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 1 mg anastrozole.

Excipient with known effect:
Each film-coated tablet contains 93 mg of lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White film-coated round biconvex tablets, debossed with “ANA” and “1” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Anastrozole is indicated for the:

– Treatment of hormone receptor-positive advanced breast cancer in postmenopausal women.
– Primary prevention of breast cancer in postmenopausal women at moderate or high risk.

4.2 Posology and method of administration

Posology

The recommended dose of anastrozole for adults including the elderly is one 1 mg tablet once a day.

For postmenopausal women with hormone receptor-positive early invasive breast cancer, the recommended duration of adjuvant endocrine treatment is 5 years.

For the primary prevention of breast cancer in postmenopausal women at moderate or high risk, the treatment duration is 5 years. Anastrozole treatment for the primary prevention of breast cancer should only be initiated by a medical practitioner experienced in prescribing for this indication, and as part of a shared care pathway arrangement, with appropriate patient identification, management and follow up. Before commencing treatment, an assessment of the potential benefits and risks is essential, including calculating a patient's risk of developing

breast cancer according to local guidelines and risk assessment tools. Validated algorithms are available that calculate breast cancer risk based on features such as age, family history, genetic factors, reproductive factors and history of breast disease. The use of anastrozole should be as part of a program including regular breast surveillance tailored to the individual woman, taking into account her risk of breast cancer.

Special populations

Paediatric population
Anastrozole is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 4.4 and 5.1).

Renal impairment
No dose change is recommended in patients with mild or moderate renal impairment. In patients with severe renal impairment, administration of anastrozole should be performed with caution (see section 4.4 and 5.2).

Hepatic impairment
No dose change is recommended in patients with mild hepatic disease. Caution is advised in patients with moderate to severe hepatic impairment (see section 4.4).

Method of administration

Anastrozole should be taken orally.

4.3 Contraindications

Anastrozole is contraindicated in:
– Pregnant or breast-feeding women.
– Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General

Anastrozole should not be used in premenopausal women. The menopause should be defined biochemically (luteinizing-hormone [LH], follicle stimulating hormone [FSH], and/or estradiol levels) in any patient where there is doubt about menopausal status. There are no data to support the use of anastrozole with LHRH analogues.

Co-administration of tamoxifen or oestrogen-containing therapies with anastrozole should be avoided as this may diminish its pharmacological action (see section 4.5 and 5.1).

In the IBIS-II primary prevention study, due to the limited number of women with a confirmed BRCA1 or 2 mutation, there is uncertainty about the absolute benefit in these patients treated with anastrozole for primary prevention of breast cancer.

Higher proportions of women had hypertension (including essential hypertension, hypertension, accelerated hypertension, malignant hypertension and systolic hypertension), hypercholesterolaemia (including hypercholesterolaemia, hyperlipidaemia and blood cholesterol increased) and cardiovascular events when treated with anastrozole rather than with the placebo in the IBIS-II study. Such cardiovascular risks must be considered when starting anastrozole for primary prevention in healthy individuals as well as a potential cause of new onset/deterioration of these conditions in those already receiving treatment with anastrozole.

Effect on bone mineral density

As anastrozole lowers circulating estrogen levels it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture (see section 4.8).

Women with osteoporosis or osteopenia, or at risk of osteoporosis or osteopenia, should have their bone mineral density formally assessed at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis or osteopenia should be initiated as appropriate and carefully monitored , as per local guidelines. The use of specific treatments, e.g., bisphosphonates, may stop further bone mineral loss caused by anastrozole in postmenopausal women and could be considered (see section 4.8).

Patients with severe osteoporosis, that is, T score <–4.0, or more than two vertebral fractures are not suitable for anastrozole use in primary prevention.

Hepatic impairment

Anastrozole has not been investigated in breast cancer patients with moderate or severe hepatic impairment. Exposure to anastrozole can be increased in subjects with hepatic impairment (see section 5.2); administration of anastrozole in patients with moderate and severe hepatic impairment should be performed with caution (see section 4.2). Treatment should be based on a benefit-risk evaluation for the individual patient.

Renal impairment

Anastrozole has not been investigated in breast cancer patients with severe renal impairment. Exposure to anastrozole is not increased in subjects with severe renal impairment (GRF<30ml/min, see section 5.2); in patients with severe renal impairment, administration of anastrozole should be performed with caution (see section 4.2).

