NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ARIMIDEX® 1 mg film coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 1 mg anastrazole.

3. PHARMACEUTICAL FORM

Film coated tablet.

ARIMIDEX is presented as a round, white, biconvex film-coated tablet containing 1 mg of anastrozole. The tablets are 6 mm in diameter and are compressed to a weight of 100 mg. A logo consisting of the letter 'A' with an arrow head attached to the foot of the extended right leg of the 'A' is impressed on one side and a tablet strength marking ('Adx1') is impressed on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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 ARIMIDEX as adjuvant treatment for early breast cancer.

Treatment of advanced breast cancer in post-menopausal women.

4.2 DOSAGE AND METHOD OF ADMINISTRATION

Adults Including the Elderly

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

Children

The use of ARIMIDEX is not recommended in children, as efficacy has not been established (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

ARIMIDEX must not be administered during pregnancy or lactation.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

ARIMIDEX 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).

ARIMIDEX 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 ARIMIDEX.

As ARIMIDEX 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.

Tendonitis and tenosynovitis may occur with the use of third generation aromatase inhibitors. Further, untreated tendonitis of a particular degree may lead to tendon rupture. Treating physicians should monitor the patients for signs and symptoms of tendon disorders.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Antipyrine and cimetidine clinical interaction studies indicate that the co-administration of ARIMIDEX 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 ARIMIDEX 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 ARIMIDEX as they may diminish its pharmacological action.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

ARIMIDEX is contraindicated in pregnant women.

Breast-feeding

ARIMIDEX is contraindicated in breast-feeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ARIMIDEX is unlikely to impair the ability of patients to drive and operate machinery. However, asthenia and somnolence have been reported with the use of ARIMIDEX and caution should be observed when driving or operating machinery while such symptoms persist.

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

Common (≥ 1% and < 10%)	*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**
	Metabolism and nutrition	• Anorexia, mainly mild in nature • Hypercholesterolaemia mainly mild or moderate in nature
	Musculoskeletal and connective tissue disorders:	• Bone pain • Myalgia
Uncommon (≥ 0.1% and <1%)	*Metabolism and nutrition:*	• Hypercalcaemia (with or without an increase in parathyroid hormone)
	Hepatobilary disorders:	• Increases in gamma-GT and bilirubin • Hepatitis
	Skin and subcutaneous tissue:	• Urticaria
	Musculoskeletal and connective tissue disorders:	• 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

* Events of Carpal Tunnel Syndrome have been reported in patients receiving ARIMIDEX 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.

** 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 ARIMIDEX. If bleeding persists, further evaluation should be considered.

Description of selected adverse reactions:

Ischemic cardiovascular events: In a large phase III study conducted in 9366 postmenopausal women with operable breast cancer treated for 5 years, ischaemic cardiovascular events were reported more frequently in patients treated with ARIMIDEX compared to those treated with tamoxifen, although the difference was not statistically significant. The observed difference was mainly due to more reports of angina pectoris and was associated with a sub-group of patients with pre-existing ischaemic heart disease.

Aromatase Inhibitor class effects: There have been cases of the following adverse reaction reported during treatment with other third generation aromatase inhibitors which might also occur during treatment with ARIMIDEX: Tendonitis, tenosynovitis, tendon rupture (see section 4.4).

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 OVERDOSAGE

There is limited clinical experience of overdose of ARIMIDEX. There are no reports where a patient has taken a dose in excess of 60 mg. No toxicity was observed and no clinically relevant adverse effects have been seen.

Acute toxicity was seen in animals at a dose greater than 45 mg/kg (equivalent to 2.7 g). Clinical trials have been conducted with various dosages of ARIMIDEX, 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 dosages were well tolerated. A single dose of ARIMIDEX that results in life-threatening symptoms has not been established.

There is no specific antidote to over-dosage 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 ARIMIDEX 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

ARIMIDEX is a potent and highly selective non-steroidal aromatase inhibitor. In post-menopausal 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. Reducing circulating oestradiol levels has been shown to produce a beneficial effect in women with breast cancer. In post-menopausal women, ARIMIDEX at a daily dose of 1 mg produced oestradiol suppression of greater than 80% using a highly sensitive assay.

