

New Zealand Data Sheet

1 PRODUCT NAME

Rolin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Anastrozole 1 mg tablets

3 PHARMACEUTICAL FORM

Rolin tablets are white, round, biconvex film coated tablets, plain on both sides with a diameter of 5.5 mm and a thickness of approximately 2.3 mm. Each tablet contains 1 mg of anastrozole. Do not halve the tablet. Dose equivalence when the tablet is divided has not been established.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Advanced breast cancer in post-menopausal women.

4.2 Dose and method of administration

Adults Including the Elderly

1 mg (one tablet) to be taken once per day. Do not halve the tablet. Dose equivalence when the tablet is divided has not been established.

Children

Efficacy has not been determined in children, therefore anastrozole is not recommended for children (see sections 5.1 and 5.2).

Renal Impairment

No dosage change is advised.

Hepatic Impairment

No dosage change is advised.

4.3 Contraindications

Anastrozole should not be used during pregnancy or in mothers who are breastfeeding.

Identified hypersensitivity to anastrozole or to any of the excipients (Please refer to Pharmaceutical Particulars, List of Excipients).

4.4 Special warnings and precautions for use

Anastrozole tablets are not recommended for children or in patients who are classed as pre-menopausal women as efficacy and safety are yet to be determined (Please refer to Pharmacodynamic Properties and Pharmacokinetic Properties).

For patients with severe renal or hepatic impairment, anastrozole has not been investigated. Before treatment with anastrozole is initiated, the potential benefits and risks to patients must be considered.

Circulation oestrogen levels are decreased with the use of anastrozole and may potentially instigate a decrease in bone mineral density. Due to this, there may be a possible consequential heightened risk of fracture. This increased risk must be carefully managed in accordance to treatment guidelines for the management of bone health in postmenopausal women.

4.5 Interaction with other medicines and other forms of interaction

The administration of anastrozole alongside other medications are not likely to result in any clinically significant medication interactions facilitated by cytochrome P450. This was shown in clinical interaction studies on antipyrine and cimetidine.

An analysis of the clinical trial safety database did not uncover clinically significant evidence of interactions in patients who were administered anastrozole and other medications prescribed often. No clinically significant interactions with bisphosphonates were observed.

Therapies that contain oestrogen, for example, tamoxifen, should not be administered alongside anastrozole as they may reduce anastrozole's pharmacological process.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy

Anastrozole should not be used in pregnancy.

Use in Lactation

Anastrozole should not be used in mothers who are breastfeeding.

4.7 Effects on ability to drive and use machines

Anastrozole is not likely to affect the patient's ability to drive and operate machinery. Please note that asthenia and somnolence have been observed with the usage of anastrozole and therefore care must be taken when driving or operating machinery if these symptoms continue.

4.8 Undesirable effects

The below frequency categories (except if detailed) were determined from the number of adverse effects observed in a phase III study completed in 9,366 women with operable breast cancer (post-menopause), treated for five years and except if it was detailed, no observation was completed of the incidence within the comparative treatment group or whether the researcher believed it to be related to study medication.

Adverse reactions are graded under title of frequency using the following principle: very common $\geq 10\%$; common $\geq 1\%$ to $< 10\%$; uncommon $\geq 0.1\%$ to $< 0.01\%$; rare $\geq 0.01\%$ to $< 0.1\%$ and very rare $< 0.01\%$, including isolated reports.

Frequency	Description of Adverse Effect
Gastrointestinal	
Very Common:	Nausea of mild to moderate effect.
Common:	Diarrhoea and vomiting of mild to moderate effect.

General	
Very Common:	Asthenia of mild to moderate effect.
Hepatobiliary Disorders	
Common:	Increase in alanine aminotransferase, alkaline phosphatase and aspartate aminotransferase.
Uncommon:	Increase in gamma-GT, increase in bilirubin and hepatitis.
Metabolism and Nutrition	
Common:	Anorexia and hypercholesterolaemia of mild to moderate effect.
Uncommon:	Hypercalcaemia – with or without an increase in parathyroid hormone.
Muskuloskeletal, connective tissue and bone	
Very Common:	Arthralgia (joint stiffness) and arthritis.
Common:	Bone pain and myalgia.
Uncommon:	Trigger finger.
Nervous System	
Very Common:	Headache of mild to moderate effect.
Common:	Carpal Tunnel Syndrome*, sensory disturbances (paraesthesia, taste loss and taste perversion), somnolence.
Reproductive System and Breast	
Common:	Vaginal bleeding** of mild to moderate effect and vaginal dryness of mild to moderate effect.
Skin and subcutaneous tissue	
Very Common:	Rash of mild to moderate effect.
Common:	Allergic reactions, alopecia of mild to moderate effect.
Uncommon:	Urticaria.
Rare:	Anaphylactoid reaction, cutaneous vasculitis (some observations of Henoch-Schönlein purpura) and erythema multiforme.
Very rare:	Angioedema and Stevens-Johnson syndrome.
Vascular	
Very Common:	Hot flushes of mild to moderate effect.

