COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Anastrozol Accord 1 mg, film-coated tablets (anastrozole)

NL/H/4558/001/DC

Date: 2 March 2023

This module reflects the scientific discussion for the approval of Anastrozol Accord 1 mg, film-coated tablets. The procedure was finalised in the United Kingdom (UK/H/1153/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Public Assessment Report

Decentralised Procedure

Anastrozole 1mg Tablets
Anastrozole

UK/H/1153/01/DC

PL 20075/0075

Applicant: Accord Healthcare Limited

LAY SUMMARY

The MHRA granted Accord Healthcare Limited Marketing Authorisation (licence) for the medicinal product Anastrozole 1mg Film-coated Tablets (PL 20075/0075) on 21st October 2008. This is a prescription-only medicine (POM).

Anastrozole tablets are one of a group of medicines called aromatase inhibitors. This means that it interferes with some of the actions of aromatase, an enzyme within the body which affects the level of certain female sex hormones such as oestrogens. It is used to treat breast cancer in post-menopausal women.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Anastrozole film-coated tablets outweigh the risks, hence a Marketing Authorisation has been granted.

TABLE OF CONTENTS

Module 1: Information about initial procedure Page 4

Module 2: Summary of Product Characteristics Page 5

Module 3: Product Information Leaflet Page 12

Module 4: Labelling Page 18

Module 5: Scientific Discussion Page 34

1 Introduction
2 Quality aspects
3 Non-clinical aspects
4 Clinical aspects
5 Overall conclusions

Module 6 Steps taken after initial procedure Page 41

Module 1

Product Name	Anastrozole 1mg Film-coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Anastrozole
Form	Film-coated Tablets
Strength	1mg
MA Holder	Accord Healthcare limited
RMS	UK
CMS	CY, CZ, EE, EL, ES, LT, LV, MT, PL, PT, RO, SI, SK
Procedure Number	UK/H/1153/01/DC
Timetable	Day 210– 11th September 2008

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Anastrozole 1mg Film-coated Tablets

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

Excipient: Lactose monohydrate 95.250mg.

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 with "AHI" debossing on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of advanced breast cancer in postmenopausal women. Efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen.

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

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

4.2 Posology and method of administration
Adults including the elderly: One 1 mg tablet to be taken orally once a day

Children and adolescents: Not recommended for use in children

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

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

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

4.3 Contraindications
Anastrozole is contraindicated in:

- patients with known hypersensitivity to anastrozole or to any of the excipients as referenced in section 6.1.
- premenopausal women.
- pregnant or lactating women.
- patients with severe renal impairment (creatinine clearance less than 20 ml/min).
- patients with moderate or severe hepatic disease.

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

Antipyrine and cimetidine clinical interaction studies indicate that the co‑administration of Anastrozole with other medicinal products 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 medicinal products.

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

Tamoxifen should not be co-administered with Anastrozole, as this may diminish its pharmacological action (see section 4.3).

4.6 Pregnancy and lactation

Anastrozole is 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

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The frequencies of undesirable effects are following: 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).

Very common (≥1/10)	*Vascular*	Hot flushes, mainly mild or moderate in nature
Common (≥1/100 to <1/10)	*General*	Asthenia, mainly mild or moderate in nature
	Musculoskeletal, connective tissue and bone	Joint pain/stiffness, mainly mild or moderate in nature
	Reproductive system and breast	Vaginal dryness, mainly mild or moderate in nature
	Skin and subcutaneous tissue	Hair thinning, mainly mild or moderate in nature

		Rash, mainly mild or moderate in nature
	Gastrointestinal	Nausea, mainly mild or moderate in nature
		Diarrhoea, mainly mild or moderate in nature
	Nervous system	Headache, mainly mild or moderate in nature
		Carpal tunnel syndrome
	Hepatobiliary disorders	Increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase
Uncommon (≥1/1,000 to <1/100)	*Reproductive system and breast*	Vaginal bleeding, mainly mild or moderate in nature*
	Metabolism and nutrition	Anorexia, mainly mild in nature
		Hypercholesterolaemia, mainly mild or moderate in nature
	Gastrointestinal	Vomiting, mainly mild or moderate in nature
	Nervous system	Somnolence, mainly mild or moderate in nature
	Hepatobiliary	Increases in gamma-GT and bilirrubin, hepatitis
Very rare (<1/10,000)	*Skin and subcutaneous tissue*	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).

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.

Undesirable 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 overdose. 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 overdose and treatment must be symptomatic.