Paediatric population

Anastrozole is not recommended for use in children and adolescents as safety and efficacy have not been established in this group of patients (see section 5.1).

Anastrozole should not be used in boys with growth hormone deficiency in addition to growth hormone treatment. In the pivotal clinical trial, efficacy was not demonstrated and safety was not established (see section 5.1). Since anastrozole reduces estradiol levels, anastrozole must not be used in girls with growth hormone deficiency in addition to growth hormone treatment. Long-term safety data in children and adolescents are not available.

Excipients

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Anastrozole inhibits CYPs 1A2, 2C8/9 and 3A4 *in vitro*. Clinical studies with antipyrine and warfarin showed that anastrozole at a 1 mg dose did not significantly inhibit the metabolism of antipyrine and R– and S-warfarin indicating the co-administration of anastrozole with other medicinal products is unlikely to result in clinically significant medicinal product interactions mediated by CYP enzymes.

The enzymes mediating metabolism of anastrozole have not been identified. Cimetidine, a weak, unspecific inhibitor of CYP enzymes, did not affect the plasma concentrations of anastrozole. The effect of potent CYP inhibitors is unknown.

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. There were no clinically significant interactions with bisphosphonates (see section 5.1).

Co-administration of tamoxifen or oestrogen-containing therapies with anastrozole should be avoided as this may diminish its pharmacological action (see section 4.4 and 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of anastrozole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Anastrozole is contraindicated during pregnancy (see section 4.3).

Breast-feeding

There are no data on the use of anastrozole during lactation. Anastrozole is contraindicated during breast-feeding (see section 4.3).

Fertility

The effects of anastrozole on fertility in humans have not been studied. Studies in animals have shown reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

Anastrozole has no or negligible influence on the ability to drive and use machines. However, asthenia and somnolence have been reported with the use of anastrozole and caution should be observed when driving or operating machinery while such symptoms persist.

4.8 Undesirable effects

The following table presents adverse reactions from clinical trials, post-marketing studies or spontaneous reports. Unless specified, the frequency categories were calculated from the number of adverse events reported in a large phase III study conducted in 9,366 postmenopausal women with operable breast cancer given adjuvant treatment for five years (the Anastrozole, Tamoxifen, Alone or in Combination [ATAC] study).

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency groupings are defined according to the following convention: 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), and very rare (<1/10,000). The most frequently reported adverse reactions were headache, hot flushes, nausea, rash, arthralgia, joint stiffness, arthritis, and asthenia.

Table 1. Adverse reactions by System Organ Class and frequency

System Organ Class	Frequency	Adverse reaction
Metabolism and nutrition disorders	Common	Anorexia Hypercholesterolaemia
	Uncommon	Hypercalcaemia (with or without an increase in parathyroid hormone)
Psychiatric disorders	Very common	Depression
Nervous system disorders	Very common	Headache
	Common	Somnolence Carpal Tunnel Syndrome* Sensory disturbances (including paraesthesia, taste loss and taste perversion)
Vascular disorders	Very common	Hot flushes
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea Vomiting
Hepatobiliary disorders	Common	Increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase
	Uncommon	Increases in gamma-GT and bilirubin Hepatitis
Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Hair thinning (alopecia) Allergic reactions
	Uncommon	Urticaria
	Rare	Erythema multiforme

		Anaphylactoid reaction Cutaneous vasculitis (including some reports of Henoch-Schönlein purpura)**
	Very rare	Stevens-Johnson syndrome Angioedema
Musculoskeletal and connective tissue disorders	Very common	Arthralgia/joint stiffness Arthritis Osteoporosis
	Common	Bone pain Myalgia
	Uncommon	Trigger finger
Reproductive system and breast disorders	Common	Vaginal dryness Vaginal bleeding***
General disorders and administration site conditions	Very common	Asthenia

* Events of Carpal Tunnel Syndrome have been reported in patients receiving anastrozole treatment in clinical trials in greater numbers than those receiving treatment with tamoxifen. However, the majority of these events occurred in patients with identifiable risk factors for the development of the condition.
** Since cutaneous vasculitis and Henoch-Schönlein purpura was not observed in ATAC, the frequency category for these events can be considered as 'Rare' ($\geq 0.01\%$ and $< 0.1\%$) based on the worst value of the point estimate.
*** 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.

The table 2 below presents the frequency of pre-specified adverse events in the ATAC study after a median follow-up of 68 months, irrespective of causality, reported in patients receiving trial therapy and up to 14 days after cessation of trial therapy.

Table 2. ATAC study pre-specified adverse events

Adverse events	**anastrozole (n=3,092)**	**tamoxifen (n=3,094)**
Hot flushes	1,104 (35.7%)	1,264 (40.9%)
Joint pain/stiffness	1,100 (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%)

Adverse events	anastrozole (n=3,092)	tamoxifen (n=3,094)
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 (pulmonary embolism)	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 1,000 patient-years and 15 per 1,000 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. The incidence of osteoporosis was 10.5% in patients treated with anastrozole and 7.3% in patients treated with tamoxifen.

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.

IBIS-II Study

The following tables present adverse event data from the large IBIS-II international randomized, controlled clinical trial investigating the efficacy and safety of chemoprevention with daily anastrozole over 5 years in postmenopausal women (see section 5.1). Over 5 years there was no significant difference in the overall rate of AEs for anastrozole *versus* placebo (89% in both groups). A summary of adverse events is included in Table 3 and this includes all predefined AEs, AEs affecting at least 5% of participants, or those that differed significantly ($p<0.02$) between groups.

Table 3 Adverse events recorded in IBIS-II study during period of medication usage

Adverse Event	Anastrozole (n=1920)	Placebo (n=1944)
Any	1709 (89%)	1723 (89%)
Fractures	164 (9%)	149 (8%)
Arm	66 (3%)	61 (3%)
Leg	65 (3%)	57 (3%)
Rib, spine, or collarbone	23 (1%)	18 (1%)
Pelvic or hip	9 (<1%)	10 (1%)
Skull	1 (<1%)	1 (<1%)
Musculoskeletal	1226 (64%)	1124 (58%)
Arthralgia*	972 (51%)	894 (46%)
Mild	385 (20%)	386 (20%)
Moderate	422 (22%)	363 (19%)
Severe	151 (8%)	123 (6%)
Joint stiffness	143 (7%)	96 (5%)
Pain in hand or foot	178 (9%)	147 (8%)
Carpal tunnel syndrome or	67 (3%)	43 (2%)

nerve compression		
Vasomotor*†	1090 (57%)	961 (49%)
Mild	550 (29%)	504 (26%)
Moderate	390 (20%)	330 (17%)
Severe	150 (8%)	127 (7%)
Gynaecological	460 (24%)	423 (22%)
Vaginal dryness	357 (19%)	304 (16%)
Haemorrhage or bleeding	65 (3%)	81 (4%)
Vaginal or uterine prolapse	13 (1%)	31 (2%)
Vulvovaginal pruritus	40 (2%)	60 (3%)
Vascular	152 (8%)	127 (7%)
Hypertension	89 (5%)	55 (3%)
Myocardial infarction or cardiac failure	8 (<1%)	9 (<1%)
Thrombosis or embolism	19 (1%)	17 (1%)
Phlebitis	9 (<1%)	8 (<1%)
Cerebrovascular accident	3 (<1%)	6 (<1%)
Eye	348 (18%)	335 (17%)
Dry eyes	83 (4%)	58 (2%)
Conjunctivitis	12 (1%)	5 (<1%)
Glaucoma	12 (1%)	24 (1%)
Cataract	90 (5%)	95 (5%)
Infections	230 (12%)	217 (11%)
Influenza	25 (1%)	12 (1%)
Otitis media	18 (1%)	6 (<1%)

Data presented as n (%). *Assessments of severity broadly based on Common Terminology Criteria for Adverse Events, but some discretion by clinicians was allowed. †Vasomotor symptoms defined as hot flushes or night sweats.

During the long-term follow-up period (up to 12 years), only major AEs (defined as other cancers, cardiovascular events, fractures, and deaths) were routinely collected. Overall, there was no significant difference between anastrozole and placebo for any of the major adverse events. Less serious AEs, such as development of hypertension, were not routinely collected in the long-term follow-up.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: Aromatase inhibitorsATC code: L02B G03

Mechanism of action and pharmacodynamic effects

Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. In postmenopausal women, estradiol is produced primarily from the conversion of androstenedione to estrone through the aromatase enzyme complex in peripheral tissues. Estrone is subsequently converted to estradiol. Reducing circulating estradiol levels has been shown to produce a beneficial effect in women with breast cancer.

