Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Arimidex 1mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg anastrozole.
Excipients: each film-coated tablet contains 93 mg lactose monohydrate.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

Product imported from the United Kingdom
White, biconvex, 6mm in diameter embossed with a logo on one side and a tablet strength marking on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of early breast cancer in postmenopausal women who are hormone-receptor positive.

Treatment of advanced breast cancer in postmenopausal women.

4.2 Posology and method of administration

Adults includes the elderly:

One 1mg tablet to be taken orally once a day.

Children:

Arimidex is not recommended for use in children due to insufficient data on safety and efficacy (*see sections 4.4 and 5.1).*

Renal Impairment: No dose change is recommended.
Hepatic Impairment: No dose change is recommended.

4.3 Contraindications

Arimidex must not be administered during pregnancy or lactation.

Patients with known hypersensitivity to anastrozole or to any of the excipients referenced in *Section 6.1*.

4.4 Special warnings and precautions for use

Arimidex is not recommended for use in children or in premenopausal women as safety and efficacy have not been established in these groups of patients *(see sections 5.1).*

Arimidex 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, Arimidex 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.

Arimidex has not been investigated in patients with severe hepatic or severe renal impairment. The potential risk/benefit to such patients should be carefully considered before administration of Arimidex.

As Arimidex lowers circulating oestrogen levels, it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture. This possible increased risk should be managed according to treatment guidelines for managing bone health in postmenopausal women.

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 Arimidex 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 Arimidex who also received other commonly prescribed drugs. There were no clinically significant interactions with bisphosphonates *(see section 5.1).*

Tamoxifen and/or oestrogen-containing therapies should not be co-administered with Arimidex as they may diminish its pharmacological action.

4.6 Fertility, pregnancy and lactation

Arimidex is contraindicated in pregnant or lactating women.

4.7 Effects on ability to drive and use machines

Arimidex is unlikely to impair the ability of patients to drive and operate machinery. However, asthenia and somnolence have been reported with the use of Arimidex 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 5 years and unless specified, no account was taken of the frequency within the comparative treatment group or whether the investigator considered it to be related to study medication.

System Organ Class	Frequency	Adverse reaction
Metabolism and nutrition	Common (≥1/100 to <1/10)	Anorexia, mainly mild in nature Hypercholesterolemia, mainly mild or moderate in nature
Nervous system disorders	Very common (≥ 1/10)	Headache, mainly mild or moderate in nature
	Common (≥1/100 to <1/10)	Somnolence, mainly mild or moderate in nature Carpal Tunnel Syndrome*
Vascular disorders	Very common (≥ 1/10)	Hot flushes, mainly mild or moderate in nature
Gastrointestinal disorders	Very common (≥ 1/10)	Nausea, mainly mild or moderate in nature
	Common (≥ 1/100 to <1/10)	Diarrhoea, mainly mild or moderate in nature Vomiting, mainly mild or moderate in nature
Hepatobiliary disorders	Common (≥ 1/100 to <1/10)	Increases in alkaline phosphatase, alanine aminotransferase and aspirate aminotransferase
	Uncommon (≥ 1/1000 to < 1/100)	Increases in gamma-GT and bilirubin Hepatitis
Skin and Subcutaneous disorders	Very common (≥ 1/10)	Rash, mainly mild or moderate in nature.
	Common (≥ 1/100 to < 1/10)	Hair thinning (Alopecia) mainly mild or moderate in nature Allergic reactions
	Uncommon (≥ 1/1000 to < 1/100)	Urticaria
	Rare (≥ 1/10,000 to < 1/1000)	Erythema multiforme Anaphylactoid reaction Cutaneous vasculitis (including some reports of Henoch-Schönlein purpura)
	Not known	Stevens-Johnson syndrome *** Angioedema ***
Musculoskeletal and connective tissue disorders	Very common (≥ 1/10)	Arthralgia/Joint stiffness Arthritis
	Common (≥ 1/100 to <1/10)	Bone pain
	Uncommon (≥ 1/1000 to <1/100)	Trigger finger
Reproductive system and breast disorders	Common (≥ 1/100 to <1/10)	Vaginal dryness, mainly mild or moderate in nature Vaginal bleeding, mainly mild or moderate in nature **
General disorders and	Very common (≥ 1/10)	Asthenia, mainly mild or moderate in nature

administration site conditions		

*Events of Carpal Tunnel Syndrome have been reported in patients receiving Arimidex treatment in clinical trials in greater numbers that those receiving treatment with tamoxifen. However, the majority of these events occurred in patients with identifiable risk factors for the development of the condition.

