# NEW ZEALAND DATA SHEET

# ANATROLE

## 1. Product Name

Anatrole 1 mg film-coated tablet.

## 2. Qualitative and Quantitative Composition

Each film-coated tablet contains 1 mg of anastrozole.

Excipient with known effect: Lactose monohydrate

Allergen declaration: Lactose

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical Form

White, film-coated, round, biconvex tablet debossed with 'ANA' and '1' on one side.

## 4. Clinical Particulars

### *4.1 Therapeutic indications*

- Treatment of early breast cancer in hormone receptor positive postmenopausal 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 postmenopausal women receiving anastrozole as adjuvant treatment for early breast cancer.
- Treatment of advanced breast cancer in postmenopausal women.

### *4.2 Dose and method of administration*

**Dose**

***Adults, including the elderly***

The recommended dose is one tablet (1 mg) once a day.

***Special populations***

**Paediatric**

Not recommended for use 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).

### Method of administration

Anatrole should be taken orally. Do not halve the tablet. Dose equivalence when the tablet is divided has not been established.

## *4.3 Contraindications*

Anastrozole must not be administered during pregnancy or breastfeeding.

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

## *4.4 Special warnings and precautions for use*

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 (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.

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 patient for signs and symptoms of tendon disorders.

## *4.5 Interaction with other medicines and other forms of interaction*

Antipyrine and cimetidine clinical interaction studies indicate that the co-administration 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

Anastrozole is contraindicated in pregnant women.

### Breastfeeding

Anastrozole is contraindicated in breastfeeding women.

### Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

## *4.7 Effects on ability to drive and use machines*

Anatrole 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.

## *4.8 Undesirable effects*

Unless specified, the following frequency categories were determined from the number of adverse effects 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.

The frequency of adverse events listed below is defined using the following conventions:
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).

| System Organ Class | Frequency | Adverse reaction |
|---|---|---|
| Metabolism and nutrition disorders | Common | Anorexia, mainly mild in nature<br>Hypercholesterolaemia, mainly mild or moderate in nature |
| | Uncommon | Hypercalcaemia (with or without an increase in parathyroid hormone) |
| Psychiatric disorders | Very common | Depression |
| Nervous system disorders | Very common | Headache, mainly mild or moderate in nature |
| | Common | Somnolence, mainly mild or moderate in nature<br>Carpal Tunnel Syndrome*<br>Sensory disturbances (including paraesthesia, taste loss and taste perversion) |
| Vascular disorders | Very common | Hot flushes, mainly mild or moderate in nature |
| Gastrointestinal disorders | Very common | Nausea, mainly mild or moderate in nature |
| | Common | Diarrhoea, mainly mild or moderate in nature<br>Vomiting, mainly mild or moderate in nature |
| Hepatobiliary disorders | Common | Increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase |
| | Uncommon | Increases in gamma-GT and bilirubin<br>Hepatitis |
| Skin and subcutaneous tissue disorders | Very common | Rash, mainly mild or moderate in nature |
| | Common | Hair thinning (Alopecia), mainly mild or moderate in nature<br>Allergic reactions |
| | Uncommon | Urticaria |

| System Organ Class | Frequency | Adverse reaction |
|---|---|---|
| | Rare | Erythema multiforme<br>Anaphylactoid reaction<br>Cutaneous vasculitis (including some reports of Henoch-Schönlein purpura) |
| | Very rare | Stevens-Johnson syndrome<br>Angioedema |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia/Joint stiffness<br>Arthritis<br>Osteoporosis |
| | Common | Bone pain<br>Myalgia |
| | Uncommon | Trigger finger |
| Reproductive system and breast disorders | Common | Vaginal dryness, mainly mild or moderate in nature<br>Vaginal bleeding, mainly mild or moderate in nature** |
| General disorders | Very common | Asthenia, mainly mild or moderate in nature |

* 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.

** Vaginal bleeding has been commonly observed, 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.

### Description of selected adverse reactions

Ischaemic 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 anastrozole 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 reactions reported during treatment with other third generation aromatase inhibitors which might also occur during treatment with anastrozole: 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 Overdose*

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

Acute toxicity has been seen in animals at a dose greater than 45 mg/kg (equivalent to 2.7 g). Clinical trials have been completed with various doses 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) and 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 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.

For risk assessment and 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*

Pharmacotherapeutic group: Aromatase inhibitors, ATC code: L02BG03

### Mechanism of action and pharmacodynamic effects

Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. 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. 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 1 mg produced oestradiol suppression of greater than 80% using a highly sensitive assay.

In clinical trials, treatment with anastrozole at a dose of 1 mg 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 required.

Extensive phase III clinical study programs 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 postmenopausal 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 statistically significantly reduced for anastrozole compared to 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 combination 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 (Austrian Breast and Colorectal Cancer Study Group [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 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 for 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 similar trials (GABG/ARNO 95 and ITA) with anastrozole, as well as a combined analysis of ABCSG 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 postmenopausal women with hormone-receptor positive early breast cancer.

***Study of anastrozole with the bisphosphonate risedronate (SABRE)***

Bone mineral density (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. Patients 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 group received anastrozole 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 anastrozole in combination with a 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.

This study provides evidence that postmenopausal women with early breast cancer scheduled to be treated with anastrozole 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 anastrozole alone and in those treated with anastrozole plus a bisphosphonate.

## Paediatric population

Three clinical trials have been 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 (aged 11-18 years inclusive) with gynaecomastia of greater than 12 months duration 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 was seen in 55.6% (20/36) of the boys after 6 months.

***McCune-Albright Syndrome (MAS) study***

Trial 0046 was an international, multi-centre, open-label, exploratory trial of anastrozole in 28 girls (aged 2 to $\leq$ 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 $\geq$ 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 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.

### 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.

### 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 in 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, 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 Preclinical 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 have been completed in both 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) are 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 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 oncogenicity study in rats showed 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*

Anatrole film coated tablets also contain:

Tablet core

- Lactose monohydrate
- Sodium starch glycollate
- Povidone
- Magnesium stearate

Tablet film coat

- Macrogol
- Hypromellose
- Titanium dioxide

### *6.2 Incompatibilities*

Not applicable.

### *6.3 Shelf life*

2 years.

### *6.4 Special precautions for storage*

Store at or below 25°C.

### *6.5 Nature and contents of container*

Blister pack of PVC/PE/PVDC/Aluminium foil strips enclosed in a carton.
Pack size of 30 film coated tablets.

### *6.6 Special precautions for disposal and other handling*

No special requirements.

## 7. Medicines Schedule

Prescription Medicine

## 8. Sponsor Details

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## 9. Date of First Approval

29 April 2010

## 10. Date of Revision of the Text

3 June 2025

**Summary table of changes**

| Section | Summary of new information |
|---|---|
| 4.2 | Caution advised for use in patients with renal or hepatic impairment |
| 4.3, 4.8, 4.9, 5.1 | Minor editorial changes |
| 4.4, 4.8 | Tendonitis & tenosynovitis updated |
| 4.8 | Updated ADR reporting website |
| 5.1 | Updated statistical information for Gynaecomastia study |
| 5.2 | Updated absorption section, renal and hepatic impairment section and paediatric population section<br><br>Deletion of Excretion section |