In postmenopausal women, anastrozole at a daily dose of 1 mg produced estradiol suppression of greater than 80% using a highly sensitive assay.

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

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

Clinical efficacy and safety

Advanced breast cancer

First-line therapy in postmenopausal women with advanced breast cancer

Two double-blind, controlled clinical studies of similar design (Study 1033IL/0030 and Study 1033IL/0027) were conducted to assess the efficacy of anastrozole compared with tamoxifen as first-line therapy for hormone receptor-positive or hormone receptor-unknown locally advanced or metastatic breast cancer in postmenopausal women. A total of 1,021 patients were randomised to receive 1 mg of anastrozole once daily or 20 mg of tamoxifen once daily. The primary endpoints for both trials were time to tumour progression, objective tumour response rate, and safety.

For the primary endpoints, Study 1033IL/0030 showed that anastrozole had a statistically significant advantage over tamoxifen for time to tumour progression (Hazard ratio (HR) 1.42, 95% Confidence Interval (CI) [1.11, 1.82], Median time to progression 11.1 and 5.6 months for anastrozole and tamoxifen respectively, p=0.006); objective tumour response rates were similar for anastrozole and tamoxifen. Study 1033IL/0027 showed that anastrozole and tamoxifen had similar objective tumour response rates and time to tumour progression.

Results from the secondary endpoints were supportive of the results of the primary efficacy endpoints. There were too few deaths occurring across treatment groups of both trials to draw conclusions on overall survival differences.

Second-line therapy in postmenopausal women with advanced breast cancer

Anastrozole was studied in two controlled clinical trials (Study 0004 and Study 0005) in postmenopausal women with advanced breast cancer who had disease progression following tamoxifen therapy for either advanced or early breast cancer. A total of 764 patients were randomised to receive either a single daily dose of 1 mg or 10 mg of anastrozole or megestrol acetate 40 mg four times a day. Time to progression and objective response rates were the primary efficacy variables. The rate of prolonged (more than 24 weeks) stable disease, the rate of progression, and survival were also calculated. In both studies there were no significant differences between treatment arms with respect to any of the efficacy parameters.

Adjuvant treatment of early invasive breast cancer for hormone receptor-positive patients

In a large phase III study conducted in 9,366 postmenopausal women with operable breast cancer treated for 5 years (see below), 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.

Table 4. 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=3,125)	**tamoxifen (n=3,116)**	**anastrozole (n=2,618)**	**tamoxifen (n=2,598)**
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	

Efficacy endpoints	Number of events (frequency)			
	Intention to treat population		Hormone receptor positive tumour status	
	anastrozole (n=3,125)	tamoxifen (n=3,116)	anastrozole (n=2,618)	tamoxifen (n=2,598)
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.

The combination of anastrozole and tamoxifen did not demonstrate any efficacy benefits in comparison with tamoxifen in all patients as well as in the hormone receptor-positive population. This treatment arm was discontinued from the study.

With an updated follow-up at a median of 10 years, long term comparison of the treatment effects of anastrozole relative to tamoxifen were shown to be consistent with previous analyses.

Adjuvant treatment of early invasive breast cancer for hormone receptor positive patients being treated with adjuvant tamoxifen

In a phase III trial (Austrian Breast and Colorectal Cancer Study Group [ABCSG] 8) conducted in 2,579 postmenopausal women with hormone receptor positive early breast cancer who had received surgery with or without radiotherapy and no chemotherapy (see below), 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.

Table 5. ABCSG 8 trial endpoint and results summary

Efficacy endpoints	Number of events (frequency)	
	anastrozole (n=1,297)	tamoxifen (n=1,282)
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 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.

