Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Anastrozole 1mg Film-Coated Tablets
UK/H/1818/001/DC
UK licence no: PL 27583/0075

Apotex Europe BV

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted Apotex Europe BV a Marketing Authorisation (licence) for the medicinal product Anastrozole 1mg Film-Coated Tablets. This medicine is available on prescription only.

Anastrozole 1mg 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 1mg Film-Coated Tablets can inhibit aromatase and so can slow or stop the growth of many types of breast cancer cells that need oestrogen to grow.

The test product was considered the same as the original product Arimidex® 1mg Tablets (Astra Zeneca, UK) based on the bioequivalence study submitted and no new safety issues arose as a result of this study. No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Anastrozole 1mg Film-Coated Tablets outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Anastrozole 1mg Film-Coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Anastrozole
Form	Film-Coated Tablet
Strength	1mg
MA Holder	Apotex Europe BV, Darwinweg 20, 2333 CR, Leiden, Netherlands. Italy: DOC Generici S.r.l., Via Manuzio 7, 20124 Milan, Italy
RMS	UK
CMS	Belgium, Czech Republic, Italy, The Netherlands, Poland and Portugal
Procedure Number	UK/H/1818/001/DC
Timetable	Day 210 – 17/02/2010

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Anastrozole 1 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film- coated tablet contains anastrozole 1 mg.

Excipient: Lactose monohydrate 91.0 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
White to off-white, round, biconvex, film-coated tablets

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 (see section 5.1 and 5.2).

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.

For early disease, the recommended duration of treatment should be 5 years.

Method of administration
Oral use

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 known hypersensitivity to anastrozole or to any of the excipients as referenced 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 (see sections 5.1 and 5.2).

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 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.

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

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 (see section 5.1).

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

Use in Pregnancy

Anastrozole is contraindicated in pregnant women.

Use in Lactation

Anastrozole is contraindicated in breast-feeding 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

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 five years (ATAC study).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following undesirable effects may occur under treatment with Anastrozole 1 mg tablets. Frequencies are defined as follows:
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)

Frequency	*System Organ class*	Adverse reactions
Very common (≥ 1/10)	*Vascular*	Hot flushes, mainly mild or moderate in nature
	General	Asthenia, mainly mild or moderate in nature
	Musculoskeletal, connective tissue and bone	Joint pain/stiffness, mainly mild or moderate in nature
	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
Common (≥ 1% and <10%)	*Skin and subcutaneous tissue*	Hair thinning, 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 modearate in nature Carpal Tunnel Syndrome
	Hepatobiliary disorders	Increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase
	Reproductive system and breast	Vaginal dryness, mainly mild or moderate in nature. Vaginal bleeding, mainly mild or moderate in nature*
	Metabolism and nutrition	Anorexia, mainly mild in nature Hypercholesterolaemia, mainly mild or moderate in nature

Uncommon (≥0.1% and <1%)	*Hepatobiliary disorders*	Increases in gamma-GT and bilirubin Hepatitis
	Skin and subcutaneous tissue	*Urticaria*
	Musculoskeletal, connective tissue and bone	Trigger finger
Rare (≥0.01% and <0.1%)	*Skin and subcutaneous tissue*	Erythema multiforme Anaphylactoid reaction
Not Known	*Skin and subcutaneous tissue*	Stevens-Johnson syndrome** Angioedema**

*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.

**Cannot be estimated from the available data.

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 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. 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

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 Aanastrozole 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 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 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 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			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 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.

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 Anastrazole 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 Anastrazole alone (N=42), those in the moderate group were randomised to Anastrazole plus risedronate 35 mg once a week (N=77) or Anastrazole plus placebo (N=77) and those in the high risk group received Anastrazole 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 Anastrazole 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 Anastrazole 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 Anastrazole.

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

Paediatrics
Three clinical trials were conducted in paediatric patients (2 in pubertal boys with gynaecomastia and 1 in girls with McCune-Albright Syndrome).

Gynaecomastia studies
Trial 0006 was a randomised, double-blind, multi-centre study of 82 pubertal boys (aged 11-18 years inclusive) with gynaecomastia of greater than 12 months duration treated with Anastrazole 1 mg/day or placebo daily for up to 6 months. No significant difference in the number of patients who had a 50% or greater reduction in total breast volume after 6 months of treatment was observed between the anastrozole 1 mg treated group and the placebo group.

Trial 0001 was an open-label, multiple-dose pharmacokinetic study of Anastrazole 1mg/day in 36 pubertal boys with gynaecomastia of less than 12 months duration.
The secondary objectives were to evaluate the proportion of patients with reductions from baseline in the calculated volume of gynaecomastia of both breasts combined of at least 50% between day 1 and after 6 months of study treatment, and patient tolerability and safety.

A pharmacodynamic subpopulation of 25 boys was selected in this study to explore the potential benefits of anastrozole. It was noted a decrease in total breast volume of 50% or greater at 6 months was seen in 55.6% (as measured by ultrasound) and 77.8% (as measured by caliper) of the boys (observational data only, no statistical analysis conducted on these results).

McCune-Albright Syndrome study

Trial 0046 was an international, multi-centre, open-label exploratory trial of Anastrazole in 28 girls (aged 2 to ≤10 years) with McCune-Albright Syndrome (MAS). The primary objective was to evaluate the safety and efficacy of anastrozole 1 mg/day in patients with MAS. The efficacy of study treatment was based on the proportion of patients fulfilling defined criteria relating to vaginal bleeding, bone age, and growth velocity.

No statistically significant change in the frequency of vaginal bleeding days on treatment was observed.

There were no clinically significant changes in Tanner staging, mean ovarian volume or mean uterine volume. No statistically significant change in the rate of increase in bone age on treatment compared to the rate during baseline was observed. Growth rate (in cm/year) was significantly reduced ($p<0.05$) from pre-treatment through month 0 to month 12, and from pre-treatment to the second 6 months (month 7 to month 12). Of the patients with baseline vaginal bleeding, 28% experienced a ≥50% reduction in the frequency of bleeding days on treatment; 40% experienced a cessation over a 6-month period, and 12% experienced a cessation over a 12-month period.

The overall assessment of the adverse events in children less than 18 years of age raised no safety or tolerability concerns.

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 postmenopausal women.

In boys with pubertal gynaecomastia, anastrozole was rapidly absorbed, was widely distributed, and was eliminated slowly with a half-life of approximately 2 days. Clearance of anastrozole was lower in girls than in boys and exposure higher. Anastrozole in girls was widely distributed and slowly eliminated, with an estimated half-life of approximately 0.8 days.

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

Tablet core:
- Lactose monohydrate
- Povidone K 30
- Sodium starch glycolate Type A
- Magnesium stearate

Film-coating:
- Hypromellose
- Titanium dioxide (E171)
- Macrogol 6000
- Talc

6.2 Incompatibilities

No incompatibilities known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container
PVC/PVDC/Aluminium -Blister pack of 28, 30 and 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Apotex Europe BV
Darwinweg 20
2333 CR Leiden
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)
PL 27583/0075

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/03/2010

10 DATE OF REVISION OF THE TEXT
12/03/2010

Module 3
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Anastrozole 1 mg film-coated tablets
Anastrozole

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 gets 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 tablets are one of a group of medicines called aromatase inhibitors. Anastrozole is used to treat breast cancer in post menopausal women (women who no longer get their periods). Anastrozole works by decreasing the amount of oestrogen the body makes. This can slow or stop the growth of many types of breast cancer cells that need oestrogen to grow.

2. BEFORE YOU TAKE ANASTROZOLE

Do not take Anastrozole
- if you are allergic (hypersensitive) to anastrozole or any of the other ingredients.
- if you are pregnant, or breast-feeding.
- if you are a child or young person under the age of 18.
- if you have not gone through the menopause.
- if you have severe kidney or liver disease or moderate liver disease
- if you are taking oestrogen-containing medicines, for example hormone replacement therapy.
- if you are taking tamoxifen.

