Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Anastrozole 1mg Tablets

UK/H/911/001/DC

Teva UK Ltd

Medicines and Healthcare products Regulatory Agency

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Teva UK Ltd a Marketing Authorisation (licence) for the medicinal product Anastrozole 1 mg Film-coated Tablets (Product Licence number: 00289/0966). This medicine is available on prescription only.

Anastrozole 1 mg Film-coated Tablets are used to treat breast cancer in women who have had their menopause. Many breast cancers need the hormone oestrogen to grow. In women who have had their menopause, the main source of oestrogen comes from turning a type of hormone called androgen into oestrogen. This process is carried out by an enzyme called aromatase. Anastrozole 1 mg Film-coated Tablets inhibit aromatase and so reduces the amount of oestrogen in the body.

The data submitted in support of the application for Anastrozole 1 mg Film-coated Tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about decentralised procedure

Name of the product in the Reference Member State	Anastrozole 1 mg Tablets
Type of application (Eudratrack details)	Level 1 Abridged Level 2 Initial Level 3 10.1 Level 4 Chemical substance Level 5 Prescription only
Name of the active substance (INN)	Anastrozole
Pharmacotherapeutic classification (ATC code)	Hormone antagonists (LO2BG03)
Pharmaceutical form and strength	Tablet, 1 mg
Reference numbers for the Mutual Recognition Procedure	UK/H/911/001/DC
Reference Member State	United Kingdom
Member States concerned	AT, BE, CZ, DE, DK, EE, ED, FI, FR, HU, IE, IT, LT, LU, LV, NL, NO, PL, PT, SE, SI, SK
Date of start of the procedure	31 July 2006
End date of decentralised procedure	19 August 2007
Marketing Authorisation Number	PL 00289/0966
Name and address of the authorisation holder	Teva UK Ltd Brampton Road, Hampden Park Eastbourne, East Sussex, BN22 9AG

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Anastrozole 1 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg of anastrozole.
Excipients:
Each tablet contains 87 mg of lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White to off white, film coated round shaped tablet. One side of the tablet debossed with the number "93". The other side of the tablet debossed with the number "A10".

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.

4.2 Posology and method of administration

Adults including the elderly	One 1 mg tablet to be taken orally once a day
Children	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 20 ml/min).
- patients with moderate or severe hepatic disease.
- patients with hypersensitivity to anastrozole or to any of the excipients as referenced in section 6.1.

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).

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. 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 product contains lactose. Patients with rare hereditary problems of galactose intolerance, the 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 metabolised via cytochrome P450.

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

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 contraindicated in pregnant or 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

Very common (≥1/10)	*Vascular disorders*	Hot flushes, mainly mild or moderate in nature
Common (≥1/100 to < 1/10)	*Nervous system disorders*	Headache, mainly mild or moderate in nature
	Gastrointestinal disorders	Nausea, mainly mild or moderate in nature Diarrhoea, mainly mild or moderate

		in nature
	Skin and subcutaneous tissue disorders	Hair thinning, mainly mild or moderate in nature Rash, mainly mild or moderate in nature
	Musculoskeletal and connective tissue disorders	Joint pain/stiffness, mainly mild or moderate in nature
	General disorders and administration site conditions	Asthenia, mainly mild or moderate in nature
	Reproductive system and breast disorders	Vaginal dryness, mainly mild or moderate in nature
Uncommon (≥ 1/1,000 to <1/100)	*Nervous system disorders*	Somnolence, mainly mild or moderate in nature
	Gastrointestinal disorders	Vomiting, mainly mild or moderate in nature
	Metabolism and nutrition disorders	Anorexia, mainly mild in nature Hypercholesterolaemia, mainly mild or moderate in nature
	Reproductive system and breast disorders	Vaginal bleeding, mainly mild or moderate in nature*
Very rare (<1/10,000)	*Skin and subcutaneous tissue disorders*	Erythema multiforme Stevens-Johnson syndrome Allergic reactions including angioedema, urticaria and anaphylaxis

*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).

Elevated gamma-GT and alkaline phosphatase have been reported uncommonly (≥0.1% and <1%). A causal relationship for these changes has not been established.