Primary reduction of breast cancer risk

Anastrozole reduces, but does not eliminate the risk of breast cancer. The International Breast cancer Intervention Study, IBIS-II, was a large international, multicentre, double-blind, randomised, placebo-controlled trial which investigated the efficacy and safety of chemoprevention with daily anastrozole over 5 years in postmenopausal women aged 40–70 years who were at an increased risk of breast cancer. The inclusion criteria defined an increased risk of breast cancer based on various family and personal history criteria that corresponded to a relative risk compared to the general population. Key exclusion criteria included: premenopausal status; any previous diagnosis of breast cancer (except for ER+ ductal carcinoma in situ diagnosed less than 6 months previously and treated by mastectomy); any invasive cancer in the previous 5 years (except for non-melanoma skin cancer or cervical cancer); present or previous use of selective oestrogen receptor modulators for more than 6 months (unless as part of IBIS-I and treatment was completed at least 5 years before study entry); intention to continue hormone replacement therapy; prophylactic mastectomy; evidence of severe osteoporosis (T score <–4.0 or more than two vertebral fractures).

19,399 women-years of follow-up were available (9727 in the anastrozole group and 9672 in the placebo group), with a median follow-up period of 5.0 years (IQR 3.0–7.1). At this time point, 51% (979 women) in the anastrozole group and 50% (975) in the placebo group had completed the full 5 years of treatment.

The primary study endpoint was histologically confirmed breast cancer (defined as invasive cancer or non-invasive ductal carcinoma in situ), which demonstrated significantly fewer

breast cancer cases in the anastrozole group (40, 2%) in comparison to the placebo group (85, 4%; HR 0.47, 95% CI 0.32–0.68, p<0.0001) at this time point.

Additional long-term follow-up (12 years) was undertaken in the post-treatment period.

This analysis included 3864 women (1920 assigned to the anastrozole group and 1944 were assigned to placebo group). Mean follow-up for this analysis was 131 months, which consisted of a total of 41,295 women-years of follow-up (20,803 women-years for anastrozole and 20,491 women-years for placebo), of this 22,367 women-years came after the 5-year treatment period.
For the primary study endpoint, there was a significant reduction in breast cancer cases in the anastrozole group (85, 4.4%) compared to placebo (165, 8.5%, p<0.0001). This corresponds to a 49% reduction for all breast cancer cases with anastrozole (HR 0.51, 95% CI 0.39–0.66, p<0.0001). A Kaplan-Meier survival curve (figure 1) was constructed which allowed the calculation of an estimated risk of breast cancer during the 12-year follow-up period. These figures were calculated to be 5.3% in the anastrozole group versus 8.8% in placebo group. Based on these results, anastrozole had a number needed to treat of 29 in order to prevent one breast cancer case (over 12 years).

