

NEW ZEALAND DATA SHEET

1. AREMED TABLET

Aremed tablet 1mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Aremed tablet 1mg: 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

Treatment of advanced breast cancer in post-menopausal women.

4.2 Dose and method of administration

Adults including the elderly: 1 tablet (1 mg) daily.

Hepatic or Renal Impairment: No change in dosage required.

Children: Not recommended for use in children as efficacy has not been established.

4.3 Contraindications

- Pregnant or lactating women
- Hypersensitivity to any of the ingredients in this product

4.4 Special warnings and precautions for use

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

Use of Aremed has not been investigated in patients with severe renal or hepatic

impairment. The potential risk should be weighed against the possible benefit before administration to these patients.

Anastrozole lowers circulating oestrogen levels and may cause a reduction in bone mineral density. This can increase the risk of osteoporosis for patients receiving anastrozole (especially long term use), and bone mineral density should be monitored by bone densitometry. This possibly increased risk should be managed according to treatment guidelines for managing bone health in post-menopausal women.

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.

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

4.6 Fertility, pregnancy and lactation

Category C

The use of Aremed during pregnancy and lactation is contraindicated.

4.7 Effects on ability to drive and use machines

Aremed is unlikely have any effect on a patient's ability to drive or operate machinery. However, asthenia and somnolence have been reported and caution should be taken when these symptoms occur.

4.8 Undesirable effects

Anastrozole is usually well tolerated well tolerated with adverse events being similar to those reported for other aromatase inhibitors e.g. tamoxifen. Most are mild to moderate in nature.

Very common ($\geq 10\%$)

Vascular

General

Musculoskeletal, connective tissue and bone

Nervous system

Gastrointestinal

Skin and subcutaneous tissue

Hot flushes

Asthenia

Joint pain/stiffness

Headache

Nausea

Rash

Common ($\geq 1\%$ and $< 10\%$)

Reproductive system and breast Vaginal dryness, vaginal bleeding[^]

Skin and subcutaneous tissue Hair thinning, allergic reactions

Gastrointestinal Diarrhoea, vomiting

Nervous system

Hepatobiliary disorders

Metabolism and nutrition

Somnolence, Carpal Tunnel Syndrome*

Increases in alkaline phosphatase, alanine

aminotransferase and aspartate

aminotransferase

Anorexia, hypercholesterolaemia

Uncommon ($\geq 0.1\%$ and $< 1\%$)

Hepatobiliary disorders Increases in γ -GT and bilirubin, hepatitis

Skin and subcutaneous tissue

Musculoskeletal, connective tissue and

Bone

Rare ($> 0.01\%$ and $< 0.1\%$)

Skin and subcutaneous tissue

Urticaria

Trigger finger

Erythema multiforme, anaphylaxis

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.

4.9 Overdose

Symptoms

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. Clinical trials have been conducted with various dosages of anastrozole (up to 60 mg in a single dose to healthy male volunteers and up to 10 mg daily given to post-menopausal women with advanced breast cancer) and these doses were well tolerated. A single dose of anastrozole that results in life-threatening symptoms has not been established.

Treatment

There is no specific antidote and treatment should be symptomatic. When managing 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 of assistance. General supportive care including frequent monitoring of vital signs and close observation of the patient is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Anastrozole, a benzyltriazole derivative, is a potent, highly selective non-steroidal aromatase inhibitor. Anastrozole selectively inhibits the conversion of androgens to estrogens without affecting synthesis of adrenal corticosteroid, aldosterone or thyroid hormone.

In post-menopausal women, ovarian secretion of oestrogen declines, and conversion of adrenal androgens (mainly androstenedione and testosterone) into estrone and estradiol in peripheral tissues (adipose, muscle and liver), catalysed by the aromatase enzyme (oestrogen synthase) is the principal source of estrogens. Anastrozole selectively inhibits the conversion of androgens to estrogens by inhibiting the aromatase enzyme complex through competitive binding to the haeme of the cytochrome P450 unit of the enzyme. Suppression of oestrogen biosynthesis in all tissues reduces serum concentrations of circulating estrogens, including estrone, estradiol, and estrone sulphate with a subsequent beneficial effect in breast cancer.

The suppression of estradiol production after a 1 mg dose has been measured at greater than 80%. Because of this mode of action, aromatase inhibitors are suitable only for post-menopausal women with ER-positive disease. Anastrozole has been shown to be an effective treatment of early and advanced breast cancer in post-menopausal women. In a trial of 9366 post-menopausal women with operable breast cancer, it was shown to be statistically superior to tamoxifen in recurrence-free survival especially in patients with receptor positive status.

Administration of anastrozole significantly reduced the incidence of contralateral breast cancer and time to distant recurrence was also numerically superior. No efficacy benefit seen when anastrozole was administered in combination with tamoxifen, when compared to administration of tamoxifen alone.

In a further trial of 2579 post-menopausal women with hormone receptor positive early breast cancer treated with adjuvant tamoxifen, anastrozole provided a superior disease-free survival in patients switched to anastrozole from tamoxifen when compared to patients continuing on tamoxifen. Time to recurrence, whether local or distant, was also statistically better for those switched to anastrozole. The incidence of contralateral breast cancer had a numerical advantage for anastrozole although the incidence was very low in each treatment arm.

Further trials have supported these results with the safety profile being consistent with the known safety profile in post-menopausal women with hormone-receptor positive early breast cancer.

Studies assessing bone mineral density in patients using anastrozole have been conducted. Patients were initially assessed as being high, moderate or low risk according to their risk of fragility fracture. All patients received vitamin D and calcium.

Low risk patients were treated with anastrozole, high risk were treated with anastrozole and bisphosphonate with the moderate risk being treated with either anastrozole and bisphosphonate or anastrozole and placebo. After 12 months it was found that patients in the moderate and high risk groups treated with anastrozole and bisphosphonate had their bone health successfully managed, while those in the low risk group who received anastrozole showed no change in their bone mineral density. This study provides evidence that post-menopausal women with early breast cancer scheduled to be treated with anastrozole should have their bone status managed according to treatment guidelines already available for post-menopausal women at similar risk of fragility fracture. There was a neutral effect on plasma lipids in patients treated with anastrozole and those treated with both anastrozole and bisphosphonate.

Clinical studies have been conducted in children – 2 studies in pubertal boys with gynecomastia and 1 in girls with McCune Albright Syndrome. In both gynecomastia studies reduction of >50% in total breast volume was observed in boys treated with anastrozole 1 mg per day for 6 months. In the exploratory trial of anastrozole in girls aged 2-10 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 bleeding, 28% experienced a >50% reduction of bleeding days on treatment, 40% experienced a cessation over a 6-month period and 12% 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 was significantly reduced from pre-treatment through month 0 to month 12, and from pre-treatment to the second 6 months (month 7 to month 12).

5.2 Pharmacokinetic properties

Anastrozole is rapidly absorbed into the systemic circulation after oral administration with peak plasma concentrations being achieved within 2 hours of dosing under fasting conditions. Anastrozole is eliminated slowly with a plasma elimination half life of 40-50 hours. Plasma concentrations approach steady state after about 7 days of once daily dosing with the steady state concentrations being approximately 3 to 4 times higher than concentrations achieved after a single dose. Food decreases the rate but not the extent of absorption. In boys with pubertal gynecomastia, anastrozole is rapidly absorbed, widely distributed and eliminated slowly with the pharmacokinetic parameters being similar to those of post-menopausal women. In girls anastrozole was widely distributed and slowly eliminated with an estimated half life of approximately 0.8 days. Anastrozole is 40% bound to plasma proteins. Hepatic metabolism accounts for approximately 85% of the elimination. Within 72 hours of dosing approximately 60% of the dose is excreted in the urine as metabolites and only 10% as the unchanged drug. The metabolism of anastrozole is by N-dealkylation, hydroxylation and glucuronidation with the metabolites being mainly excreted via the urine. Three metabolites of anastrozole have been identified in human plasma and urine. Several minor (less than 5% of the dose) metabolites have not been identified. The known metabolites are triazole (the major metabolite which has no pharmacological activity attributed to it), a glucuronide conjugate of hydroxy-anastrozole, and a glucuronide of anastrozole. Renal clearance of anastrozole decreases proportionally with creatinine clearance but this has very little effect on total body clearance. No dosage adjustments are therefore required for patients with impaired renal function.

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.

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 25°C.

6.4 Special precautions for storage

Store below 25°C. 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

February 2019

SUMMARY TABLE OF CHANGES

Date	Section(s) Changed	Change (s)
February 2019	All	Reformat consistent with new Medsafe Data Sheet Template.