*Incidents of Carpal Tunnel Syndrome have been observed in clinical trials in patients having anastrozole treatment in larger quantities than patients having tamoxifen treatment. Please note, most of these incidents were observed in patients with risk factors that were identifiable for the condition developing.

** Uncommonly vaginal bleeding has been observed. This occurs predominantly in patients with breast cancer that is advanced and through the initial few weeks after substituting current hormonal therapy to anastrozole treatment. If bleeding continues, additional evaluation must be considered.

Ischaemic cardiovascular incidents were observed frequently in a substantial phase III study completed in 9,366 postmenopausal women who had operable breast cancer that had been treated for five years and had been treated with anastrozole in comparison to patients to had been treated with tamoxifen. However, the difference between the two treatments was not significant statistically. The difference observed was primarily due to added observations of angina pectoris and was also correlated with an associate group of patients who had pre-existing ischaemic heart disease.

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://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

There is incomplete clinical knowledge of overdose with anastrozole. There are no descriptions where a patient has administered a dosage that exceeds 60 mg. No adverse effects that are considered clinically relevant or toxicity have been observed.

Clinical trials have been completed with different doses of anastrozole., In an individual dose up to 60 mg of anastrozole provided to male healthy volunteers and up to 10 mg once per day provided to women (post-menopausal) with advanced stage of breast cancer; these doses provided were well accepted. An individual dosage of anastrozole that causes serious life-threatening symptoms has not been determined. In animals administered a dosage larger than 45 mg per kg (comparable to 2.7g), acute toxicity was observed.

There are no specific antidotes to an overdose of anastrozole and treatment should be symptomatic. While managing an overdose, attention must be given to the likelihood that numerous medications may have been consumed. If the patient is alert, vomiting may be induced. As anastrozole is not very protein bound, dialysis may be useful.. General supportive care, incorporating regular observation of vital signs and close monitoring of the patient is indicated.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aromatase inhibitors (ATC code L02BG)

Anastrozole is a highly selective non-steroidal and strong aromatase inhibitor. Oestradiol is produced from the transition of androstenedione to oestrone through the aromatase enzyme complex in peripheral tissues in post-menopausal women. Oestrone is then changed to oestradiol. Decreasing circulating oestradiol concentrations have been indicated to create a positive effect in women who have breast cancer. In post-menopausal women, a daily dosage of 1 mg of anastrozole, yielded oestradiol suppression of larger than 80% with the use of a very sensitive assay.

In clinical trials anastrozole treatment at a dosage of 1 mg has displayed significant extension of survival time.

Anastrozole does not have any androgenic, progestogenic, or oestrogenic activity.

Anastrozole given up to 10 mg per day does not have any outcome on cortisol or aldosterone secretion, determined prior or following normal ACTH challenge testing. Corticoid supplements are consequently not required.

Anastrozole has been shown to be an effective treatment of early and advanced breast cancer (in post-menopausal women) in extensive phase III clinical study programs appropriate for endocrine therapy.

Early breast cancer - Primary adjuvant treatment

In an extensive phase III study carried out in 9,366 postmenopausal women with breast cancer that was operable, anastrozole was displayed to be statistically greater to tamoxifen in survival recurrence free. In comparison to tamoxifen, the incidence of contralateral breast cancer was statistically reduced significantly for anastrozole. Time to isolated recurrence was numerically greater for anastrozole as well. The combination of both anastrozole and tamoxifen did not result in any benefits in contrast to tamoxifen alone.

Greater superiority statistically was reported for the receptor positive population, for recurrence-free survival in support of anastrozole compared to tamoxifen. Once again, the anastrozole and tamoxifen combination did not result in any benefits in contrast to tamoxifen alone in this group of patients.

Early breast cancer - Adjuvant treatment for patients being treated with adjuvant tamoxifen

In a phase III study (ABCSG 8) carried out in 2,579 postmenopausal women with early breast cancer (hormone receptor positive) having treatment with adjuvant tamoxifen, patients had a greater survival (disease-free) when changed to anastrozole treatment, in comparison with patients who continued with tamoxifen treatment.