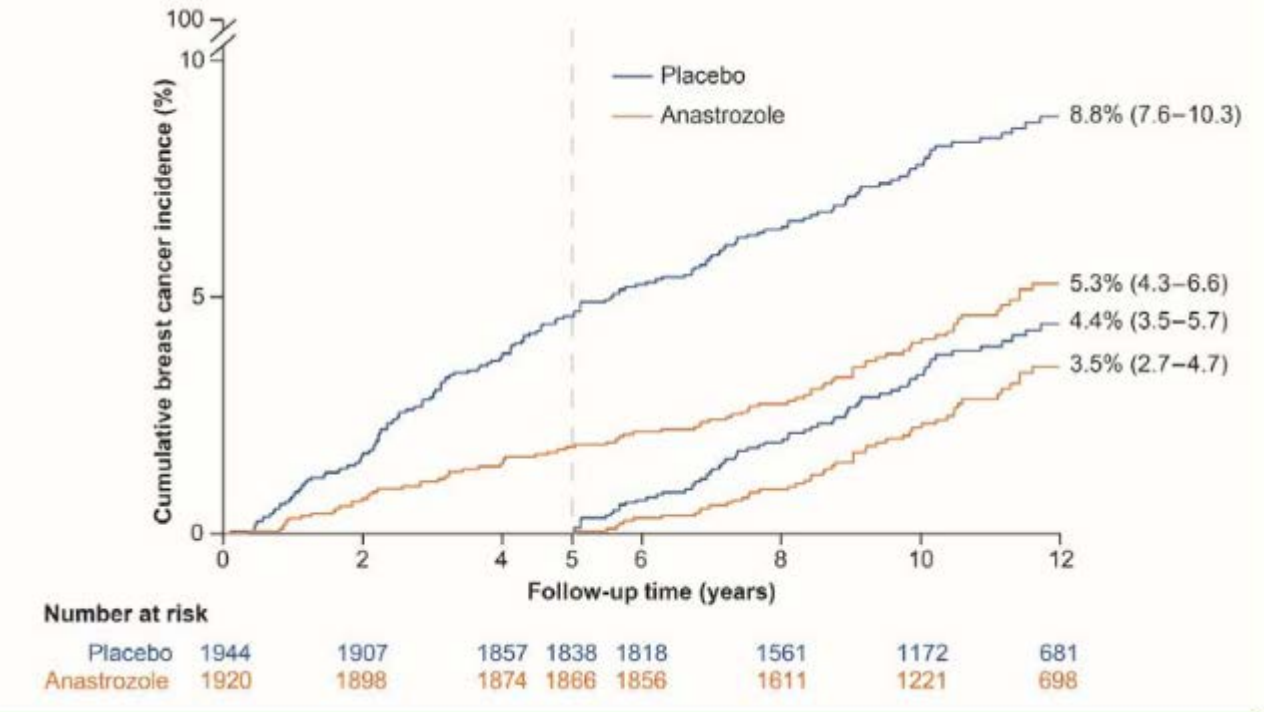


Figure 1: risk from start of treatment (0 years) and risk after the end of active treatment (5 years) to show comparison of risk reduction over 0–5 years period and post–5 years period.

These results show that the reduction in breast cancer incidence with anastrozole over placebo was greatest during the 5 years of treatment, with a smaller (but still significant) reduction seen over the subsequent follow-up period.
Bone mineral density (BMD)

In the phase III/IV study (Study of Anastrozole with the Bisphosphonate Risedronate [SABRE]), 234 postmenopausal women with hormone receptor-positive early breast cancer scheduled for treatment with anastrozole 1 mg/day were stratified to low, moderate and high risk groups according to their existing risk of fragility fracture. The primary efficacy

parameter was the analysis of lumbar spine bone mass density using DEXA scanning. All patients received treatment with vitamin D and calcium. Patients in the low risk group received anastrozole alone (N=42), those in the moderate group were randomised to anastrozole plus risedronate 35 mg once a week (N=77) or anastrozole plus placebo (N=77) and those in the high risk group received anastrozole plus risedronate 35 mg once a week (N=38). The primary endpoint was change from baseline in lumbar spine bone mass density at 12 months.

The 12-month main analysis has shown that patients already at moderate to high risk of fragility fracture showed no decrease in their bone mass density (assessed by lumbar spine bone mineral density using DEXA scanning) when managed by using anastrozole 1 mg/day in combination with risedronate 35 mg once a week.

In addition, a decrease in BMD which was not statistically significant was seen in the low risk group treated with anastrozole 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 could be considered in the management of possible bone mineral loss in postmenopausal women with early breast cancer scheduled to be treated with anastrozole.

IBIS-II Bone Health Study
A total of 1410 women were enrolled from the main IBIS-II study into three stratified groups depending on baseline T score: Stratum I, women with healthy T score (at least –1·0); Stratum II, women who were osteopenic (T score at least –2·5 but less than –1·0); and Stratum III, osteoporotic women with a T score of less than –2·5 but greater than –4·0 or those with one to two low trauma fragility fractures (as assessed by spinal radiographs from up to 2 years before randomisation).

The primary objective of the bone substudy was to compare the effect of risedronate *versus* placebo on bone density in women taking anastrozole (Stratum II).

Within Stratum II, patients receiving anastrozole showed a linear bone mineral density loss at both the lumber spine and hip, that was significantly reduced by co-administration of risedronate. These conclusions were strengthened through analysis of patients in the other strata.

Paediatric population

Anastrozole is not indicated for use in children and adolescents. Efficacy has not been established in the paediatric populations studied (see below). The number of children treated was too limited to draw any reliable conclusions on safety. No data on the potential long-term effects of anastrozole treatment in children and adolescents are available (see also section 5.3).

The licensing authority has waived the obligation to submit the results of studies with anastrozole in one or several subsets of the paediatric population in short stature due to growth hormone deficiency (GHD), testotoxicosis, gynaecomastia, and McCune-Albright syndrome (see section 4.2).