In the management of an overdose, consideration should be given to the possibility that multiple agents may have been taken. Vomiting may be induced 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 Anastrozole up to 10 mg do not have any effect on cortisol or aldosterone secretion, measured before or after standard ACTH challenge testing. Corticoid supplements are therefore not needed.

Primary adjuvant treatment of early breast cancer

In a large phase III study conducted in 9366 postmenopausal women with operable 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 tumor 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 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 local or distant recurrence	22 (1.7)	41 (3.2)
Hazard ratio	0.52	
2-sided 95% CI	0.31 to 0.88	
p-value	0.015	
New contralateral breast cancer	7 (0.5)	15 (1.2)
Odds ratio	0.46	
2-sided 95% CI	0.19 to 1.13	
p-value	0.090	
Overall survival	43 (3.3)	45 (3.5)
Hazard ratio	0.96	
2-sided 95% CI	0.63 to 1.46	
p-value	0.840	

Two further similar trials (GABG/ARNO 95 and ITA), in one of which patients had received surgery and chemotherapy, as well as a combined analysis of ABCSG 8 and GABG/ARNO 95, supported these results.

The Anastrozole safety profile in these 3 studies was consistent with the known safety profile established in postmenopausal women with hormone receptor positive early breast cancer.

5.2 Pharmacokinetic properties

Absorption of anastrozole is rapid and maximum plasma concentrations typically occur within two hours of dosing (under fasted conditions). Anastrozole is eliminated slowly with a plasma elimination half-life of 40 to 50 hours. Food slightly decreases the rate but not the extent of absorption. The small change in the rate of absorption is not expected to result in a clinically significant effect on steady-state plasma concentrations during once daily dosing of Anastrozole tablets. Approximately 90 to 95% of plasma anastrozole steady-state concentrations are attained after 7 daily doses. There is no evidence of time or dose-dependency of anastrozole pharmacokinetic parameters.

Anastrozole pharmacokinetics are independent of age in 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 undesirable 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

Anastrozole 1 mg Tablets:

Core tablet:
Lactose Monohydrate

Povidone K-30
Sodium Starch Glycolate (Type A)
Magnesium Stearate

Film-coating:
Hypromellose E-5
Macrogol 300
Titanium Dioxide E171

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
No specific storage conditions recommended.

6.5 Nature and contents of container
PVC/PVDC/Aluminium blister

Anastrozole Tablets are packed in blisters in pack of 28 tablets.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Accord Healthcare Limited
Sage House,
319 Pinner Road,
North Harrow,
Middlesex HA1 4HF,
UK.

8 MARKETING AUTHORISATION NUMBER(S)
PL 20075/0075

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/10/2008

10 DATE OF REVISION OF THE TEXT
21/10/2008

Module 3

Patient Information Leaflet

accord

PACKAGE LEAFLET :
INFORMATION FOR THE USER

ANASTROZOLE 1mg 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 Tablets is and what it is used for
2. Before you take Anastrozole Tablets
3. How to take Anastrozole Tablets
4. Possible side effects
5. How to store Anastrozole Tablets
6. Further information

1. What Anastrozole Tablets is and what it is used for

Anastrozole Tablets are one of a group of medicines called aromatase inhibitors. This means that it interferes with some of the actions of aromatase, an enzyme within the body which affects the level of certain female sex hormones such as oestrogens. It is used to treat breast cancer in post-menopausal women.

2. Before you take Anastrozole Tablets

Do not take Anastrozole Tablets:
- If you are allergic (hypersensitive) to anastrozole or any of the other 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 osteoporosis 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.
- Are unsure whether or not you have gone through menopause yet. Your doctor should check your hormone levels.

Using 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 a prescription.

Taking Anastrozole Tablets 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 Tablets if you are pregnant or breast-feeding your babies. Ask your doctor or pharmacist for advice before using any medicine.

Driving and using machines:
Anastrozole Tablets are unlikely to adversely affect your ability to drive a car or to operate machinery. However, some patient may occasionally feel weak or sleepy. If this happens to you, you should not drive or operate machinery.

Important information about some of the ingredients:
Anastrozole Tablets contains lactose. If your doctor has told you that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Anastrozole Tablets

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

- The usual adult dose is one tablet taken daily.
- Swallow the tablet whole with a drink of water.
- Try to take your tablet at the same time each day.
- Do not stop taking your tablets even if you are feeling well, unless your doctor tells you.

If you take more Anastrozole Tablets than you should:
If you have taken more Anastrozole Tablets than you were told to, or if someone else has taken any Anastrozole Tablets, contact accident and emergency department of your nearest hospital. Take any left over tablets or empty box with you for easier identification.

If you forget to take Anastrozole Tablets:
Do not take double dose to make up for a forgotten dose, just resume your usual schedule.