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%)
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 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. 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 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 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.
In a large phase III study conducted in 9366 postmenopausal women with operable breast cancer treated 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	35 (1.1)	59 (1.9)	26 (1.0)	54 (2.1)

breast primary				
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 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 Anastrazole 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 Anastrazole, 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 Anastrazole. Overall survival was similar for the two treatment groups.

ABCSG 8 trial endpoint and results summary		
Efficacy endpoints	Number of events (frequency)	
	Anastrazole (N=1297)	Tamoxifen (N=1282)
Disease-free survival	65 (5.0)	93 (7.3)
Hazard ratio	0.67	
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	29 (2.2)	51 (4.0)

recurrence		
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 The Anastrazole 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. 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. 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 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

Core

Lactose monohydrate
Magnesium stearate (E572)
Povidone K-30
Sodium starch glycolate type A

Coating

Hypromellose (E464)
Macrogol 400 and macrogol 6000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
30 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Transparent PVC/PVdC aluminium blisters.
Pack sizes:
1, 20, 28, 30, 30 (3 x 10), 56, 60, 84, 90, 98, 100 & 300 film-coated tablets.
Hospital packs of 84 film-coated tablets.
Hospital unit dose: 10 (10 x 1), 50 (50 x 1) film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
TEVA UK Limited, Eastbourne, BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/0966

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/02/2008

10 DATE OF REVISION OF THE TEXT
05/02/2008

Module 3

Product Information Leaflet

ANASTROZOLE 1 mg FILM-COATED TABLETS

PACKAGE LEAFLET: INFORMATION FOR THE USER

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:

1 WHAT ANASTROZOLE IS AND WHAT IT IS USED FOR

- Anastrozole belongs to a group of medicines called aromatase inhibitors. Anastrozole works by interfering with the action of an enzyme called aromatase, which affects the level of certain female sex hormones such as oestrogens.
- Anastrozole is used in the treatment of advanced breast cancer in post-menopausal women.

2 BEFORE YOU TAKE ANASTROZOLE

Do NOT take Anastrozole:
- If you are allergic (hypersensitive) to anastrozole or any other of the ingredients of this medicine
- If you have not yet had the menopause
- If you are pregnant or breast-feeding
- If you have severe kidney problems
- If you have moderate or severe liver disease
- If you are taking medicines that contain oestrogen (see also 'Taking other medicines', below)
- If you are taking tamoxifen (see also 'Taking other medicines', below).

Take special care with Anastrozole:
Tell your doctor before you start to take this medicine if you:
- Have osteoperosis or have had any condition that affects the strength of your bones. Anastrozole lowers the levels of female hormones and this may lead to a loss of the mineral content of bones, which might decrease their strength. You may have to have bone density tests during treatment. Your doctor can give you medicine to prevent or treat the bone loss.
- Are taking LHRH analogues (medicines used to treat breast cancer, certain gynaecological problems or infertility). No studies have been done on the combination of LHRH analogues and anastrozole. Therefore, anastrozole and LHRH analogues should not be used in combination.
- If you are unsure whether or not you have gone through menopause yet. Your doctor should check your hormone levels.

Taking other medicines
You should not take Anastrozole if you are taking any of the following (see also 'Do NOT take Anastrozole', above):
- Medicines that contain oestrogen
- Tamoxifen, another breast cancer treatment.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription.

Pregnancy and breast-feeding
Anastrozole should not be taken if you are pregnant or breast-feeding.

Driving and using machines
Anastrozole may make you feel tired and sleepy. If you experience these symptoms you should not drive or operate machinery.

Important information about some of the ingredients of Anastrozole
Anastrozole contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3 HOW TO TAKE ANASTROZOLE

Always take Anastrozole exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults including the elderly:
Take one tablet daily. Swallow with a glass of water.

Children:
Anastrozole is not recommended for children.

If you take more Anastrozole than you should
If you (or someone else) swallow a lot of the tablets all together, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately. Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.

If you stop taking Anastrozole
Do not stop taking your tablets even if you are feeling well, unless your doctor tells you.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 POSSIBLE SIDE EFFECTS

Like all medicines, Anastrozole can cause side effects, although not everybody gets them.
If you experience the following, stop taking Anastrozole and tell your doctor immediately or go to the casualty department of the nearest hospital:
- A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing).