Take special care with Anastrozole
Check with your doctor or pharmacist before taking your medicine if:
- you have osteoporosis or have any other condition that affects the strength of your bones.

Anastrozole lowers the levels of female hormones in the body which may lead to thinning of the bones. This can reduce bone strength therefore you may be required to have bone density tests before and during your treatment. Your doctor may give you medicine to prevent or treat bone loss.
- you are taking LHRH analogues (medicines used to treat breast cancer, certain gynaecological conditons and infertility).
- you are not sure if you have reached menopause. Your doctor may check your hormone levels.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
- medicines that contain oestrogen
- other breast cancer treatments (such as Tamoxifen)

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Anastrozole.

Taking Anastrozole with food and drink
There is no effect on absorption of Anastrozole tablets when taken with meal.

Pregnancy and breast-feeding
Do not take Anastrozole if:
- you are pregnant
- you are breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
It is unlikely that Anastrozole will affect your ability to drive a car or to operate machinery. However, some patients may occasionally feel weak or sleepy. If this happens to you, ask your doctor or pharmacist if you are unsure.

Important information about some of the ingredients of Anastrozole tablets
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 medicinal product.

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.

- The usual dose is one tablet daily.
- The tablets should be swallowed whole with a drink of water.
- Try to take your tablets at the same time each day.

If you take more Anastrozole than you should
Tell your doctor or contact the nearest hospital, taking the medicine or this leaflet with you.

If you forget to take Anastrozole
If you miss a dose, just carry on next one as usual. Do not take a double dose to make up for a forgotten tablet.

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.

The following side effects may happen with this medicine:

Tell your doctor straight away if you notice the following serious side effect – you may need urgent medical treatment:
- Extremely severe skin reactions with lesions, ulcers or blisters (Stevens-Johnson syndrome)
- Allergic reaction with swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing and/or breathing (angiodema).

If you get any of the above tell your doctor straight away. This side effect is uncommon.

Very common side effects (affects more than 1 in 10 people)
- hot flushes
- feeling weak
- joint pain or joint stiffness
- headaches
- feeling sick (nausea)
- skin rash

Common side effects (affects less than 1 in 10 people)
- thinning of the hair
- diarrhoea
- vomiting (being sick)
- feeling sleepy
- allergic reactions
- Carpal tunnel syndrome (tingling feeling in your hands)
- abnormal liver tests
- vaginal dryness
- vaginal bleeding (occurs usually in the first few weeks of treatment)
- menstrual problems
- loss of apetite
- increased levels of fatty substances called lipids in your blood

Uncommon side effects (affects less than 1 in 100 people)
- hepatitis
- pink or red rashes on your skin which may have a clear centre
- difficulty in opening and closing your fingers

Rare side effects (affects less than 1 in 1,000 people)
- Stevens- Johnsons syndrome (blisters on your skin, mouth, eyes and genitals)

Other possible side effects:
Anastrozole lowers the level of female hormones and this may lead to a loss of the mineral content of bones, which might decrease their strength and in some cases might result in fractures.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ANASTROZOLE

Keep out of the reach and sight of children.
Do not use Anastrazole after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store below 25°C.

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 substance is anastrozole. Each film-coated tablet contains 1 mg anastrozole. The other ingredients are lactose monohydrate, povidone K 30, sodium starch glycolate Type A and magnesium stearate, hypromellose, titanium dioxide (E171), macrogol 6000 and talc.

What Anastrozole looks like and contents of the pack
Anastrozole tablets are round white film-coated tablets. The tablets are available in blister packs of 28, 30 and 100 tablets. Not all pack sizes may be marketed

Marketing Authorisation Holder

Apotex Europe B.V.
Darwinweg 20, 2333 CR
Leiden, the Netherlands

Manufacturer(s)

Apotex Nederland B.V.,
Archimedesweg 2, 2333 CN
Leiden, the Netherlands

This leaflet was last approved in February 2010.

APOTEX

Module 4
Labelling

Carton-
Pack size- 28 film coated tablets

Blister

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Anastrozole 1 mg film-coated tablets, in the

- 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

is approvable.

This application is made under Article 10.1 of 2001/83 EC, as amended, Anastrozole 1mg Film-Coated Tablets, has been shown to be a generic product of Arimidex® 1mg Tablets which was first granted to AstraZeneca UK Ltd, authorised since 11th August 1995, over 10 years ago.

Anastrozole is an orally-active, selective, non-steroidal aromatase inhibitor. It selectively blocks the conversion of androgens to oestrogen in adipose and other peripheral tissues. In postmenopausal women, ovarian secretion of oestrogen declines, and conversion of adrenal androgens to estrone and oestradiol in peripheral tissues is the principal source of oestrogens. Anastrozole can reduce serum oestrogen by more than 95% in this population, and does not affect synthesis of adrenal corticosteroid, aldosterone or thyroid hormone. Anastrozole is widely used in the treatment of post-menopausal women with metastatic oestrogen-dependent breast cancer.

No new preclinical or clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of the originator product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, batch release 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.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

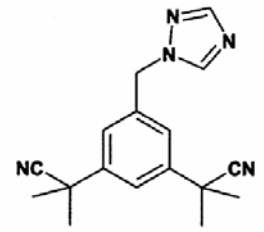
II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Anastrozole 1mg Film-Coated Tablets
Name(s) of the active substance(s) (INN)	Anastrozole
Pharmacotherapeutic classification (ATC code)	L02BG03, Hormone Antagonist
Pharmaceutical form and strength(s)	Film-Coated Tablet, 1mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1818/01/DC
Reference Member State	United Kingdom
Member States concerned	Belgium, Czech Republic, Italy, The Netherlands, Poland and Portugal
Marketing Authorisation Number(s)	PL 27583/0075
Name and address of the authorisation holder	Apotex Europe BV, Darwinweg 20, 2333 CR, Leiden, Netherlands. IT: DOC Generici S.r.l., Via Manuzio 7, 20124 Milan, Italy

III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
S. Active substance

General Information
Nomenclature
INN: Anastrozole
BAN: Anastrozole
USAN: Anastrozole
Chemical: α,α,α', α'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-benzenediacetonitrile (CAS)
α,α,α',α'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-mbenzenediacetonitrile (WHO)
2,2''-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylen]di(2-methylpropionitrile) (IUPAC)
Other Names: Anastrozolum
CAS No.: 120511-73-1

Structure:



Molecular formula: $C_{17}H_{19}N_5$

Relative molecular mass:
293.37

Chirality:

Anastrozole does not contain any asymmetric carbon centres.

Description:	White to almost white crystalline powder
Solubility:	Freely soluble in methanol, acetone, isopropyl acetate and DMF; sparingly soluble in 2M hydrochloric acid and slightly soluble in 2 M sodium hydroxide and water.
Melting point:	about 84°C

Manufacture
An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance anastrozole. The active substance specification provided is acceptable.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient. Suitable certificates of analysis have been provided for all reference standards used.

An appropriate specification is provided for the active substance anastrozole, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning foodstuff.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other ingredients consist of pharmaceutical excipients namely, lactose monohydrate and povidone K30, sodium starch glycolate type A and magnesium stearate within the tablet core.

The film-coating contains hypromellose, titanium dioxide (E171), macrogol 6000 and talc.
All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

Pharmaceutical Development

The aim of the development work was to obtain a product that was the same pharmaceutical form, same composition and be essentially similar to the innovator Arimidex reference product.

Dissolution and impurity profiles

Dissolution and impurity profiles of drug product were found to be similar to those for the reference product.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Validations of the analytical methods have been presented. Process validation has been carried out on three pilot-scale batches, this is satisfactory. In addition, a validation protocol has been provided for full scale batches. The batch analysis results show that the finished product meet the specification proposed. Certificates of analysis have been provided for any working standards used.

Container Closure System
The product is packaged in blisters composed of polyvinylchloride/polyvinylidene chloride/aluminium (PVC/PVdC/Al). Specifications and a certificate of analysis for the packaging type used have been provided. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 28, 30 and 100 film-coated tablets. Not all pack sizes may be marketed. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are "Store below 25^{o}C.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Label
The SmPC, PIL and labels are pharmaceutically acceptable.

MAA form
The application form is pharmaceutically acceptable.

Expert Report
The pharmaceutical expert report has been written by a suitably qualified person is an appropriate summary of the pharmaceutical dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

The proposed product has met the requirements of a generic medicinal product with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

III.2 Non clinical aspects
The pharmacological, pharmacokinetic and toxicological properties of anastrozole are well known. As anastrozole is a well known active substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

The non-clinical overview has been written by a suitably qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology. The overview refers to 22 references dated 1974 to 2006.

The marketing authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment.

There are no objections to the approval of Anastrozole 1mg film coated tablets from a non-clinical point of view.

III.3 Clinical aspects
Pharmacokinetics

To support the application, the applicant has submitted a single bioequivalence study.

Study design

The applicant has submitted a report of a clinical study to assess the bioequivalence of the proposed product Anastrozole 1 mg film-coated tablets with the reference product Arimidex 1 mg film-coated tablets. This was a randomised, single dose, two way, two period cross-over study, using healthy volunteers.

36 healthy volunteers were recruited, 19 of whom were women, aged 18-35, according to the inclusion and exclusion criteria stated in the protocol. After randomisation, a single dose of either the test product Anastrozole 1mg film-coated tablet or the reference product Arimidex 1mg Film-coated tablet (Astra Zeneca S.A., from the Spanish market,) was administered in the fasted state. The wash-out period was 20 days. Venous sampling was carried out pre-dose and up-to 120 hours after administration. The parent compound anastrozole was analysed in plasma using a validated LC/MS analytical method, by laboratory personnel blinded to treatment allocation. It should be noted that the reference product used in the bioequivalence study, Arimidex 1mg Film-coated tablet- manufactured in Spain, is considered to be equivalent to the UK reference product Arimidex 1mg Film-coated tablet.

The primary PK variables were C_{max}, T_{max} and AUC_{0-t}. The secondary PK variables were $AUC_{0-\infty}$, elimination constant (k), Half-life ($t_{1/2}$) and clearance (Cl). In the protocol, acceptance criteria for C_{max} of 75-133% were prospectively defined. This was justified by the variability of kinetic parameters for anastrozole, and the unlikely role of C_{max} in safety. The kinetic parameters C_{max} and AUC were compared using ANOVA, after logarithmic transformation, considering the following factors: subject, period, treatment sequence and formulation.

Results

Two subjects were randomized but did not attend either study period, and a further subject did not attend the second period, for personal reasons. Data from the remaining 33 out of the original 36 subjects was analysed. The results of the study are summarised below:

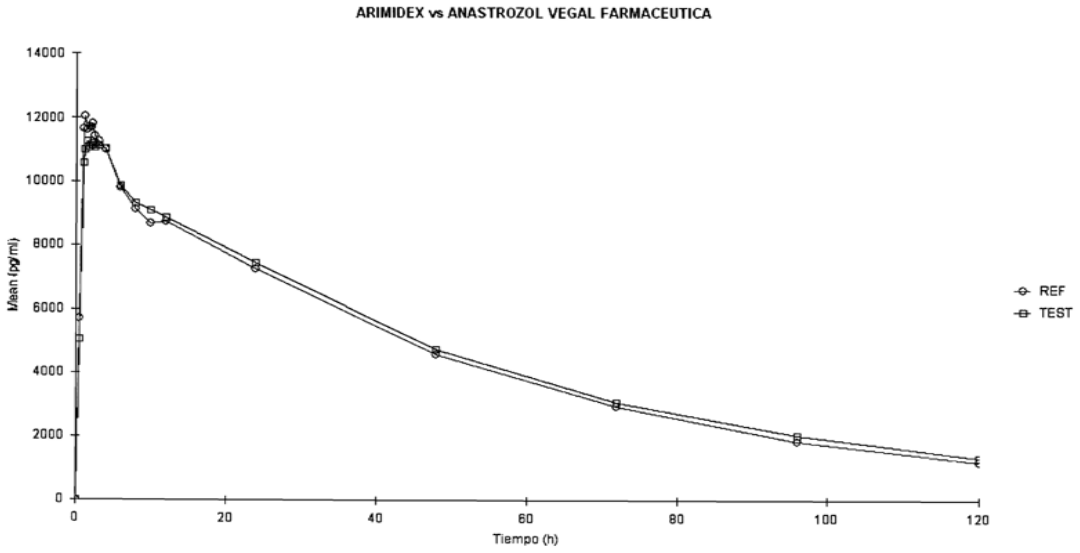
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} pg/ml/h	$AUC_{0-\infty}$ pg/ml/h	C_{max} pg/ml	t_{max} h	$T_{1/2}$ h
Test	543534.34 ±103588.33	633893.72 ±139469.52	12326.87 ±2488.08	1.5 (0.5-12.0)	38.74 ±8.37
Reference	526000.89 ±107878.78	599278.01 ±127521.62	13045.26 ±2173.78	1.5 (0.5-4.0)	36.53 ±7.29
***Ratio (90% CI)**	104.49% **(98.21-111.17)**	105.68% (101.02-110.56)	94.09% **(89.97-98.40)**	-0.25[$] (-0.25, +0.75)	

$AUC_{0-\infty}$	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*

$ *median of the differences(non-parametric Hauschke test)*



No period or sequence effects were reported.

Three subjects were not sampled for 120 hours as per protocol. Subject no. 29 was sampled until 96 hours following the reference drug and until 48 hours following the test drug. Subject no. 31 was sampled for 72 hours following the test drug and no. 32 was sampled for 24 hours following the reference drug. The % extrapolated AUC was > 20% for 3 concentration-time curves following the reference product, and 5 concentration-time curves following the test product.

No pre-dose levels were detected at the start of period 2, indicating a sufficient wash-out period. T_{max} occurred at 0.5 hours (time of first blood sample) in 2 subjects after taking the test product and in one subject after taking the reference product.

A total of 8 adverse events were reported by 6 subjects during the study. Assessment of the adverse event data raises no safety concerns as regards the test product.

Pharmacokinetic Conclusion

The 90% confidence intervals for AUC_{0-t} and C_{max} are within the required acceptance criteria 80-125%. Therefore bioequivalence has been demonstrated.

Clinical efficacy
No novel efficacy data are required for this generic application. However the applicant has provided a clinical overview that adequately summarises the published literature confirming the efficacy of anastrozole.

Clinical safety
No novel safety data are required for this generic application. However the applicant has provided a clinical overview that adequately summarises the published literature confirming the safety of anastrozole.

Pharmacovigilance system
The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan
The current application for authorisation concerns a generic version of Arimidex® (anastrozole) by AstraZeneca UK Limited, authorised in the European Union since 11 August 1995. The product has also been marketed in countries outside the European Union for many years. As a result, the safety profile of anastrozole-containing medicinal products is well established and has maintained a positive benefit/risk ratio after many years of extensive patient exposure. There has been no implementation of special measures for risk minimisation for anastrozole-containing medicinal products.

Therefore the applicant proposes to use routine pharmacovigilance, as described in Volume 9A of the Rules governing medicinal products in the European Union, and does not plan to install special risk minimisation measures for Anastrozole.

This is acceptable.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Label
The SmPC, PIL and labels are medically acceptable.

MAA form
The application form is pharmaceutically acceptable.

Expert Report
The medical expert report has been written by a suitably qualified person is an appropriate summary of the clinical dossier.

Conclusion
A marketing authorisation should be granted.

V OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Anastrozole 1mg 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 new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence data has been demonstrated between the applicant's Anastrozole1mg Film-Coated Tablets and Arimidex® 1 mg Tablets.

No new or unexpected safety concerns arise from this application.

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

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with anastrozole is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome