For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

Anastrozole Tablets 1 mg
ANAST 1

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1. Name of the medicinal product

Anastrozole Tablets 1 mg

2. Qualitative and quantitative composition

Anastrozole Tablets 1 mg
Each film coated tablet contains:
Anastrozole Ph.Eur. 1 mg

3. Pharmaceutical form

White to off white, round, biconvex, film coated tablets with "AHI" debossing on one side and plain on other side.

4. Clinical particulars

4.1 Therapeutic indications

Anastrozole is indicated for adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer.

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.

4.2 Posology and method of administration

Adults including elderly	: One 1 mg tablet to be taken orally once a day
Children	:Anastrozole Tablets is not recommended for use in children
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 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 referenced on the carton.

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

4.4 Special warnings and precautions for use

Anastrozole Tablets 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 Tablets 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 Tablets 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 Tablets in postmenopausal women and could be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Antipyrine and cimetidine clinical interaction studies indicate that the co-administration of Anastrozole Tablets 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 Tablets who also received other commonly prescribed drugs. There were no clinically significant interactions with biphosphonates .

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

Tamoxifen should not be co-administered with Anastrozole Tablets, as this may diminish its pharmacological action. 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-desmethyltamoxifen.

4.6 Pregnancy and lactation

Anastrozole Tablets are contraindicated in pregnant or lactating women.

4.7 Effects on ability to drive and use machines

Anastrozole is unlikely to impair the ability to drive and use machines. 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 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	Vascular	• Hot flushes, mainly mild or moderate in nature.
(≥ 10%)	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 or moderate in nature. • Hypercholesterolaemia, mainly mild or moderate in nature.
	Musculoskeletal and	• Bone pain

	connective tissue disorders	• Myalgia
Uncommon (≥ 0.1% and <1%)	Metabolism and nutrition Hepatobiliary disorders Skin and subcutaneous tissue Musculoskeletal and connective tissue disorders	• Hypercalcaemia (with or without an increase in parathyroid hormone) • Increases in gamma-GT and bilirubin • Hepatitis • Urticaria • 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 Tablets. 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.

Table 2 Pre-specified adverse events in postmenopausal women with operable breast cancer treated for 5 years from the ATAC

Adverse events	**Anastrozole (N=3,092)**	**Tamoxifen (N=3,094)**
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%)

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 Tablets had an increase in joint disorders (including arthritis, arthrosis, and arthralgia) compared with patients receiving tamoxifen. Patients receiving Anastrozole Tablets 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 Tablets 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 Tablets 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 Tablets, although the clinical significance has not been determined.

4.9 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 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 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Enzyme inhibitors, ATC code: L02B G03 (Enzyme inhibitors)

Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. In postmenopausal women, estradiol is produced primarily from the conversion of androstenedione to estrone through the aromatase enzyme complex in peripheral tissues. Estrone is subsequently converted to estradiol. Reducing circulating estradiol 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 estradiol suppression of greater than 80% using a highly sensitive assay.

Anastrozole does not possess any progestogenic, androgenic, or estrogenic activity.

Daily doses of Anastrozole up to 10 mg do not have any effect on cortisol or aldosterone secretion, measured before or after standard adrenocorticotropic hormone (ACTH) challenge testing. Corticoid supplements are therefore not needed.

Primary adjuvant treatment of early breast cancer

In a large phase III study conducted in 9366 postmenopausal women with operable breast cancer treated for 5 years, Anastrozole Tablet 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 Tablet versus tamoxifen for the prospectively defined hormone receptor positive population.

Anastrozole Tablet was statistically superior to tamoxifen in time to recurrence. The difference was of greater magnitude than in disease free survival for both the Intention-To-Treat (ITT) population and hormone receptor positive population. Anastrozole Tablet was statistically superior to tamoxifen in terms of time to distant recurrence.

The incidence of contralateral breast cancer was statistically reduced for Anastrozole Tablet compared to tamoxifen. Following 5 years of therapy, anastrozole is at least as

effective as tamoxifen in terms of overall survival. However, due to low death rates, additional follow-up is required to determine more precisely the long-term survival for anastrozole relative to tamoxifen. With 68 months median follow-up, patients in the ATAC study have not been followed up for sufficient time after 5 years of treatment, to enable a comparison of long-term post treatment effects of Anastrozole Tablet relative to tamoxifen.

