PACKAGE INSERT

AREMED

PRODUCT NAME

Aremed 1 film-coated tablets 1mg

NAME AND STRENGHT OF ACTIVE SUBSTANCE

Each film-coated tablet contains 1 mg anastrozole.

Excipient(s) with known effect
This product contains 65 mg lactose.

PRODUCT DESCRIPTION

Film-coated tablet.

White, round, film-coated tablets with a diameter of 6,6 mm approximately.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy; Hormone antagonists and related agents, Aromatase inhibitors, ATC code: L02BG03

Mechanism of action and pharmacodynamics effects
Aremed is a potent and highly selective non-steroidal aromatase inhibitor. In postmenopausal women, estradiol is produced primarily from the conversion of androstenedione to estrone through the aromatase enzyme complex in peripheral tissues. Estrone is subsequently converted to estradiol. Reducing circulating estradiol levels has been shown to produce a beneficial effect in women with breast cancer. In postmenopausal women, anastrozole at a daily dose of 1 mg produced estradiol suppression of greater than 80% using a highly sensitive assay.

Anastrozole does not possess any progestogenic, androgenic or 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 adrenocorticotrophic hormone (ACTH) challenge testing. Corticoid supplements are therefore not needed.

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 the 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. 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.

The apparent oral clearance of anastrozole in volunteers with stable hepatic cirrhosis or renal impairment was in the range observed in health volunteers.

Preclinical safety data

Acute toxicity
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
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.

Oral administration of anastrozole to female rats produced a high incidence of infertility at 1 mg/kg/day and increase 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.

CLINICAL PARTICULARS

Indications

Aremed is indicated for the treatment of advanced breast cancer in postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer. Efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen.

Dosage and method of administration

Posology
The recommended dose of Aremed for adults including the elderly in one 1 mg tablet once a day.

Special populations

Paediatric population:
Aremed is not recommended for use in children and adolescents due to insufficient data on safety and efficacy.

Renal impairment:
No dose change is recommended in patients with mild or moderate renal impairment.

Hepatic impairment:
No dose change is recommended in patients with mild hepatic disease.

Method of administration
Oral administration.

Contraindications

Aremed is contra-indicated in:

- premenopausal women.
- pregnant or breast-feeding women.
- patients with severe renal impairment (creatinine clearance <20ml/min).
- patients with moderate or severe hepatic disease.
- hypersensitivity to the active substance(s) or to any of the excipients listed in section List of excipients.
- concurrent oestrogen-containing therapies.
- concurrent tamoxifen therapy.

Warnings and precautions

General
Anastrozole is contraindicated in premenopausal women. The menopause should be defined biochemically (luteinizing-hormone [LH], follicle stimulating hormone [FSH], and/or estradiol levels) in any patients where there is doubt about menopausal status. There are no data to support the use of anastrozole with LHRH analogues.

Co-administration of tamoxifen or estrogen-containing therapies with anastrozole is contraindicated as this may diminish its pharmacological action.

Effect on bone mineral density
As anastrozole lowers circulating estrogen levels it may cause 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 at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored. The use of specific treatments, e.g., bisphosphonates may stop further bone mineral loss caused by anastrozole in postmenopausal women and could be considered.

There are no data to support the safe use of Aremed in patients with moderate or severe hepatic impairment, or patients with severe impairment of renal function (creatinine clearance less than 20ml/min).

Paediatric population
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. In the pivotal clinical trial, efficacy was not demonstrated and safety was not established. 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.

Hypersensitivity to lactose
This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine

Interactions

Anastrozole inhibits CYPs 1A2, 2C8/9 and 3A4 in vitro. Clinical studies with antipyrine and warfarin showed that anastrozole at a 1 mg dose did not significantly inhibit the metabolism of antipyrine and R- and S-warfarin indicating the co-administration of anastrozole with other medicinal products is unlikely to result in clinically significant medicinal product interactions mediated by CYP enzymes.

The enzymes mediating metabolism of anastrozole have not been identified. Cimetidine, a weak, unspecific inhibitor of CYP enzymes, did not affect the plasma concentrations of anastrozole. The effect of potent CYP inhibitors is unknown.

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 medicinal products. There were no clinically significant interactions with bisphosphonates.

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

Pregnancy and lactation

Pregnancy
There are no data from the use of anastrozole in pregnant women. Studies in animals have shown reproductive toxicity. Anastrozole is contraindicated during pregnancy.

Breast-feeding
There are no data on the use of anastrozole during lactation. Anastrozole is contraindicated during breast-feeding.

Fertility
The effects of anastrozole on fertility in humans have not been studied. Studies in animals have shown reproductive toxicity.

Effects on ability to drive and use machines

Anastrozole has no or negligible influence on the ability to drive and use machines. 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

The following table presents adverse reactions from clinical trials, post-marketing studies or spontaneous reports. Unless specified, the frequency categories were calculated from the number of adverse events reported in a large phase III study conducted in 9,366 postmenopausal women with operable breast cancer given adjuvant treatment for five years (the Anastrozole, Tamoxifen, Alone or in Combination [ATAC] study).

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency groupings are defined according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). The most frequently reported adverse reactions were headache, hot flashes, nausea, rash, arthralgia, joint stiffness, arthritis and asthenia.