This is a serious but very rare side effect. You may need urgent medical attention or hospitalisation.

The following side effects have been reported at the approximate frequencies shown:

Very common (affecting more than one person in 10):
- Hot flushes.

Common (affecting fewer than one person in 10 but more than one person in 100):
- Lethargy
- Joint pain or stiffness
- Vaginal dryness
- Hair thinning
- Rash
- Feeling sick, diarrhoea
- Headache.

Uncommon (affecting fewer than one person in 100 but more than one person in 1,000):
- Vaginal bleeding, mainly during the first few weeks of treatment, after changing from existing hormonal therapy. It is important to tell your doctor immediately if you have any unusual (persisting) vaginal bleeding, or menstrual irregularities, when you are taking Anastrozole or anytime afterwards.
- Loss of appetite
- High cholesterol levels
- Vomiting
- Sleepiness.

Very rare (affecting fewer than one person in 10,000):
- Pink/red rash that may have a clear centre
- Blistering of the skin, mouth, eyes and genitals (Stevens-Johnson syndrome)
- Allergic reactions including nettle rash.

Other possible side effects:
Anastrozole lowers oestrogen levels, this may cause reduction in the bone mineral content that can decrease bone strength and in some cases may result in fractures.
If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5 HOW TO STORE ANASTROZOLE

Keep out of the reach and sight of children.
Do not use Anastrozole after the expiry date which is stated on the outer packaging after 'EXP'. The expiry date refers to the last day of that month.
This medicinal product does not require any special storage conditions.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

What Anastrozole contains:
- The active ingredient is anastrozole. Each film-coated tablet contains 1 mg anastrozole.
- The other ingredients are:
  tablet core: lactose monohydrate, magnesium sterate (E572), povidone K-30, sodium starch glycolate type A
  coating: hypermellose (E464), macrogol 400 and 6000 and titanium dioxide (E171).

What Anastrozole looks like and contents of the pack:
- Anastrozole 1 mg Film-Coated Tablets are white to off white, round tablets. One side of the tablet is marked with the number "93" and the other side with "A10"
- Anastrozole 1 mg Film-Coated Tablets are available in pack sizes of 1, 20, 28, 30 (3 x 10), 56, 60, 84, 90, 98, 100 and 300 tablets. Hospital packs of 84 tablets and hospital unit dose packs of 10 (10 x 1) and 50 (50 x 1) film-coated tablets are also available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
TEVA UK Limited, Eastbourne, BN22 9AG

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria:	Anastrozol TEVA 1mg-Filmtabletten
Belgium:	Anastrozole TEVA 1 mg filmomhulde tabletten
Czech Republic:	Anastrozol – Teva 1 mg
Germany:	Anastrozol-GRY 1 mg Filmtabletten
Denmark:	Anastrozol Teva 1 mg filmovertrukne tabletter
Estonia:	Anastrozole-Teva 1 mg
Spain:	Anastrozol TEVA 1 mg comprimidos recubiertos con película EFG
Finland:	Anastrozole TEVA 1 mg
France:	Anastrozole TEVA 1 mg, comprimé pelliculé
Hungary:	Anastrozol-Teva 1 mg filmtabletta
Ireland:	Anastrozole 1 mg Film-coated tablets
Italy:	Anastrozolo TEVA 1 mg compresse rivestite con film
Lithuania:	Anastrozole-Teva 1 mg plėvele dengtos tabletės
Luxembourg:	Anastrozole TEVA 1 mg comprimés pelliculés
Latvia:	Anastrozole-Teva 1 mg apvalkotās tablets
Netherlands:	Anastrozol 1 PCH, filmomhulde tabletten 1 mg
Norway:	Anastrozole TEVA 1 mg
Poland:	Anastrozol Teva
Portugal:	Anastrozol Teva 1 mg Comprimidos
Sweden:	Anastrozole TEVA 1 mg
Slovenia:	Anastrozol TEVA 1mg filmsko obložene tablete
Slovak Republic:	Anastrozol – Teva 1 mg

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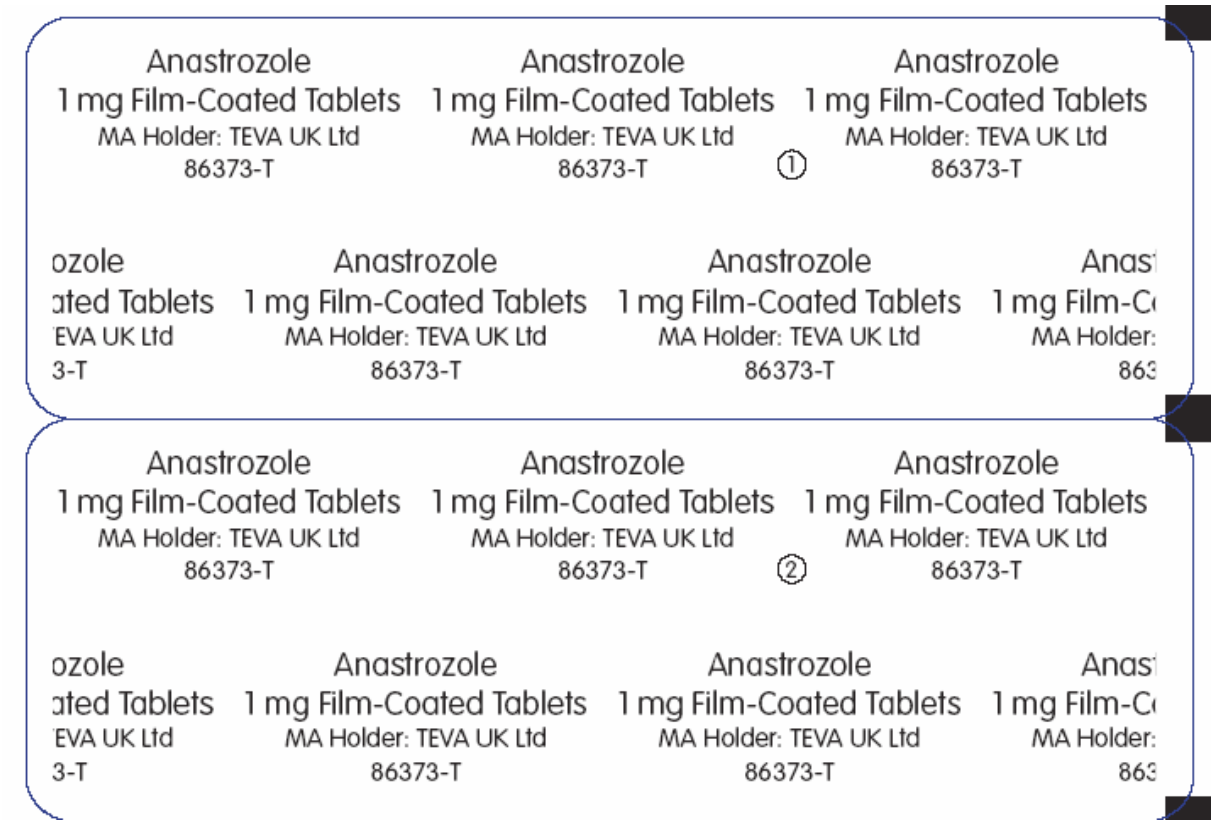
PL 00289/0966

86374-T

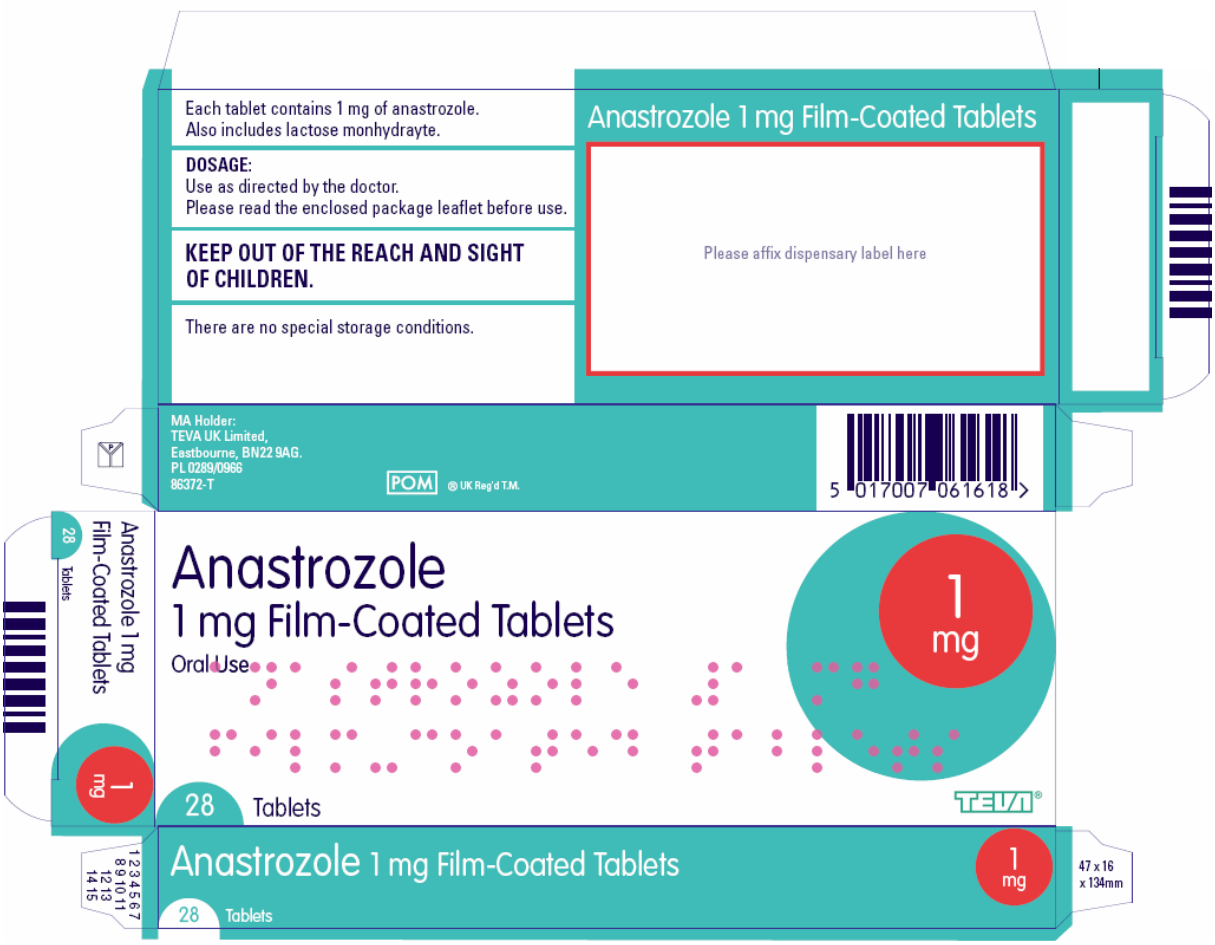
Module 4

Labelling

Blister:



Carton:


Each tablet contains 1 mg of anastrozole.
Also includes lactose monhydrayte.
DOSAGE:
Use as directed by the doctor.
Please read the enclosed package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
There are no special storage conditions.
Anastrozole 1 mg Film-Coated Tablets
Please affix dispensary label here
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 0289/0966
86372-T
POM
® UK Reg'd T.M.
5 017007 061618
Anastrozole
1 mg Film-Coated Tablets
Oral Use
1 mg
28 Tablets
TEVA
Anastrozole 1 mg Film-Coated Tablets
28 Tablets
1 mg
47 x 16 x 134mm

Module 5

Scientific discussion during initial procedure

I RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Anastrazole 1 mg film-coated tablets in the treatment of breast cancer in post menopausal women is approvable.

II EXECUTIVE SUMMARY

II.1 Problem statement

This abridged decentralised application concerns a generic version of anastrozole submitted under Article 10.1. The originator product is Arimidex 1 mg Film-coated Tablets (PL 17901/0002) authorised to AstraZeneca UK Ltd on 17 January 1996. The legal basis for this application is satisfactory.

With the UK as the Reference Member State in this Decentralised Procedure, Teva UK Ltd is applying for Marketing Authorisations for Anastrozole 1mg tablets in Austria, Belgium, the Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, Hungay, Ireland, Italy, Lithuania, Luxembourg, Latvia, The Netherlands, Norway, Poland, Portugal, Sweden, Slovenia and the Slovak Republic.

II.2 About the product

Anastrozole belongs to a group of medicines known as the hormone antagonists. Anastrozole is a non-steroidal aromatase inhibitor and acts predominantly by blocking the conversion of androgen to oestrogen in the peripheral tissues. It is indicated for use in adjuvant treatment of oestrogen-receptor-positive early and advanced breast cancer in postmenopausal women.

II.3 General comments on the submitted dossier

The submitted dossier is of adequate standard.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing

sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The chemical-pharmaceutical documentation and Expert Report in relation to Anastrozole 1 mg tablets are of sufficient quality in view of present European regulatory requirements. The active substance anastrozole is not described in the European Pharmacopoeia. An EDMF and relevant letter of access have been submitted to the MHRA. The drug substance specification is acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period is acceptable.

Drug Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis results show that the finished product meets the proposed specifications. The conditions used in the stability studies are according to the ICH stability guidelines. The control tests and specifications for the drug product are adequately drawn up. The proposed shelf-life of 30 months when packaged in the proposed blisters is acceptable.

III.2 Non clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of anastrozole are well known. As anastrozole is a well known active substance, no further new non-clinical data are required and the applicant has not provided any.

III.3 Clinical aspects

Pharmacokinetics

The applicant has submitted a bioequivalence study comparing bioavailability between Anastrozole 1 mg Tablets (Teva Pharmaceutical Industries Ltd) and the reference product, Arimidex® 1 mg Tablets in healthy subjects.

This was an open label, single dose, randomized, two-period, two treatment, crossover study designated to evaluate the comparative bioavailability of two formulations of anastrazole 1 mg tablets administered to 22 postmenopausal or surgically sterile healthy female subjects.

Study drugs were administered under fasting conditions. The washout period was 21 days. Blood samples were collected prior to drug administration and regularly up to 192 hours following drug administration.

Twenty-two subjects were dosed in period 1 and 22 completed the study. No subjects withdrew from the study.

Descriptive statistics were calculated for the PK parameters AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and T_{half}. ANOVA was carried out on the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}.

The results showed that the ratios of the geometric means for AUC and Cmax lie within the accepted range of 80-125%, in line with current guidelines (CPMP/EWP/QWP/1401/98 Note for guidance on the investigation of bioavailability and bioequivalence).

Pharmacokinetic parameters (arithmetic mean)

Treatment	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng.h/ml	**t_{max}** h	**$T_{1/2}$** h
Test	745.892	793.352	17.336	1.34	44.44
Reference	770.503	828.737	17.914	1.22	45.86
***Ratio (90% CI) Geometric means**	93.81-100.95	92.87-100.70	93.01-100.85	-	-
CV (%)	7	8	8	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
$T_{1/2}$ half-life

**ln-transformed values*

Based on this study, Anastrozole 1 mg Film-coated Tablets is considered bioequivalent to the reference product.

Pharmacodynamics

No new data have been submitted and none are required. Anastrozole is a well known potent and selective non-steroidal aromatase inhibitor that reduces levels of circulating estradiol. This effect has been shown to be beneficial in postmenopausal women with breast cancer.

Clinical efficacy

No new efficacy data have been submitted and none are required for this application.

Clinical safety

No new safety data have been submitted and none are required for this application.

IV BENEFIT RISK ASSESSMENT

The bioequivalence study has shown that the applicant's product is bioequivalent to the reference product. The benefit risk assessment is considered positive and approval is recommended.

Overall conclusion

QUALITY

The important quality characteristics of Anastrozole 1 mg Film-coated Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No preclinical data is needed for this application.

No new or unexpected safety concerns arise from these applications.

EFFICACY

Clinical studies have demonstrated the efficacy of this type of medicinal product in the treatment of breast cancer in post menopausal women.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.