A statistical advantage for anastrozole was time to any recurrence, time to local or distant recurrence and time to distant recurrence. These were consistent with the disease-free survival results. For contralateral breast cancer, the incidence was especially low in the two treatments, with a numerical benefit for anastrozole. The overall survival was comparable for both treatment groups.

Two other anastrozole trials that were similar (GABG/ARNO 95 and ITA) as well as a combined analysis of the studies ABCSG 8 and GABG/ARNO 95, reinforced these conclusions.

The anastrozole safety profile in all three studies were reliable and consistent with the safety profile known and instituted in post-menopausal women with early breast cancer that was hormone-receptor positive.

Study of anastrozole with the bisphosphonate risedronate (SABRE) Bone Mineral Density (BMD)

In a phase III/IV SABRE study carried out in 234 postmenopausal women with hormone receptor positive early breast cancer, the patients were organised for anastrozole treatment and were arranged into low, moderate and high-risk groups corresponding to the patient's current risk of fragility fracture. Every patient obtained treatment with calcium and vitamin D. The patients group considered low risk, received anastrozole treatment only, patients in the group considered moderate risk were randomised to anastrozole treatment with bisphosphonate or anastrozole treatment with a placebo and patients who were considered high risk received anastrozole treatment with bisphosphonate.

The main analysis over twelve months showed that patients considered moderate to high risk of fragility fracture had their bone health managed successfully by treatment with anastrozole in combination with a bisphosphonate. Bone health was evaluated by bone formation, bone mineral density and resorption markers. Furthermore, no variations in BMD were observed in the low risk group with anastrozole treatment alone and provided with calcium and vitamin D. These results were also observed in the secondary variable of efficacy of a difference from baseline in total hip BMD at twelve months.

This clinical study shows evidence that women who have early breast cancer while postmenopausal and that are arranged to have treatment with anastrozole must have their bone status managed accordingly to the treatment guidelines currently available for postmenopausal women at a comparable risk of fragility fracture.

Lipids

In the SABRE study, with patients who were treated with anastrozole only or patients who were treated with anastrozole and a bisphosphonate, there was an impartial effect on plasma lipids.

Paediatrics

In paediatric patients there have been three clinical trials conducted, two were conducted in pubertal boys with gynaecomastia and one was conducted in paediatric girls with McCune Albright Syndrome.

Gynaecomastia Study

A randomised, double-blind, multi-centre study (Trial 0006), was conducted in 80 pubertal boys (aged between eleven and eighteen years) with gynaecomastia of more than twelve months duration. The patients were treated with anastrozole 1 mg per day or a placebo for a time period of up to six months. A reduction of $\geq 50\%$ in the total breast volume assessed by an ultrasound was observed in 38.5% (15 patients out of 39) from the anastrozole treatment and 31.4% (11 patients out of 35) of the placebo treated group, (odds ratio = 1.513, 95% CI 0.496 to 4.844, $p=0.4687$).

An open-label, multiple-dose pharmacokinetic (PK) study (Trial 0001) of anastrozole 1 mg per day in 36 pubertal boys with gynaecomastia of below twelve months duration was completed. A reduction of 50% or greater in the total breast volume at six months was observed in 55.6% (20 patients out of 36) of the boys.

McCune Albright Syndrome (MAS) Study

An international, multi-centre, open-label, exploratory study (Trial 0046) was conducted of anastrozole treatment in 28 girls (aged between two and ten years) with McCune

Albright Syndrome (MAS). There was no statistically significant variation in the incidence of vaginal bleeding on days of treatment were observed. From the patients with baseline vaginal bleeding, 28% experienced a $\geq 50\%$ decrease in the incidence of bleeding days on treatment; 40% experienced a stop to bleeding over a 6-month period, and 12% experienced a stop to bleeding over a 12-month period. There was no clinically significant variations in mean ovarian volume, mean uterine volume or Tanner staging. No statistically significant variation was observed in the degree of increase in bone age on treatment in comparison to the degree during baseline. The growth rate (measured in cm per year) was significantly decreased ($p < 0.05$) from before treatment through month zero to month twelve, and from before treatment to the second six months i.e. month seven to month twelve.

In general, the assessment of adverse effects in children aged less than eighteen years of age have produced no tolerability and safety issues.

5.2 Pharmacokinetic properties

Anastrozole is absorbed rapidly and maximum plasma concentrations usually happen within two hours of taking the dose with fasting conditions. Elimination of anastrozole is slow with a plasma elimination half-life of forty to fifty hours. The intake of food decreases this rate slightly but not the amount of absorption. The minor variation in the degree of absorption is not expected to cause a clinically significant effect on steady-state plasma concentrations throughout once per day administration of anastrozole tablets. After taking anastrozole for seven days, approximately 90% to 95% of plasma steady-state concentrations are achieved. There is no evidence of dose-dependency or time-dependency of anastrozole pharmacokinetic parameters.