Table 1 Adverse reactions by System Organ Class and frequency

Adverse reactions by SOC and frequency		
Metabolism and nutrition disorders	Common	Anorexia Hypercholesterolaemia
	Uncommon	Hypercalcaemia (with or without an increase in parathyroid hormone)
Nervous system disorders	Very common	Headache
	Common	Somnolence Carpal Tunnel Syndrome* Sensory disturbances (including paraesthesia, taste loss and taste perversion)
Vascular disorders	Very common	Hot flushes
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea Vomiting
Hepatobiliary disorders	Common	Increased in alkaline phosphate, alanine aminotransferase and aspartate aminotransferase
	Uncommon	Increased in gamma-GT and bilirubin Hepatitis
Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Hair thinning (alopecia) Allergic reactions
	Uncommon	Urticaria
	Rare	Erythema multiforme Anaphylactoid reaction

		Cutaneous vasculitis (including some reports of Henoch-Schönlein purpura)**
	Very rare	Stevens-Johnson syndrome Angioedema
Musculoskeletal and connective tissue disorders	Very common	Arthralgia/joint stiffness Arthritis Osteoporosis
	Common	Bone pain Myalgia
	Uncommon	Trigger finger
Reproductive system and breast disorders	Common	Vaginal dryness Vaginal bleeding***
General disorders and administration site conditions	Very common	Asthenia
Psychiatric disorders	Very common	Depression

* Events of Carpal Tunnel Syndrome have been reported in patients receiveing 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.
** Since cutaneous vasculitis and Henoch- Schönlein purpura was not observed in ATAC, the frequency category for these events can be considered as 'Rare' (≥0.01% and <0.1%) based on the worst value of the point estimate.
*** Vaginal bleeding has been reported commonly, 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.

The table below presents the frequency of pre-specified adverse events in the ATCA study after a median follow-up of 68 months, irrespective of causality, reported in patients receiving trial therapy and up to 14 days after cessation of trial therapy.

Table 2 ATAC study pre-specified adverse events

Adverse effects	Anastrozole (N=3,092)	Tamoxifen (N=3,094)
Hot flushes	1,104 (35.7%)	1,264 (40.9%)
Joint pain/stiffness	1,100 (35.6%)	911 (29.4%)
Mood disturbances	597 (19.3%)	554 (17.9%)
Fatigue/asthenia	575 (18.6%)	544 (17.6%)
Nausea and vomiting	393 (12.7%)	384 (12.4%)
Fractures	315 (10.2%)	209 (6.8%)
Fractures of the spine, hip, or wrist/Colles	133 (4.3%)	91 (2.9%)
Wrist/Colles fractures	67 (2.2%)	50 (1.6%)
Spine fractures	43 (1.4%)	22 (0.7%)
Hip fractures	28 (0.9%)	26 (0.8%)
Cataracts	182 (5.9%)	213 (6.9%)

Vaginal bleeding	167 (5.4%)	317 (10.2%)
Ischaemic cardiovascular disease	127 (4.1%)	104 (3.4%)
Angina pectoris	71 (2.3%)	51 (1.6%)
Myocardial infarct	37 (1.2%)	34 (1.1%)
Coronary artery disorder	25 (0.8%)	23 (0.7%)
Myocardial ischaemia	22 (0.7%)	14 (0.5%)
Vaginal discharge	109 (3.5%)	408 (13.2%)
Any venous thromboembolic event	87 (2.8%)	140 (4.5%)
Deep venous thromboembolic events including PE (pulmonary embolism)	48 (1.6%)	74 (2.4%)
Ischaemic cerebrovascular events	62 (2.0%)	88 (2.8%)
Endometrial cancer	4 (0.2%)	13 (0.6%)

The ATAC trial data showed that patients receiving anastrozole had an increase in joint disorders (including arthritis, arthrosis, and arthralgia) compared with patients receiving tamoxifen. Patients receiving anastrozole had an increase in the incidence of fractures (including fractures of spine, hip and wrist) compared with patients receiving tamoxifen. These differences were statistically significant.

Fracture rates of 22 per 1,000 patient-years and 15 per 1,000 patient-years were observed for the anastrozole and tamoxifen groups, respectively, after a median follow-up of 68 months. The observed fracture rate for anastrozole is similar to the range reported in age-matched postmenopausal populations.
The incidence of osteoporosis was 10.5% in patients treated with anastrozole and 7.3% in patients treated with tamoxifen.

It has not been determined whether the rates of fracture and osteoporosis seen in ATAC in patients on anastrozole treatment reflect a protective effect of tamoxifen, a specific effect of anastrozole, or both.

Patients receiving anastrozole had a decrease in hot flushes, vaginal bleeding, vaginal discharge, endometrial cancer, venous thromboembolic events (including deep venous thrombosis) and ischaemic cerebrovascular events compared with patients receiving tamoxifen. These differences were statistically significant.
Results from the ATAC trial bone substudy, at 12 and 24 months demonstrated that patients receiving anastrozole had a mean decrease in both lumbar spine and total hip bone mineral density (BMD) compared to baseline. Patients receiving tamoxifen had a mean increase in both lumbar spine and total hip BMD compared to baseline. Slight increases in total cholesterol have also been observed in clinical trials with anastrozole, although the clinical significance has not been determined.

Overdose

There is limited clinical experience of accidental overdose. 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 overdose 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.

PHARMACEUTICAL PARTICULARS

List of excipients

Core
Lactose monohydrate
Maize starch
Povidone
Microcrystalline cellulose
Sodium starch glycolate
Colloidal silicon dioxide
Magnesium stearate
Talc

Coating
Hypromellose
Polyethylene glycol 400
Titanium dioxide E171
Talc

Shelf life

5 years.

Storage conditions

Do not store above 30 °C. Protect from light and moisture.

Keep out of the reach and sight of children.

Presentation

PVC/Aluminium blisters. Pack-sizes of 28 film-coated tablets.

Manufacturer

Remedica Ltd.
Aharnon Str., Limassol Industrial Estate, 3056 Limassol, Cyprus

Product registrant

Goldplus Universal Pte Ltd
103 Kallang Avenue #06-02, Singapore 339504

Date of revision of the text

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