IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0585/036/001
Case No: 2044112

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Pliva Pharma Limited

Vision House, **Bedford Road**, **Petersfield**, **Hampshire GU32 3QB**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Anastrozole 1mg Film-coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **24/07/2009** until **23/07/2014**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Anastrozole 1mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1mg of anastrozole

Excipient(s):
Each tablet contains 48.94 mg of lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Description:

White or almost white, round, biconvex, film-coated tablet, embossed with 'AA' on one side and '1' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of advanced breast cancer in postmenopausal women.

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

Adjuvant treatment of postmenopausal women with hormone receptor-positive early invasive breast cancer.

Adjuvant treatment of early breast cancer in hormone receptor-positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.

4.2 Posology and method of administration

Adults including the elderly: One 1 mg tablet to be taken orally once a day

Children and adolescents: 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 1 mg Film-coated Tablets are contraindicated in:
- patients with known hypersensitivity to anastrozole or to any of the excipients as referenced in section 6.1.
- premenopausal women
- pregnant or lactating women (see section 4.6)
- patients with severe renal impairment (creatinine clearance less than 20 ml/min) (see section 4.4).
- patients with moderate or severe hepatic disease (see section 4.4)
- oestrogen-containing therapies should not be co-administered with anastrozole as they would negate its pharmacological action
- concurrent tamoxifen therapy (see section 4.5)

4.4 Special warnings and 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 hormonal 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 20 ml/min) (see section 4.3).

Women with osteoporosis or at risk of osteoporosis, should have their bone mineral 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. Adequate data to show the effect of bisphosphonates on bone mineral density loss caused by anastrozole, or their utility when used prophylactically, are not currently available.

This medicine contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Anastrozole inhibited cytochrome P450, 1A2, 2C8/9 and 3A4 in vitro, but a clinical interaction study with warfarin indicated that anastrozole at a 1 mg dose does not significantly inhibit the metabolism of substances that are metabolized via cytochrome P450.

No clinically significant interactions between anastrozole and bisphosphonates have been identified. 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).

4.6 Pregnancy and lactation

Anastrozole is contra-indicated in pregnant or lactating women (see section 4.3).

Pregnancy
There are no adequate data on the use of anastrozole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
Anastrozole is contraindicated in pregnant women.

Lactation
It is unknown whether anastrozole is excreted in human milk. Anastrozole is contraindicated in lactating women.

4.7 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.

4.8 Undesirable effects

Adverse events observed with anastrozole are classified in body systems and listed below as 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); very rare (<1/10,000), not known (cannot be estimated from the available data):

Nervous system disorders	Uncommon	Somnolence, mainly mild or moderate in nature
	Common	Headache, mainly mild or moderate in nature Carpal tunnel syndrome
Gastrointestinal disorders	Uncommon	Vomiting, mainly mild or moderate in nature
	Common	Nausea, mainly mild or moderate in nature Diarrhoea, mainly mild or moderate in nature
Hepatobiliary disorders	Common	Increases in alkaline phosphates, alanine aminotransferase and aspartate aminotransferase
	Uncommon	Elevated gamma-GT and bilirubin Hepatitis
Skin and subcutaneous tissue disorders	Very rare	Erythema multiforme Stevens-Johnson syndrome Allergic reactions including angioedema, urticaria and anaphylaxis
	Common	Hair thinning, mainly mild or moderate in nature Rash, mainly mild or moderate in nature
Musculoskeletal, connective tissue and bone disorders	Common	Joint pain/stiffness, mainly mild or moderate in nature
Metabolism and nutrition disorders	Uncommon	Anorexia, mainly mild in nature Hypercholesterolaemia, mainly mild or moderate in nature
Vascular disorders	Very common	Hot flushes, mainly mild or moderate in nature

General disorders and administration site conditions	Common	Asthenia, mainly mild or moderate in nature
Reproductive system and breast disorders	Uncommon	Vaginal bleeding, mainly mild or moderate in nature*
	Common	Vaginal dryness, mainly mild or moderate in nature

*Vaginal bleeding has been reported uncommonly, 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.

As anastrozole lowers circulating oestrogen levels, it may cause a reduction in bone mineral density placing some patients at a higher risk of fracture (see section 4.4).

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 events	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%)
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%)

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.

4.9 Overdose

There is limited clinical experience of accidental overdose. 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 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 overdose 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 of 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: Antineoplastic and immunomodulating agents - Endocrine therapy - Hormone antagonists and related agents - Enzyme inhibitors, ATC Code: L02B G03

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 level 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 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 needed.

Primary adjuvant treatment of early breast cancer
In a large phase III study conducted in 9366 postmenopausal women with operable breat cancer treatment for 5 years, 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. Anastrozole was statistically superior to tamoxifen in time to recurrence. The difference was of even greater magnitude than in disease-free survival for both the Intention To Treat (ITT) population and hormone receptor positive population. Anastrozole was statistically superior to tamoxifen in terms of time to distant recurrence. The incidence of contralateral breast cancer was statistically reduced for anastrozole 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 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 (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			
2-sided 95% CI		0.78 to 0.97			0.73 to 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)	
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 recurrence [c]	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 recurrence [d]	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 occurence 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 occurence of distant recurrence or death (for any reason).
c Time to recurrence is defined as the first occurence of loco-regional recurrence, contralateral new breast cancer, distant recurrence of 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.

As with all treatment decisions, women with breast cancer and their physician should assess the relative benefits and risks of the treatment.

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 estradiol suppression produced by anastrozole.

Adjuvant treatment of early breast cancer for patients being treated with adjuvant tamoxifen
In a phase III trial (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, 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.

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.

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	067	
2-sided 95% CI	0.49 to 0.92	
p-value	0.014	
Time to any recurrence	36 (2.8)	66 (5.1)
Hazard ratio	0.53	
2-sided 95% CI	0.35 to 0.79	
p-value	0.002	
Time to local or distant recurrence	29 (2.2)	51 (4.0)
Hazard ratio	0.55	
2-sided 95% CI	0.35 to 0.87	
p-value	0.011	
Time to distant recurrence	22 (1.7)	41(3.2)
Hazard ratio	0.52	
2-sided 95% CI	0.31 to 0.88	

p-value			0.015			
New contralateral breast cancer		7 (0.5)			15 (1.2)	
Odds ratio			0.46			
2-sided 95% CI			0.19 to 1.13			
p-value			0.090			
Overall survival		43(3.3)			45 (3.5)	
Hazard ratio			0.96			
2-sided 95% CI			0.63 to 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.

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 doses. There is no evidence of time or dose-dependency of anastrozole pharmacokinetic parameters.

Anastrozole pharmacokinetics are independent of age in postomenopausal women.

Pharmacokinetics have not been studied in children.

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 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 occured 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

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Povidone K25
Sodium laurilsulfate
Silica, colloidal anhydrous
Starch, Pregelatinized (maize starch)
Croscarmellose sodium
Magensium stearate

Coating:
Hypromellose E464
Lactose monohydrate
Titanium dioxide E171
Marcogol 4000
Sodium citrate dihydrate E331(c)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

2 years

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

PVC/PVdC/Al blister
Pack sizes: 28,30,100 and hospital packs of 3 x 28 and 3 x 30

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Pliva Pharma Limited
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8 MARKETING AUTHORISATION NUMBER

PA585/36/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th July 2009

10 DATE OF REVISION OF THE TEXT