Pharmacokinetics of anastrozole are independent of age in women (post-menopausal).

Anastrozole was absorbed rapidly in boys with pubertal gynaecomastia and was extensively distributed. Anastrozole was also eliminated gradually with a half-life of approximately two days. The PK parameters in boys were similar to those of postmenopausal women. Anastrozole clearance was less in girls than in boys and the exposure was higher. Anastrozole in girls was extensively distributed and gradually eliminated, with a half-life of approximately 0.8 days.

Anastrozole is only bound to 40 percent of plasma proteins.

In women (post-menopausal), Anastrozole is considerably metabolised with less than 10% of the dosage excreted in the urine unaffected within seventy-two hours of taking anastrozole. The metabolism of anastrozole happens by N-dealkylation, hydroxylation and glucuronidation. The metabolites are excreted mostly via urine. A major metabolite (triazole) in plasma and urine, does not obstruct aromatase.

In volunteers (with stable hepatic cirrhosis or renal impairment), the evident oral clearance of anastrozole was in the extent observed for healthy volunteers.

5.3 Preclinical safety data

Acute toxicity

For rodents, in acute toxicity studies the median lethal dosage of anastrozole was larger than 100 mg per kg via the oral route and larger than 50 mg per kg via the

intraperitoneal route. For dogs, in an acute toxicity study the median lethal dosage was larger than 45 mg per kg via the oral route.

Chronic toxicity

Multiple dosage toxicity studies were completed in both rats and dogs. There were no no-effect levels established for anastrozole in these toxicity studies, however, the effects that were reported at the low dosage of 1 mg per kg per day and middle dosages (dog 3 mg per kg per day and rat, 5 mg per kg per day) were associated to the pharmacological or enzyme inducing anastrozole properties and were unaided by degenerative or toxic variations.

Mutagenicity

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

Reproductive toxicology

Anastrozole given through oral administration to pregnant rabbits and rats produced no teratogenic effects at dosages of up to 0.2 mg per kg per day and 1.0 mg per kg per day respectively. The observations that were reported such as placental enlargement and pregnancy failure in rats and rabbits respectively were associated to the pharmacology of anastrozole.

Anastrozole given through oral administration to female rats resulted in a high incidence of infertility at 1 mg per kg per day and an amplified pre-implantation loss at 0.02 mg per kg per day. These results were associated to the pharmacology of anastrozole and were reversed entirely following a five-week anastrozole withdrawal phase.

The survival of the offspring born to rats provided with anastrozole at 0.02 mg per kg per day and higher from day 17 of pregnancy to day 22 post-partum, was effected. These results were in relation to the pharmacological results of anastrozole on parturition. There were no adverse effects observed on the behaviour or reproductive performance of the first-generation offspring attributable to the treatment with anastrozole on the mother.

Carcinogenicity

A rat oncogenicity study over two years, resulted in an incidence increase of hepatic neoplasms and uterine stromal polyps in female rats and thyroid adenomas in male rats at the large dosage of 25 mg per kg per day only. These variations arose at a dosage which signifies 100 times greater exposure of anastrozole than happens at human therapeutic dosages, and are believed to not be clinically appropriate to the therapy of patients with anastrozole.

A mouse oncogenicity study over two years, resulted in the stimulation of benign ovarian tumours and a disruption in the incidence of lymphoreticular neoplasms with less histiocytic sarcomas in females and further deaths as a consequence of lymphomas. These variations are deemed to be mouse-specific results of aromatase inhibition and not clinically appropriate to the therapy of patients with anastrozole.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica, isopropyl alcohol, lactose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, opadry white 04F58804, purified water, sodium starch glycolate.

6.2 Incompatibilities

None known.

6.3 Shelf life

Shelf life is 36 months (3 years) from manufacture.

6.4 Special precautions for storage

Store Rolin film coated tablets at or below 25°C.

6.5 Nature and contents of container

Rolin film coated tablets are available in PVC/Al/VMCH blister strips of 10 tablets. Each carton contains 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

REX Medical Limited
PO Box 18-119
Glen Innes
Auckland 1743

Telephone: (09) 574 6060

Fax: (09) 574 6070

9 DATE OF FIRST APPROVAL

18 October 2007

10 DATE OF REVISION OF THE TEXT

19th September 2017

V2 © REX Medical Ltd

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information