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

4. Possible side effects

Like all medicines, Anastrozole Tablets can cause side effects, although not everybody gets them.

Possible side effects are listed under headings of frequency, using the following categories:
Very common side effects: at least 1 of 10 patients treated

Common side effects: at least 1 of 100 patients treated
Uncommon side effects: at least 1 of 1,000 patients treated
Rare side effects: at least 1 of 10,000 patients treated
Very rare side effects: less than 1 of 10,000 patients treated.

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
- Hot flushes.

Common
- Lethargy
- Joint pain or stiffness
- Vaginal dryness
- Hair thinning
- Rash
- Feeling sick, diarrhoea
- Headache
- Carpal tunnel syndrome (tingling feeling in hand)
- Abnormal liver tests

Uncommon
- 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
- Hepatitis

Very rare
- 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 bone mineral content that can decrease bone strength and in some cases may result in fractures.

If your medicine affects you in any other way, you should tell your doctor, nurse or pharmacist. This can occur but this will usually disappear if your dose of Anastrozole Tablets reduced by your doctor or if your doctor prescribes you an additional medicine.

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

5. How to store Anastrozole Tablets

- Keep out of the reach and sight of children.
- No specific storage conditions recommended.
- Always return any leftover medicine to your pharmacist. Only keep it if your doctor tells you to.
- Do not use the Anastrozole Tablets after the expiry date, which is stated on the carton after (EXP). The expiry date refers to the last day of that month.
- 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 Tablets contains:

The active substance is 1mg as Anastrozole.

The other ingredient(s) are:
Core tablet: Lactose Monohydrate, Povidone K-30, Sodium starch glycolate (type A), Magnesium Stearate
Film-coating: Titanium dioxide (E171), Macrogol 300, Hypromellose E-5

What Anastrozole Tablets looks like and content of the pack:
Anastrozole Tablets are white to off white in colour, round, biconvex, film-coated tablets with 'AHI' debossing on one side and plain on other side.
Anastrozole Tablets are packed in blisters in pack of 28 tablets.

Marketing Authorisation Holder:
Accord Healthcare Limited, Sage House, 319, Pinner Road, North Harrow, Middlesex HA1 4HF, UK

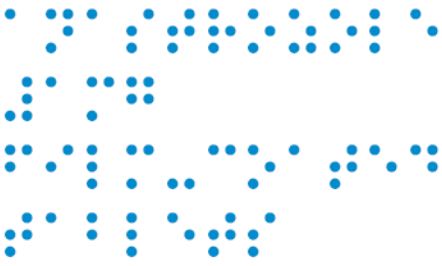
Manufacturer:
Accord Healthcare Limited, Sage House, 319, Pinner Road, North Harrow, Middlesex HA1 4HF, UK

The leaflet was last approved in October 2008

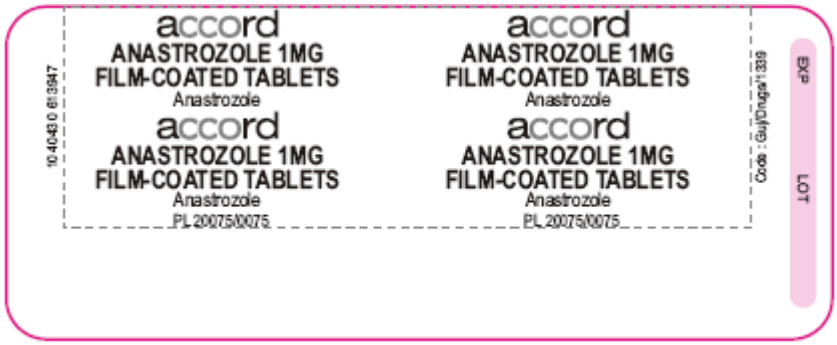
10 4044 0 613172

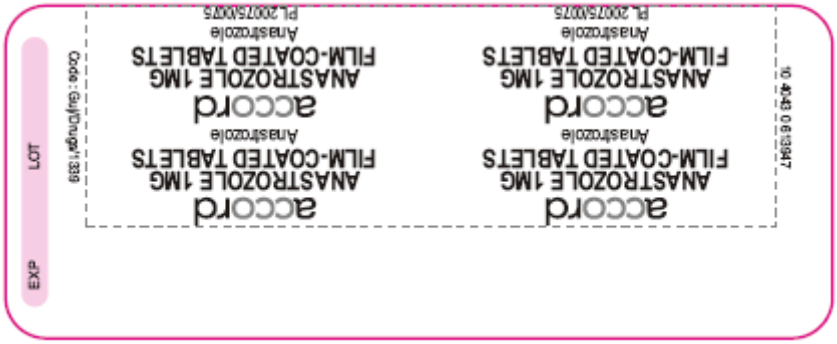
MODULE 4

Labelling



Anastrozole
#1mg
Film-coated
Tablets


accord
ANASTROZOLE 1MG
FILM-COATED TABLETS
Anastrozole
PL 20075/0075
10 40 43 0 613947
Code : Gu/Drug/1339
EXP
LOT


accord
ANASTROZOLE 1MG
FILM-COATED TABLETS
Anastrozole
PL 20075/0075
10 40 43 0 613947
Code : Gu/Drug/1339
EXP
LOT

