11-18 years inclusive) treated with anastrozole 1 mg/day or placebo for up to 6 months. A decrease of ≥50% in total breast volume measured by ultrasound was seen in 38.5% (15/39) of the anastrozole and 31.4% (11/35) of the placebo treated group, (odds ratio = 1.513, 95% CI 0.496 to 4.844, p=0.4687).

Trial 0001 was an open-label, multiple-dose pharmacokinetic (PK) study of anastrozole 1 mg/day in 36 pubertal boys with gynaecomastia of less than 12 months duration. A decrease in total breast volume of 50% or greater at 6 months was seen in 55.6% (20/36) of the boys.

McCune Albright Syndrome (MAS) Study

Trial 0046 was an international, multi-centre, open-label, exploratory trial of anastrozole in 28 girls (aged 2 to ≤10 years) with McCune Albright Syndrome. No statistically significant change in the frequency of vaginal bleeding days on treatment was observed. Of the patients with baseline vaginal bleeding, 28% experienced a >50% reduction in the frequency of bleeding days on treatment, 40% experienced a cessation over a 6-month period and12% experienced a cessation over a 12-month period. There were no clinically significant changes in Tanner staging, mean ovarian volume or mean uterine volume. No statistically significant change in the rate of increase in bone age on treatment compared to the rate during baseline was observed. Growth rate (in cm/year) was significantly reduced ($p<0.05$) from pre-treatment through month 0 to month 12, and from pre-treatment to the second 6 months (month 7 to month 12).

The overall assessment of the AEs in children less than 18 years of age raised no safety and tolerability concerns.

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 tablets. Approximately 90 to 95% of plasma anastrozole steady-state concentrations are attained after 7 daily doses, and accumulation is 3- to 4-fold. There is no evidence of time or dose-dependency of anastrozole pharmacokinetic parameters.

Anastrozole pharmacokinetics are independent of age in postmenopausal women.

Distribution

Anastrozole is only 40% bound to plasma proteins.

Elimination

Anastrozole is eliminated slowly with a plasma elimination half-life of 40 to 50 hours. 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, the major metabolite in plasma, does not inhibit aromatase.

Renal or hepatic impairment

The apparent clearance (CL/F) of anastrozole, following oral administration, was approximately 30% lower in volunteers with stable hepatic cirrhosis than in matched controls (Study 1033IL/0014). However, plasma anastrozole concentrations in the volunteers with hepatic cirrhosis were within the range of concentrations seen in normal subjects in other trials. Plasma anastrozole concentrations observed during long-term efficacy trials in patients with hepatic impairment were within the range of plasma anastrozole concentrations seen in patients without hepatic impairment.

The apparent clearance (CL/F) of anastrozole, following oral administration, was not altered in volunteers with severe renal impairment (GFR <30ml/min) in Study 1033IL/0018, consistent with

the fact that anastrozole is eliminated primarily by metabolism. Plasma anastrozole concentrations observed during long-term efficacy trials in patients with renal impairment were within the range of plasma anastrozole concentrations seen in patients without renal impairment.

Anastrozole has not been investigated in breast cancer patients with severe hepatic or renal impairment and caution is recommended (see section 4.2 and 4.4).

Paediatric population

In boys with pubertal gynaecomastia (10-17 years), anastrozole was rapidly absorbed, was widely distributed, and was eliminated slowly with a half-life of approximately 2 days. Clearance of anastrozole was lower in girls (3-10 years) than in the older boys and exposure higher. Anastrozole in girls was widely distributed and slowly eliminated.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Acute toxicity

In animal studies toxicity was only seen at high doses. In acute toxicity studies in rodents, the median lethal dose of anastrozole was greater than 100 mg/kg/day by the oral route and greater than 50 mg/kg/day by the intraperitoneal route. In an oral acute toxicity study in the dog, the median lethal dose was greater than 45 mg/kg/day.

Chronic toxicity

In animal studies adverse effects were only seen at high doses. 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.