ATAC endpoint summary: 5-year treatment completion analysis

Efficacy endpoints	**Number of events (frequency)**			
	Intention-to-treat population		**Hormone-receptor-positive tumour status**	
	Anastrozole Tablet (N=3125)	**Tamoxifen (N=3116)**	**Anastrozole Tablet (N=2618)**	**Tamoxifen (N=2598)**
Disease-free survivala	575 (18.4)	651 (20.9)	424 (16.2)	497 (19.1)
Hazard ratio	0.87		0.83	
2-sided 95% CI	0.78 to 0.97		0.73 to 0.94	
p-value	0.0127		0.0049	
Distant disease-free survivalb	500 (16.0)	530 (17.0)	370 (14.1)	394 (15.2)
Hazard ratio	0.94		0.93	
2-sided 95% CI	0.83 to 1.06		0.80 to 1.07	
p-value	0.2850		0.2838	
Time to recurrencec	402 (12.9)	498 (16.0)	282 (10.8)	370 (14.2)
Hazard ratio	0.79		0.74	
2-sided 95% CI	0.70 to 0.90		0.64 to 0.87	
p-value	0.0005		0.0002	
Time to distant recurrenced	324 (10.4)	375 (12.0)	226 (8.6)	265 (10.2)
Hazard ratio	0.86		0.84	
2-sided 95% CI	0.74 to 0.99		0.70 to 1.00	
p-value	0.0427		0.0559	
Contralateral breast primary	35 (1.1)	59 (1.9)	26 (1.0)	54 (2.1)
Odds ratio	0.59		0.47	
2-sided 95% CI	0.39 to 0.89		0.30 to 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	
2-sided 95% CI	0.85 to 1.12		0.83 to 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 have died.

When anastrozole and tamoxifen were co-administered, the efficacy and safety were similar to tamoxifen when given alone, irrespective of hormone receptor status. The exact mechanism of this is not yet clear. It is not believed to be due to a reduction in the degree of oestradiol suppression produced by Anastrozole Tablet.

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 Tablet 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 Tablet alone (N=42), those in the moderate group were randomised to Anastrozole Tablet plus risedronate 35 mg once a week (N=77) or Anastrozole Tablet plus placebo (N=77) and those in the high risk group received Anastrozole Tablet 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 Tablet 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 Tablet 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 should be considered in the management of possible bone mineral loss in postmenopausal women with early breast cancer scheduled to be treated with Anastrozole Tablet.

Lipids

In the SABRE study there was a neutral effect on plasma lipids in those patients treated with Anastrozole Tablet plus risedronate.

5.2 Pharmacokinetic properties

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 dosesThere is no evidence of time or dose-dependency of anastrozole pharmacokinetic parameters.
Anastrozole pharmacokinetics are independent of age in postmenopausal women.
Anastrozole is only 40% bound to plasma proteins.
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.
The apparent oral clearance of anastrozole in volunteers with stable hepatic cirrhosis or renal impairment was in the range observed in healthy volunteers.

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/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 utilized rats and dogs. No no-effect levels were established for anastrozole in the toxicity studies, but those effects that were observed at the low 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

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

Lactose monohydrate
Povidone K-30
Sodium starch Glycolate (Type A)
Magnesium stearate
Film-coating: Hypromellose (E5), Macrogol 300 (PEG) & Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Anastrozole Tablets are packed in PVC/PVDC-Alu blisters with pack size of 3 x 10 tablets packed in a box.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Name and Address of Manufacturer:

Manufactured by:
Intas Pharmaceuticals Ltd.
Plot Numbers 457-458 & 191/218P
Sarkhej-Bavla Highway, Matoda, Sanand,
Ahmedabad, Gujarat-382210, India.

8. Name and Address of Product Registrant

Accord Healthcare Private Limited
6 Shenton Way, OUE Downtown #38-01
Singapore, 068809

9. Date of revision of text

January 2023