Short stature due to Growth Hormone Deficiency

A randomised, double-blind, multi-centre study evaluated 52 pubertal boys (aged 11 to 16 years inclusive) with GHD treated for 12 to 36 months with anastrozole 1 mg/day or placebo in combination with growth hormone. Only 14 subjects on anastrozole completed 36 months.

No statistically significant difference from placebo was observed for the growth-related parameters of predicted adult height, height, height SDS (standard deviation score), and height velocity. Final height data were not available. While the number of children treated was too limited to draw any reliable conclusions on safety, there was an increased fracture rate and a trend towards reduced bone mineral density in the anastrozole arm compared to placebo.

Testotoxicosis

An open-label, non-comparative, multi-centre study evaluated 14 male patients (aged 2 to 9 years) with familial male-limited precocious puberty, also known as testotoxicosis, treated with combination of anastrozole and bicalutamide. The primary objective was to assess the efficacy and safety of this combination regimen over 12 months. Thirteen out of the 14 patients enrolled completed 12 months of combination treatment (one patient was lost to follow-up). There was no significant difference in growth rate after 12 months of treatment, relative to the growth rate during the 6 months prior to entering the study.

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 anastrozole 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 anastrozole 1 mg/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 decrease in 50% or more of total breast volume was seen in 56% (20/36) of the boys after 6 months.

McCune-Albright Syndrome study

Trial 0046 was an international, multi-centre, open-label exploratory trial of anastrozole in 28 girls (aged 2 to $\leq$ 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).

5.2 Pharmacokinetic properties

Absorption

Absorption of anastrozole is rapid and maximum plasma concentrations typically occur within two hours of dosing (under fasted conditions).
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, and accumulation is 3- to 4-fold. There is no evidence of time or dose-dependency of anastrozole pharmacokinetic parameters.

Anastrozole pharmacokinetics are independent of age in postmenopausal women.

Distribution

Anastrozole is only 40% bound to plasma proteins.

Elimination

Anastrozole is eliminated slowly with a plasma elimination half-life of 40 to 50 hours. 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.

Renal or hepatic impairment

The apparent clearance (CL/F) of anastrozole, following oral administration, was approximately 30% lower in volunteers with stable hepatic cirrhosis than in matched controls (Study 1033IL/0014). However, plasma anastrozole concentrations in the volunteers with hepatic cirrhosis were within the range of concentrations seen in normal subjects in other trials. Plasma anastrozole concentrations observed during long-term efficacy trials in patients with hepatic impairment were within the range of plasma anastrozole concentrations seen in patients without hepatic impairment.

The apparent clearance (CL/F) of anastrozole, following oral administration, was not altered in volunteers with severe renal impairment (GFR <30ml/min) in Study 1033IL/0018, consistent with the fact that anastrozole is eliminated primarily by metabolism. Plasma anastrozole concentrations observed during long-term efficacy trials in patients with renal impairment were within the range of plasma anastrozole concentrations seen in patients without renal impairment. In patients with severe renal impairment, administration of anastrozole should be performed with caution (see section 4.2 and 4.4).

Paediatric population

In boys with pubertal gynaecomastia (10-17 years), 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 (3-10 years) than in the older boys and exposure higher. Anastrozole in girls was widely distributed and slowly eliminated.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction for the indicated population.

Acute toxicity

In animal studies toxicity was only seen at high doses. 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

In animal studies adverse effects were only seen at high doses. Multiple dose toxicity studies utilised 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

In a fertility study weanling male rats were dosed orally with 50 or 400 mg/l anastrozole via their drinking water for 10 weeks. Measured mean plasma concentrations were 44.4 (±14.7) ng/ml and 165 (±90) ng/ml respectively. Mating indices were adversely affected in both dose groups, whilst a reduction in fertility was evident only at the 400 mg/l dose level. The reduction was transient as all mating and fertility parameters were similar to control group values following a 9-week treatment-free recovery period.

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
Sodium starch glycolate (type A)
Povidone (K31) (E1201)
Magnesium stearate (E572)

Film-coating
Macrogol 400
Hypromellose (E464)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Cardboard boxes containing PVC/PE/PVDC/Aluminium blisters of 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 or 300 tablets and hospital blisters (PVC/PE/PVDC/ Aluminium) with 28, 50, 84, 98, 300 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Consilient Health Ltd.,
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Dublin 2, D02 Y754,
Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 24837/0116

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

06/2024