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 breast cancer in post menopausal women, is approvable.

This abridged decentralised application concerns a generic version of anastrozole submitted under Article 10.1. The originator product is Arimidex 1mg tablets authorised to AstraZeneca UK Ltd since 1995. The legal basis is satisfactory.

With the UK as the Reference Member State in this Decentralised Procedure, Accord Healthcare Limited is applying for the Marketing Authorisations for Anastrozole 1mg tablets in CY, CZ, EE, EL, ES, LT, LV, MT, PL, PT, RO, SI and SK.

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

No new preclinical or clinical studies were conducted and none are required for an application of this type. This application for a generic product refers to Armidex 1mg Tablets, which has been licensed within the EEA for over 10 years.

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.

The applicant has submitted a phase I clinical bioequivalence study and it has been conducted under GCP guidelines.

II. ABOUT THE PRODUCT

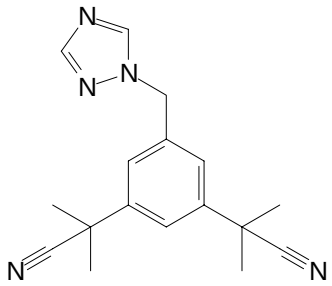
Name of the product in the Reference Member State	Anastrozole 1mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	Anastrozole
Pharmacotherapeutic classification (ATC code)	L02B G03
Pharmaceutical form and strength(s)	1mg Film-coated Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/1153/01/DC
Reference Member State	United Kingdom
Member States Concerned	CY, CZ, EE, EL, ES, LT, LV, MT, PL, PT, RO, SI and SK
Marketing Authorisation Number(s)	PL 20075/0075
Name and address of the authorisation holder	Accord Healthcare Limited Sage House, 319 Pinner Road, North Harrow HA1 4HF, Middlesex, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug Substance

Nomenclature and structure



Description: White or almost white powder

Solubility: Moderately soluble in water, Freely soluble in methanol, acetone, ethanol and THF and very soluble in acetonitrile

Chemical name: 1,3-benzenediacetonitrile, α, α, α', α'-tetramethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)

2-[3-(1-cyano-1-methylethyl)-5-(1*H*,1,2,4-triazol-1-ylmethyl)phenyl]-2-methylpropanenitrile

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

Melting range: 81-84°C

The active substance used in the manufacture of the final product is in compliance with GMP.

A letter of access to the new EDMF is provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active anastrozole is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data has been provided.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, povidone K30, macrogol 300, titanium dioxide, hydroxypropylmethylcellulose 5, sodium starch glycolate, magnesium stearate and water purified. All excipients used comply with their respective European Pharmacopoeia monograph.

Satisfactory certificates of analysis have been provided for all excipients.

The only excipients used that contain material of animal or human origin are lactose anhydrous and magnesium stearate. The applicant has provided a declaration that the milk used in the production of lactose anhydrous is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce a product containing anastrozole 1mg film-coated tablets are tolerable and which could be considered as generic product to the originator product Arimidex 1mg Tablets.

Dissolution and impurity profiles

Dissolution and impurity profiles for the drug product were found to be similar to that 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. Process validation has been carried out on batches. The results are satisfactory.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Product is packaged in to PVDV/PVC/Aluminium blisters. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. 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 2 years with no storage condition has been set. These are acceptable.

SPC, PIL, Labels

The SPC, PIL and labels are pharmaceutically acceptable.

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.

Conclusion

The proposed product has been shown to be a generic product of the reference product and has met the requirements with respect to qualitative and quantitative content of the active substance. Similar dissolution profiles have been demonstrated for the proposed and reference products. It is recommended that Marketing Authorisation should be granted for this application.

PRE-CLINICAL ASPECTS

No new preclinical data have been supplied with this application and none are required for applications of this type.

