APPROVED PI FOR ANASTROZOLE SANDOZ 1 MG

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

ANASTROZOLE SANDOZ 1 mg (film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Anastrozole Sandoz 1 mg film-coated tablet contains 1 mg anastrozole.

Contains sugar (lactose monohydrate 64,7 mg).

3. PHARMACEUTICAL FORM

White, round, biconvex film-coated tablet without breaking notch; embossment “A1” on one side.

Diameter: 5,7 to 6,3 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of early breast cancer in postmenopausal women.

Treatment of advanced breast cancer in postmenopausal women.

Efficacy has not been demonstrated in oestrogen receptor negative patients unless they have had a previous positive clinical response to tamoxifen.

4.2 Posology and method of administration

Adults:

Take one ANASTROZOLE SANDOZ 1 mg tablet orally once a day.

Paediatric population:

ANASTROZOLE SANDOZ 1 mg is not recommended for use in children due to insufficient data on safety and efficacy (see sections 4.4 and 5.1).

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.

4.3 Contraindications

ANASTROZOLE SANDOZ 1 mg is contraindicated in:

- patients with hypersensitivity to anastrozole or to any of the excipients listed in section 6.1
- premenopausal women
- pregnant or lactating women
- patients with severe renal impairment (creatinine clearance less than 20 ml/min)
- patients with moderate or severe hepatic disease

4.4 Special warnings and precautions for use

General:

ANASTROZOLE SANDOZ 1 mg should not be used in premenopausal women. The menopause should be defined biochemically (luteinising-hormone (LH), follicle stimulating hormone (FSH), and/or oestradiol levels) in any patient where there is doubt about

menopausal status. There are no data to support the use of ANASTROZOLE SANDOZ 1 mg with LHRH analogues.

Co-administration of tamoxifen or oestrogen-containing therapies with ANASTROZOLE SANDOZ 1 mg should be avoided as this may diminish its pharmacological action (see section 4.5 and 5.1).

Vaginal bleeding:

If bleeding persists, further evaluation should be considered.

Effect on bone mineral density:

As anastrozole lowers circulating oestrogen levels it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture (see section 4.8).

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 SANDOZ 1 mg in postmenopausal women and could be considered (see section 4.8).

Hepatic impairment:

ANASTROZOLE SANDOZ 1 mg has not been investigated in breast cancer patients with moderate or severe hepatic impairment. Exposure to anastrozole can be increased in subjects with hepatic impairment (see section 5.2); administration of ANASTROZOLE SANDOZ 1 mg in patients with moderate and severe hepatic impairment is contraindicated.

Renal impairment:

ANASTROZOLE SANDOZ 1 mg has not been investigated in breast cancer patients with severe renal impairment (creatinine clearance less than 20 ml/min). In patients with severe renal impairment, administration of ANASTROZOLE SANDOZ 1 mg is contraindicated.

Paediatric population:

ANASTROZOLE SANDOZ 1 mg is not recommended for use in children and adolescents as safety and efficacy have not been established in these groups of patients (see section 5.1).

ANASTROZOLE SANDOZ 1 mg 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 (see section 5.1). Since anastrozole reduces estradiol levels, ANASTROZOLE SANDOZ 1 mg 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.

Lactose intolerance:

ANASTROZOLE SANDOZ 1 mg contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ANASTROZOLE SANDOZ 1 mg.

ANASTROZOLE SANDOZ 1 mg contains lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

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 SANDOZ 1 mg with other medicines is unlikely to result in clinically significant medicine 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 medicines.

There were no clinically significant interactions with bisphosphonates (see section 5.1).

There is no clinical information to date on the use of ANASTROZOLE SANDOZ 1 mg in combination with other anti-cancer agents.

Co-administration of tamoxifen or oestrogen-containing therapies with ANASTROZOLE SANDOZ 1 mg should be avoided, as this may diminish its pharmacological action (see section 4.4 and 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of anastrozole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). ANASTROZOLE SANDOZ 1 mg is contraindicated during pregnancy.

Breastfeeding

There are no data on the use of anastrozole during lactation. ANASTROZOLE SANDOZ 1 mg is contraindicated during breastfeeding (see section 4.3).

Fertility

The effects of anastrozole on fertility in humans have not been studied. Studies in animals have shown reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

ANASTROZOLE SANDOZ 1 mg 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 SANDOZ 1 mg and caution should be observed when driving or operating machinery while such symptoms persist.

4.8 Undesirable effects

Side effects have been arranged according to their system organ class and the frequency of their occurrence according to the following convention:

Frequent and less frequent.

Some of the side effects may be attributed to the pharmacological action of ANASTROZOLE SANDOZ 1 mg.

The most frequently reported adverse reactions were headache, hot flushes, nausea, rash, arthralgia, joint stiffness, arthritis, and asthenia.

Metabolism and nutrition disorders:

Frequent: Anorexia, hypercholesterolemia.

Less Frequent: Hypercalcaemia (with or without an increase in parathyroid hormone).

Nervous system disorders:

Frequent: Headache, somnolence, carpal tunnel syndrome, depression

Vascular disorders:

Frequent: Hot flushes.

Gastrointestinal disorders:

Frequent: Nausea, diarrhoea, vomiting.

Hepatobiliary disorders:

Frequent: Increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase.

Less Frequent: Increases in gamma-GT and bilirubin, hepatitis.

Skin and subcutaneous tissue disorders:

Frequent: Hair thinning (alopecia), rash, allergic reactions.

Less frequent: Erythema multiforme, Stevens-Johnson syndrome, urticaria, angioedema, anaphylactoid reaction cutaneous vasculitis (including some reports of Henoch-Schönlein purpura).

Musculoskeletal and connective tissue disorders:

Frequent: Arthralgia/joint stiffness, arthritis, bone pain, osteoporosis, myalgia.

Less Frequent: Trigger finger.

Reproductive system and breasts disorders:

Frequent: Vaginal dryness, vaginal bleeding*.

* 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.

General disorders and administration site conditions:

Frequent: Asthenia.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Suspected side effects can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

Clinical experience is limited regarding over dosage of ANASTROZOLE SANDOZ 1 mg.

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 SANDOZ 1 mg that results in life threatening symptoms has not been established. Refer to section 4.8 for possible symptoms of overdosage.

There is no specific antidote to overdose and treatment should 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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 21.12 Hormone inhibitors

5.1 Pharmacodynamic properties

Mechanism of action and pharmacodynamic effects

Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. In postmenopausal women, oestradiol is produced primarily by the conversion of androstenedione to oestrone through the aromatase enzyme complex in peripheral tissue. 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, a daily dose of 1 mg of anastrozole produced oestradiol 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 an effect on cortisol or aldosterone secretion, measured before or after standard adrenocorticotrophic hormone (ACTH) challenge testing. Corticoid supplements are therefore not needed.

Clinical efficacy and safety

Advanced breast cancer

First-line therapy in postmenopausal women with advanced breast cancer

Two double-blind, controlled clinical studies of similar design (Study 1033IL/0030 and Study 1033IL/0027) were conducted to assess the efficacy of anastrozole compared with tamoxifen as first-line therapy for hormone receptor-positive or hormone receptor-unknown locally advanced or metastatic breast cancer in postmenopausal women. A total of 1021 patients were randomised to receive 1 mg of anastrozole once daily or 20 mg of tamoxifen once daily. The primary endpoints for both trials were time to tumour progression, objective tumour response rate, and safety.

For the primary endpoints, Study 1033IL/0030 showed that anastrozole had a statistically significant advantage over tamoxifen for time to tumour progression (Hazard ratio (HR) 1,42, 95 % Confidence Interval (CI) (1,11, 1,82), Median time to progression 11,1 and 5,6 months for anastrozole and tamoxifen respectively, p = 0,006); objective tumour response rates were similar for anastrozole and tamoxifen. Study 1033IL/0027 showed that anastrozole and tamoxifen had similar objective tumour response rates and time to tumour progression. Results from the secondary endpoints were supportive of the results of the primary efficacy endpoints. There were too few deaths occurring across treatment groups of both trials to draw conclusions on overall survival differences.

Second-line therapy in postmenopausal women with advanced breast cancer

Anastrozole was studied in two controlled clinical trials (Study 0004 and Study 0005) in postmenopausal women with advanced breast cancer who had disease progression following tamoxifen therapy for either advanced or early breast cancer. A total of 764 patients were randomised to receive either a single daily dose of 1 mg or 10 mg of anastrozole or megestrol acetate 40 mg four times a day. Time to progression and objective response rates were the

primary efficacy variables. The rate of prolonged (more than 24 weeks) stable disease, the rate of progression, and survival were also calculated. In both studies there were no significant differences between treatment arms with respect to any of the efficacy parameters.

Adjuvant treatment of early invasive breast cancer for hormone receptor-positive patients

In a large phase III study conducted in 9366 postmenopausal women with operable breast cancer treated for 5 years (see below), anastrozole was shown to be statistically superior to tamoxifen in disease-free survival. A greater magnitude of benefit was observed for disease free survival in favour of anastrozole versus tamoxifen for the prospectively defined hormone receptor-positive population.

Table 1 ATAC endpoint summary: 5-year treatment completion analysis

Efficacy endpoints	**Number of events (frequency)**			
	Intention-to-treat population		**Hormone-receptor-positive tumour status**	
	Anastrozole (N=3125)	**Tamoxifen (N=3116)**	**Anastrozole (N=2618)**	**Tamoxifen (N=2598)**
Disease-free survival [a]	575 (18,4)	651 (20,9)	424 (16,2)	497 (19,1)
Hazard ratio	0,87		0,83	
Two-sided 95 % CI	0,78 – 0,97		0,73 – 0,94	
p-value	0,0127		0,0049	
Distant disease-free survival [b]	500 (16,0)	530 (17,0)	370 (14,1)	394 (15,2)

Efficacy endpoints	**Number of events (frequency)**			
	Intention-to-treat population		**Hormone-receptor-positive tumour status**	
	Anastrozole (N=3125)	**Tamoxifen (N=3116)**	**Anastrozole (N=2618)**	**Tamoxifen (N=2598)**
Hazard ratio	0,94		0,93	
Two-sided 95 % CI	0,83 – 1,06		0,80 – 1,07	
p-value	0,2850		0,2838	
Time to recurrence [c]	402 (12,9)	498 (16,0)	282 (10,8)	370 (14,2)
Hazard ratio	0,79		0,74	
Two-sided 95 % CI	0,70 – 0,90		0,64 – 0,87	
p-value	0,0005		0,0002	
Time to distant re-occurrence [d]	324 (10,4)	375 (12,0)	226 (8,6)	265 (10,2)
Hazard ratio	0,86		0,84	
Two-sided 95% CI	0,74 – 0,99		0,70 – 1,00	
p-value	0,0427		0,0559	
Contra-lateral breast primary	35 (1,1)	59 (1,9)	26 (1,0)	54 (2,1)
Odds ratio	0,59		0,47	

Efficacy endpoints	**Number of events (frequency)**			
	Intention-to-treat population		**Hormone-receptor-positive tumour status**	
	Anastrozole (N=3125)	**Tamoxifen (N=3116)**	**Anastrozole (N=2618)**	**Tamoxifen (N=2598)**
Two-sided 95 % CI	0,39 – 0,89		0,30 – 0,76	
p-value	0,0131		0,0018	
Overall survival [e]	411 (13,2)	420 (13,5)	296 (11,3)	301 (11,6)
Hazard ratio	0,97		0,97	
Two-sided 95 % CI	0,85 – 1,12		0,83 – 1,14	
p-value	0,7142		0,7339	

[a] Disease-free survival includes all recurrence events and is defined as the first occurrence of loco-regional recurrence, contralateral new breast cancer, distant recurrence or death (for any reason).

[b] Distant disease-free survival is defined as the first occurrence of distant recurrence or death (for any reason).

[c] Time to recurrence is defined as the first occurrence of loco-regional recurrence, contralateral new breast cancer, distant recurrence or death due to breast cancer.

[d] Time to distant recurrence is defined as the first occurrence of distant recurrence or death due to breast cancer.

[e] Number (%) of patients who had died.

The combination of anastrozole and tamoxifen did not demonstrate any efficacy benefits in comparison with tamoxifen in all patients as well as in the hormone receptor-positive population. This treatment arm was discontinued from the study.

With an updated follow-up at a median of 10 years, long-term comparison of the treatment effects of anastrozole relative to tamoxifen were shown to be consistent with previous analyses.

Adjuvant treatment of early invasive breast cancer for hormone receptor-positive 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 who had received surgery with or without radiotherapy and no chemotherapy (see below), switching to anastrozole after 2 years adjuvant treatment with tamoxifen was statistically superior in disease-free survival when compared to remaining on tamoxifen, after a median follow-up of 24 months.

Table 2 ABCSG 8 trial endpoint and results summary

Efficacy endpoints	**Number of events (frequency)**	
	Anastrozole (N=1297)	**Tamoxifen (N=1282)**
Disease-free survival	65 (5,0)	93 (7,3)
Hazard ratio	0,67	
Two-sided 95 % CI	0,49 – 0,92	
p-value	0,014	
Time to any recurrence	36 (2,8)	66 (5,1)
Hazard ratio	0,53	

Two-sided 95 % CI	0,35 – 0,79	
p-value	0,002	
Time to distant reoccurrence	22 (1,7)	41(3,2)
Hazard ratio	0,52	
Two-sided 95 % CI	0,31 – 0,88	
p-value	0,015	
New contralateral breast cancer	7 (0,5)	15 (1,2)
Odds ratio	0,46	
Two-sided 95 % CI	0,19 – 1,13	
p-value	0,090	
Overall survival	43 (3,3)	45 (3,5)
Hazard ratio	0,96	
Two-sided 95 % CI	0,63 – 1,46	
p-value	0,840	

Two further similar trials (GABG/ARNO 95 and ITA), in one of which patients had received surgery and chemotherapy, 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.

Bone mineral density (BMD)

In the phase III/IV study (Study of Anastrozole with the Bisphosphonate Risedronate (SABRE)), 234 postmenopausal women with hormone receptor-positive early breast cancer

scheduled for treatment with anastrozole 1 mg/day were stratified to low, moderate and high risk groups according to their existing risk of fragility fracture. The primary efficacy parameter was the analysis of lumbar spine bone mass density using DEXA scanning. All patients received treatment with vitamin D and calcium. Patients in the low risk group received anastrozole alone (N = 42), those in the moderate group were randomised to anastrozole plus risedronate 35 mg once a week (N = 77) or anastrozole plus placebo (N = 77) and those in the high risk group received anastrozole plus risedronate 35 mg once a week (N = 38). The primary endpoint was change from baseline in lumbar spine bone mass density at 12 months.

The 12-month main analysis has shown that patients already at moderate to high risk of fragility fracture showed no decrease in their bone mass density (assessed by lumbar spine bone mineral density using DEXA scanning) when managed by using anastrozole 1 mg/day in combination with risedronate 35 mg once a week.

In addition, a decrease in BMD which was not statistically significant was seen in the low risk group treated with anastrozole 1 mg/day alone. 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 the use of bisphosphonates could be considered in the management of possible bone mineral loss in postmenopausal women with early breast cancer scheduled to be treated with anastrozole.

Paediatric population

Anastrozole is not indicated for use in children and adolescents. Efficacy has not been established in the paediatric populations studied. The number of children treated was too limited to draw any reliable conclusions on safety. No data on the potential long-term effects of anastrozole treatment in children and adolescents are available (see also section 5.3).

5.2 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 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, and accumulation is 3- to 4-fold. There is no evidence of time or dose-dependency of anastrozole pharmacokinetic parameters.

Anastrozole pharmacokinetics are independent of time or dose, or the age of 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.

Renal or hepatic impairment:

The apparent clearance (CL/F) of anastrozole, following oral administration, was approximately 30 % lower in volunteers with mild 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 < 30 ml/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. In patients with severe renal impairment, administration of anastrozole should be performed with caution (see section 4.4).

Paediatric population:

In boys with pubertal gynaecomastia (10 – 17 years), anastrozole was rapidly absorbed, was widely distributed, and was eliminated slowly with a half-life of approximately 2 days. Clearance of anastrozole was lower in girls (3 – 10 years) than in the older boys and exposure higher. Anastrozole in girls was widely distributed and slowly eliminated.

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 for the indicated population.

Acute toxicity

In animal studies toxicity was only seen at high doses. 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

In animal studies adverse effects were only seen at high doses. Multiple dose toxicity studies utilised 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.

Reproductive toxicology

In a fertility study weanling male rats were dosed orally with 50 or 400 mg/l anastrozole via their drinking water for 10 weeks. Measured mean plasma concentrations were 44,4 (±14,7) ng/ml and 165 (±90) ng/ml respectively. Mating indices were adversely affected in both dose groups, whilst a reduction in fertility was evident only at the 400 mg/l dose level. The reduction was transient as all mating and fertility parameters were similar to control group values following a 9 week treatment-free recovery period.

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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline, hydroxypropylcellulose, hydroxypropylmethyl cellulose, lactose monohydrate, macrogol 4000, magnesium stearate, Opadry II white, silica colloidal anhydrous, sodium starch glycollate and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove from container until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

Aluminium foil/PVC, clear and colourless blisters. One blister contains 10 film-coated tablets.

One carton contains three blisters.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

The Novartis Building

Magwa Crescent West

Waterfall City, Jukskei View

Gauteng, 2090

South Africa

8. REGISTRATION NUMBER

43/21.12/0073

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 August 2011

10. DATE OF REVISION OF THE TEXT

02 September 2022

Additional countries registration details:

Country	***Product name***	***Scheduling status (or Category of distribution)***	***Registration number***
Botswana	Anastrozole Sandoz 1 mg	S2	BOT1703051
Namibia	Anastrozole Sandoz 1 mg	NS2	13/21.12/0064

ATC Code: L02BG03 – Aromatase inhibitors

Name and address of manufacturer:

Salutas Pharma GmbH,

Otto-von-Guericke-Allee-1

D-39179,Barleben,

Germany

[1]Company Reg. No.: 1990/001979/07