Mutagenicity

Genetic toxicology studies with anastrozole show that it is not a mutagen or a clastogen.

Reproductive toxicology

In a fertility study weanling male rats were dosed orally with 50 or 400 mg/l anastrozole via their drinking water for 10 weeks. Measured mean plasma concentrations were 44.4 (±14.7) ng/ml and 165 (±90) ng/ml respectively. Mating indices were adversely affected in both dose groups, whilst a reduction in fertility was evident only at the 400 mg/l dose level. The reduction was transient as all mating and fertility parameters were similar to control group values following a 9-week treatment-free recovery period.

Oral administration of anastrozole to female rats produced a high incidence of infertility at 1 mg/kg/day and increased pre-implantation loss at 0.02 mg/kg/day. These effects occurred at clinically relevant doses. An effect in man cannot be excluded. These effects were related to the pharmacology of the compound and were completely reversed after a 5-week compound withdrawal period.

Oral administration of anastrozole to pregnant rats and rabbits caused no teratogenic effects at doses up to 1.0 and 0.2 mg/kg/day respectively. Those effects that were seen (placental enlargement in rats and pregnancy failure in rabbits) were related to the pharmacology of the compound.

The survival of litters born to rats given anastrozole at 0.02 mg/kg/day and above (from Day 17 of pregnancy to Day 22 post-partum) was compromised. These effects were related to the pharmacological effects of the compound on parturition. There were no adverse effects on behaviour or reproductive performance of the first-generation offspring attributable to maternal treatment with anastrozole.

Carcinogenicity

A two-year rat oncogenicity study resulted in an increase in incidence of hepatic neoplasms and uterine stromal polyps in females and thyroid adenomas in males at the high dose (25 mg/kg/day) only. These changes occurred at a dose which represents 100-fold greater exposure than occurs at human therapeutic doses and are considered not to be clinically relevant to the treatment of patients with anastrozole.

A two-year mouse oncogenicity study resulted in the induction of benign ovarian tumours and a disturbance in the incidence of lymphoreticular neoplasms (fewer histiocytic sarcomas in females and more deaths as a result of lymphomas). These changes are considered to be mouse-specific effects of aromatase inhibition and not clinically relevant to the treatment of patients with anastrozole.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Coat

Hypromellose, macrogol 400, purified talc, titanium dioxide.

Other excipient

Colloidal silicon dioxide (colloidal), maize starch, microcrystalline cellulose, povidone (PVP K-30), purified talc, sodium starch glycolate.

Other excipient, animal origin

Lactose monohydrate, magnesium stearate

Removed in process

Ethanol, purified water q.s.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months from date of manufacture stored at or below 25oC.

6.4 Special precautions for storage

Store below 25ºC. Protect from light and moisture.

6.5 Nature and contents of container

Blister packs of 28 or 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

22 April 2010

10. DATE OF REVISION OF THE TEXT

29 April 2024

SUMMARY TABLE OF CHANGES

Date	Section(s) Changed	Change (s)
February 2019	All	Reformat consistent with new Medsafe Data Sheet Template.
April 2024	All sections	Reformat consistent with new Medsafe Data Sheet Template.
	Section 4.1	Aligned with innovator datasheet.
	Section 4.2	Caution warning added to the hepatic and renal impairment dose change.
	Section 4.4	Aligned with innovator datasheet and addition of tendon disorder section.
	Section 4.5	Aligned with innovator datasheet.
	Section 4.6	Aligned with innovator datasheet.
	Section 4.7	Aligned with innovator datasheet.
	Section 4.8	Aligned with innovator datasheet, addition of post-market adverse reactions section and update reporting of suspected adverse events reactions section.
	Section 4.9	Aligned with innovator datasheet.
	Section 5.1	Aligned with innovator datasheet.
	Section 5.2	Aligned with innovator datasheet.
	Section 5.3	Aligned with innovator datasheet.