CLINICAL ASPECTS

1. INTRODUCTION

This is a decentralised procedure submitted under article 10 (1) of Directive 2001/83/EC (as amended) for a known active substance. The UK is the reference member state (RMS) with a procedure number UK/H/1153/01/DC. The Concerned Member States (CMS) are CY, CZ, EE, EL, ES,LT, LV, MT, PL, PT, RO, SI and SK.

The proposed product Anastrozole 1 mg Tablet is claiming to be a generic of the brand leader Arimidex tablets 1 mg (AstraZeneca GmbH) (PL 17901/0002 - 0048). The active substance anastrozole, is a reversible (Type II), nonsteroidal aromatase inhibitor. The aromatase enzyme is involved in the production of oestrogen. In postmenopausal women the aromatase enzyme converts the sex hormones androstenedione and testosterone, into oestrogen. Anastrozole prevents this conversion by blocking the action of the aromatase enzyme, thus causing oestrogen levels in the body to fall. The original product is listed as Arimidex 1 mg tablet which was licensed in August 2005 in the UK.

2. 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.

3. DOSE & DOSE SCHEDULE

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

Children and adolescents: Not recommended for use in children.

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

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

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

4. TOXICOLOGY

No formal data are provided under this heading and none are required for this application.

5. CLINICAL STUDY REPORTS

Pharmacokinetics

The applicant has submitted one bioequivalence study comparing the bioavailability between Anastrozole 1 mg Tablets and the reference product Arimidex® 1 mg Tablets after a single dose in healthy subjects.

Project 002-06

The phase I bioequivalence study took place at Lambda Therapeutic Research Ltd, Ahmedabad, Gujarat, India. The study was conducted in line with GCP guidelines.

Study design

This was an open label, single dose, randomized, two-way, crossover study designated to evaluate the comparative bioavailability of two formulations of anastrozole 1 mg tablets administered to healthy male subjects.

Study drugs (one tablet 1 mg) were administered orally after an overnight fast of at least 10 hours with 240 ml of water. The washout period was 28 days. Blood samples were collected prior to drug administration and up to 288 hours post dose administration.

Test Anastrozole 1 mg film coated tablets
Reference Arimidex 1 mg film-coated Tablets

29 healthy male adults were enrolled in the trial. 28 subjects were dosed in period I. 26 subjects completed the study and plasma samples from these 26 volunteers were analysed.

Determination of anastrozole plasma concentrations was performed using a validated LC/MS/MS. Analysts were blinded of the sequence of administration of the drugs.

Pharmacokinetic Variables

T_{max}, C_{max}, $T_{1/2}$, AUC $_{(0-t)}$, AUC $_{(0-\infty)}$, AUCextrap.(%), K_{el}, λz.

Descriptive statistics were calculated for the PK parameters. Analysis of variance (ANOVA) was carried out on the log-transformed AUC_{0-t} and $C_{max.}$ Ratios of the geometric means of the test product versus reference for AUC and C_{max} were calculated together with the 90% confidence intervals of the ratios.

Results

The results are shown in tables A and B.

Table-A: Descriptive Statistics of Formulation Means for Anastrozole (n=26)

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Reference Product-A	Test Product-B
*T_{max} (h)	2.500	2.500
C_{max} (ng / mL)	15.356 ± 2.7862	15.915 ± 2.8639
AUC_{0-t} (ng.h / mL)	672.440 ± 214.2066	688.165 ± 213.7105
$AUC_{0-\infty}$ (ng.h / mL)	699.991 ± 221.8860 #	710.456 ± 217.9124
λ_z (1 / h)	0.0199 ± 0.00542 #	0.0193 ± 0.00421
t½ (h)	37.373 ± 10.3561 #	37.635 ± 8.3545
AUC_% Extrap_obs (%)	4.149 ± 2.2159 #	3.285 ± 1.3501

***Note:** Median Value

Table-B: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Anastrozole (n=26)

Parameters (Units)	Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	Reference Product-A	Test Product-B	Ratio (B / A)%	
C_{max} (ng / mL)	15.126	15.660	103.5%	99.66-107.56%
AUC_{0-t} (ng.h / mL)	641.059	657.124	102.5%	98.88-106.27%
$AUC_{0-\infty}$ (ng.h / mL)	668.108 #	679.507	101.7%	98.01-105.54%

 # n=25: Descriptive statistics of (i.e. AUC_{0-inf}, λ_Z, $t_{1/2}$, AUC_% Extrap_Obs) was computed and reported for subjects whose extrapolation area was found to be < 20%.

Safety results showed no cause of concern.

Pharmacokinetic conclusion

Based on the submitted bioequivalence study the test Anastrozole 1 mg tablet is considered bioequivalent with the reference Arimidex® 1 mg tablet.

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 the 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.

6. 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.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome