SUMMARY OF PRODUCT CHARACTERISTICS

ANASOMA 1

Anastrozole Tablets 1 mg

Rx Only

STRENGTH: 1 mg

PHARMACEUTICAL FORM: Film coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each film coated tablet contains:
Anastrozole Ph.Eur. …….1 mg

PHARMACEUTICAL FORM
Anastrozole Tablets 1 mg
White, biconvex film-coated, tablet debossed with 'A1' on one side and plain on the other side.

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

POSOLOGY AND METHOD OF ADMINISTRATION
Posology
The recommended dose of Anastrozole for adults including the elderly is one 1 mg tablet once a day.

Special populations
Paediatric population
Anastrozole is not recommended for use in children and adolescents.

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

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

Method of administration
Anastrozole should be taken orally.

CONTRAINDICATIONS
Anastrozole is contraindicated in:
- premenopausal women.
- pregnant or lactating women.
- patients with severe renal impairment (creatinine clearance less than 20ml/min).
- patients with moderate or severe hepatic disease.
- patients with known hypersensitivity to anastrozole or to any of the excipients as listed under "List of excipients".

Oestrogen-containing therapies should not be co-administered with Anastrozole as they would negate its pharmacological action.
Concurrent tamoxifen therapy.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
Anastrozole is not recommended for use in children as safety and efficacy have not been established in this group of patients.

The menopause should be defined biochemically in any patient where there is doubt about menopausal status.

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

Women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry e.g. DEXA scanning at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored.

There are no data available for the use of anastrozole with LHRH analogues. This combination should not be used outside clinical trials.

As Anastrozole lowers circulating oestrogen levels it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture. The use of bisphosphonates may stop further bone mineral loss caused by Anastrozole in postmenopausal women and could be considered.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Antipyrine and cimetidine clinical interaction studies indicate that the co-administration of ANASTROZOLE with other drugs is unlikely to result in clinically significant drug 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 drugs. There were no clinically significant interactions with bisphosphonates

Oestrogen-containing therapies should not be co-administered with Anastrozole as they would negate its pharmacological action.

Tamoxifen should not be co-administered with Anastrozole, as this may diminish its pharmacological action (see section 4.3). Co-administration of anastrozole and tamoxifen in breast cancer patients reduced anastrozole plasma concentration by 27% compared to those achieved with anastrozole alone; however, the co-administration did not affect the pharmacokinetics of tamoxifen or N-desmethyl tamoxifen.

PREGNANCY AND LACTATION
ANASTROZOLE is contraindicated in pregnant or lactating women.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Anastrozole 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.

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 (ATAC Study).

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%)	*Reproductive system and breast*	• Vaginal dryness, mainly mild or moderate in nature. • Vaginal bleeding, mainly mild or moderate in nature**
	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.
	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.
	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)
	Hepatobiliary 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 multiformae • 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 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 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.

***Since cutaneous vasculitis and Henoch-Schönlein purpura was not observed in ATAC, the frequency category for these events can be considered as 'Rare' (≥ 0.01% and < 0.1%) based on the worst value of the point estimate.

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

Adverse effects	Anastrozole(N=3092)	Tamoxifen (N=3094)
Hot flushes	1104 (35.7%)	1264 (40.9%)
Joint pain/stiffness	1100 (35.6%)	911 (29.4%)
Mood disturbances	597 (19.3%)	554 (17.9%)
Fatigue/asthenia	575 (18.6%)	544 (17.6%)
Nausea and vomiting	393 (12.7%)	384 (12.4%)
Fractures	315 (10.2%)	209 (6.8%)
Fractures of the spine, hip, or wrist/Colles	133 (4.3%)	91 (2.9%)

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• Wrist/Colles fractures	67 (2.2%)	50 (1.6%)
• Spine fractures	43 (1.4%)	22 (0.7%)
• Hip fractures	28 (0.9%)	26 (0.8%)
Cataracts	182 (5.9%)	213 (6.9%)
Vaginal bleeding	167 (5.4%)	317 (10.2%)
Ischaemic cardiovascular disease	127 (4.1%)	104 (3.4%)
• Angina pectoris	71 (2.3%)	51 (1.6%)
• Myocardial infarct	37 (1.2%)	34 (1.1%)
• Coronary artery disorder	25 (0.8%)	23 (0.7%)
• Myocardial ischaemia	22 (0.7%)	14 (0.5%)
Vaginal discharge	109 (3.5%)	408 (13.2%)
Any venous thromboembolic event	87 (2.8%)	140 (4.5%)
• Deep venous thromboembolic events including PE	48 (1.6%)	74 (2.4%)
Ischaemic cerebrovascular events	62 (2.0%)	88 (2.8%)
Endometrial cancer	4 (0.2%)	13 (0.6%)

The ATAC trial data showed that patients receiving Anastrozole had an increase in joint disorders (including arthritis, arthrosis, and arthralgia) compared with patients receiving tamoxifen. Patients receiving Anastrozole had an increase in the incidence of fractures (including fractures of spine, hip and wrist) compared with patients receiving tamoxifen. These differences were statistically significant. Fracture rates of 22 per 1000 patient-years and 15 per 1000 patient-years were observed for the Anastrozole and tamoxifen groups, respectively, after a median follow up of 68 months. The observed fracture rate for Anastrozole is similar to the range reported in age-matched postmenopausal populations. It has not been determined whether the rates of fracture and osteoporosis seen in ATAC in patients on anastrozole treatment reflect a protective effect of tamoxifen, a specific effect of anastrozole, or both.

The incidence of osteoporosis was 10.5% in patients treated with Anastrozole and 7.3% in patients treated with tamoxifen.

Patients receiving Anastrozole had a decrease in hot flushes, vaginal bleeding, vaginal discharge, endometrial cancer, venous thromboembolic events (including deep venous thrombosis) and ischaemic cerebrovascular events compared with patients receiving tamoxifen. These differences were statistically significant.

Results from the ATAC trial bone substudy, at 12 and 24 months demonstrated that patients receiving Anastrozole had a mean decrease in both lumbar spine and total hip bone mineral density (BMD) compared to baseline. Patients receiving tamoxifen had a mean increase in both lumbar spine and total hip BMD compared to baseline.

Slight increases in total cholesterol have also been observed in clinical trials with ANASTROZOLE, although the clinical significance has not been determined.

Overdose
There is limited clinical experience of accidental overdosage. In animal studies, anastrozole demonstrated low acute toxicity. Clinical trials have been conducted with various dosages of Anastrozole, up to 60mg in a single dose given to healthy male volunteers and up to 10mg daily given to postmenopausal women with advanced breast cancer; these dosages were well tolerated. A single dose of Anastrozole that results in life-threatening symptoms has not been established. There is no specific antidote to 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.

PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Enzyme inhibitors, ATC Code: L02B G03

Pharmacodynamic properties
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 1mg 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 10mg do not have any effect on cortisol or aldosterone secretion, measured before or after standard adrenocorticotrophic hormone (ACTH) challenge testing. Corticoid supplements are therefore not needed.

PHARMACOKINETIC PROPERTIES
Absorption
Absorption of anastrozole is rapid and maximum plasma concentrations typically occur within two hours of dosing (under fasted conditions). Food slightly decreases the rate but not the extent of absorption. The small change in the rate of absorption is not expected to result in a clinically significant effect on steady-state plasma concentrations during once daily dosing of Anastrozole tablets. Approximately 90 to 95% of plasma anastrozole steady-state concentrations are attained after 7 daily doses. There is no evidence of time or dose-dependency of anastrozole pharmacokinetic parameters.

Anastrozole pharmacokinetics are independent of age in postmenopausal women.

Distribution
Anastrozole is only 40% bound to plasma proteins.

Elimination
Anastrozole is eliminated slowly with a plasma elimination half-life of 40 to 50 hours. Anastrozole is extensively metabolised by postmenopausal women with less than 10% of the dose excreted in the urine unchanged within 72 hours of dosing. Metabolism of anastrozole occurs by N-dealkylation, hydroxylation and glucuronidation. The metabolites are excreted primarily via the urine. Triazole, the major metabolite in plasma, does not inhibit aromatase.

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

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

Chronic toxicity
Multiple dose toxicity studies 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 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 significant 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 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.

PHARMACEUTICAL PARTICULARS
List of excipients
Lactose monohydrate, Sodium Starch Glycolate, Povidone K-30, Isopropyl Alcohol, Magnesium Stearate, Opadry white, Purified Water.

Opadry White contains: Hypromellose, Titanium Dioxide, Macrogol

INCOMPATIBILITIES
Not applicable.

SHELF LIFE
Please refer outer package for expiry date.

SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C. Store in original pack and protect from light.

NATURE AND CONTENTS OF CONTAINER
250µ clear PVC film width 212 mm as the forming material and 25µ Aluminium foil with 7gsm heat seal lacquer coating as the lidding material.

Blister of 10 tablets (3 x 10's Blister)

Product Owner

AUROBINDO
Aurobindo Pharma Limited,
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