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

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

Daily doses of ARIMIDEX 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 ARIMIDEX 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 postmenopausal women with operable breast cancer, ARIMIDEX was shown to be statistically superior to tamoxifen in recurrence-free survival. The incidence of contralateral breast cancer was statistically significantly reduced for ARIMIDEX compared to tamoxifen. Time to distant recurrence was also numerically superior for ARIMIDEX. The combination of ARIMIDEX 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 ARIMIDEX versus tamoxifen. Again, the combination of ARIMIDEX 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 postmenopausal women with hormone receptor positive early breast cancer being treated with adjuvant tamoxifen, patients had a superior disease-free survival when switched to ARIMIDEX 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 for ARIMIDEX, 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 ARIMIDEX. Overall survival was similar for the two treatment groups.

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

The ARIMIDEX 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 ARIMIDEX 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 ARIMIDEX alone, those in the moderate group were randomised to ARIMIDEX plus bisphosphonate or ARIMIDEX plus placebo and those in the high risk group received ARIMIDEX 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 ARIMIDEX in combination with a bisphosphonate. In addition, no changes in BMD were seen in the low risk group treated with ARIMIDEX 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.

This study provides evidence that postmenopausal women with early breast cancer scheduled to be treated with ARIMIDEX should have their bone status managed according to treatment guidelines already available for postmenopausal women at similar risk of fragility fracture.

Lipids

In the SABRE study there was a neutral effect on plasma lipids both in those patients treated with ARIMIDEX alone and in those treated with ARIMIDEX 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 ARIMIDEX 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 ARIMIDEX 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 ARIMIDEX 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 ARIMIDEX in 28 girls (aged 2 to ≤10 years) with McCune Albright Syndrome (MAS). 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, 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 (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). Anastrozole is eliminated slowly with a plasma elimination half-life of 40 to 50 hours. 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 ARIMIDEX 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 post-menopausal women.

Distribution

Anastrozole is only 40% bound to plasma proteins.

Elimination

Anastrozole is extensively metabolised by post-menopausal 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.

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 sections 4.2 and 4.4).

Paediatric population

In boys with pubertal gynaecomastia, anastrozole was rapidly absorbed, was widely distributed, and was eliminated slowly with a half-life of approximately 2 days. PK

parameters in boys were comparable to those of postmenopausal women. Clearance of anastrozole was lower in girls than in boys and exposure higher. Anastrozole in girls was widely distributed and slowly eliminated, with an estimated half-life of approximately 0.8 days.

5.3 PRE-CLINICAL SAFETY DATA

Acute toxicity

In acute toxicity studies in rodents the median lethal dose of anastrozole was greater than 100 mg/kg by the oral route and greater than 50 mg/kg by the intraperitoneal route. In an oral acute toxicity study in the dog the median lethal dose was greater than 45 mg/kg.

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 dose (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 toxic or degenerative changes.

Mutagenicity

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

Reproductive toxicology

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.

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 were related to the pharmacology of the compound and were completely reversed after a 5-week compound withdrawal period.

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

- Lactose monohydrate
- Povidone
- Sodium starch glycolate
- Magnesium stearate
- Hypromellose
- Macrogol 300
- Titanium dioxide

6.2 INCOMPATIBILITIES

Not applicable

6.3 Shelf life

60 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

ARIMIDEX tablets are presented in a PVC blister/aluminium foil blister pack containing 30 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: 0800 684 432

9. DATE OF FIRST APPROVAL

15 August 1996

10. DATE OF REVISION OF TEXT

2 September 2024

Arimidex is a registered trademark of the AstraZeneca group of companies.

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Renal and Hepatic sections updated
4.4 & 4.8	Tendonitis & tenosynovitis added
5.2	Section is added on renal and hepatic impairment
8	Phone number updated