**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 Arimidex. If bleeding persists further evaluation should be considered.

*** Can not be estimated from available data.

Arimidex is a potent oestrogen-lowering agent. Lack of oestrogen is known to result in loss of bone mineral density, osteoporosis and an increased risk of fractures.

At 68 months median follow up, in the early breast cancer setting the reported incidence of all adverse events (irrespective of causality) of fractures was 10.2% for Arimidex and 6.8% for tamoxifen and the incidence of osteoporosis was 10.5% in patients treated with Arimidex and 7.3% in patients treated with tamoxifen.

In a large clinical study, patients with early breast cancer experienced more fractures whilst treated with Arimidex in comparison to patients treated with tamoxifen *(the incidence of reported fractures regardless of causality is presented in Section 5.1 "Pharmacodynamic Properties").*

4.9 Overdose

There is limited clinical experience of overdose of Arimidex. There are no reports where a patient has taken a dose exceeding 60mg. No toxicity was observed and no clinically relevant adverse effects have been seen.

Acute toxicity was seen in animals at a dose greater then 45mg/kg (equivalent to 2.7g). Clinical trials have been conducted with various dosages of Arimidex, up to 60mg in a single dose given to healthy male volunteers and up to 10mg daily given to post menopausal women with advanced breast cancer; these dosages were well tolerated. A single dose of Arimidex 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 Arimidex 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

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

Arimidex does not possess any progestogenic, androgenic or oestrogenic activity.

Daily doses of Arimidex 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.

An extensive phase III clinical study programme showed that Arimidex is an effective treatment of hormone-receptor positive breast cancer in postmenopausal women.

Primary adjuvant treatment of early breast cancer
In a large phase III study conducted in 9366 postmenopausal women with operable breast cancer after a median duration of treatment of 60 months, Arimidex was shown to be statistically superior to tamoxifen in disease-free survival for patients with hormone-receptor positive tumours (incidences = 16.2% vs 19.1% for the Arimidex and tamoxifen arms, respectively, HR = 0.83, 95% CI = 0.73 to 0.94). A beneficial effect of Arimidex over tamoxifen in disease-free survival was not seen in patients with receptor negative disease. The incidence of contralateral breast cancers was statistically significantly reduced for Arimidex compared to tamoxifen for patients with hormone-receptor positive tumours (incidences = 1.0% vs 2.1%, OR = 0.47, 95% CI = 0.30 to 0.76).

Arimidex was statistically superior to tamoxifen in time to recurrence. The difference was of greater magnitude than in disease-free survival for both the Intention To Treat (ITT) population and hormone-receptor positive population.

Arimidex was statistically superior to tamoxifen in terms of time to distant recurrence. There was also a numerical trend in favour of Arimidex for distant disease-free survival but this result was not statistically significant.

The overall survival benefit of tamoxifen was maintained with Arimidex. The additional analysis of time to death following recurrence showed a numerical trend in favour of Arimidex compared to tamoxifen, but this was a non-statistically significant advantage.

Overall, Arimidex was well tolerated. The following adverse events were reported regardless of causality. Patients receiving Arimidex had a decrease in hot flushes, vaginal bleeding, vaginal discharge, endometrial cancer, venous thromboembolic events and ischaemic cerebrovascular events compared with patients receiving tamoxifen. Patients receiving Arimidex had an increase in joint disorders (including arthritis, arthrosis and arthralgia) and the observed incidence of fractures was higher with Arimidex than with tamoxifen (10.2% vs 6.8%, respectively), although the incidence of hip fractures (those associated with the greatest degree of morbidity/mortality) was similar between the 2 groups (0.9% vs 0.8% respectively). A fracture rate of 22 per 1000 patient years was observed on Arimidex and 15 per 1000 patient years with the tamoxifen group with a median follow up of 68 months. The fracture rate for Arimidex falls within the broad range of the fracture rates reported in an age matched postmenopausal population.

The combination of Arimidex and tamoxifen did not demonstrate any efficacy benefit in comparison to tamoxifen.

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 being treated with adjuvant tamoxifen, patients had a superior disease-free survival when switched to Arimidex compared with those continuing 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 Arimidex, 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 Arimidex. Overall survival was similar for the two treatment groups.

Two further similar trials (GABG/ARNO 95 and ITA) with Arimidex, as well as a combined analysis of ABCSG 8 and GABG/ARNO 95, supported these results.

The Arimidex 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 Arimidex were stratified to low, moderate and high risk groups according to their existing risk of fragility fracture. All patients received treatment with vitamin D and calcium. Patients in the low risk group received Arimidex alone, those in the moderate group were randomised to Arimidex plus bisphosphonate or Arimidex plus placebo and those in the high risk group received Arimidex plus bisphosphonate.

The 12-month main analysis has shown that patients already at moderate to high risk of fragility fracture had their bone health (assessed by bone mineral density and bone formation and resorption markers) successfully managed by using Arimidex in combination with a bisphosphonate. In addition, no changes in BMD were seen in the low risk group treated with Arimidex alone and given vitamin D and calcium. 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 postmenopausal women with early breast cancer scheduled to be treated with Arimidex should have their bone status managed according to treatment guidelines already available for postmenopausal women at similar risk of fragility fracture.

Lipids

In the SABRE study, there was a neutral effect on plasma lipids both in those patients treated with Arimidex alone, and in those treated with Arimidex plus a bisphosphonate.

Paediatrics

Arimidex is not indicated for use in children. 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 are available *(see also section 5.3).*

The European Medicines Agency has waived the obligation to submit the results of studies with Arimidex in one or several subsets of the paediatric population in short stature due to growth hormone deficiency (GHD), testotoxicosis, gynaecomastia, and McCune-Albright syndrome.

Short stature due to Growth Hormone Deficiency

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

After 3 years anastrozole was found to statistically significantly slow bone maturation in pubertal boys on growth hormone therapy. No statistically significant difference with placebo was observed for the growth related parameters of predicted adult height, height, height SDS, 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 2-9) with familial male-limited precocious puberty, also known as testotoxicosis, treated with combination of Arimidex 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 study
Trial 0006 was a randomised, double-blind, multi-centre study of 80 pubertal boys (aged 11-18 years inclusive) with gynaecomastia of greater than 12 months duration treated with Arimidex 1 mg/day or placebo daily for up to 6 months. A decrease of ≥50% in total breast volume measured by ultrasound was seen in 38.5% (15/39) of the Arimidex and 31.4% (11/35) of the placebo treated group (odds ratio = 1.513, 95% CI 0.496 to 4.844, p=0.4687).

Trial 0001 was an open label, multiple-dose pharmacokinetic (PK) study of Arimidex 1 mg/day in 36 pubertal boys with gynaecomastia of less than 12 months duration. A decrease in total breast volume of 50% or greater at 6 months was seen in 55.6% (20/36) of the boys.

McCune-Albright Syndrome study

Trial 0046 was an international, multi-centre, open label exploratory trial of Arimidex in 28 girls (aged 2 to ≤10 years) with McCune-Albright Syndrome. No statistically significant change in the frequency of vaginal bleeding days on treatment was observed. 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. 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).

The overall assessment of the adverse events in children less than 18 years of age raised no safety and 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 Arimidex 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. Pharmacokinetic parameters in boys were comparable to those of postmenopausal women. 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, a major metabolite in plasma and urine, 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 100mg/kg/day by the oral route and greater than 50mg/kg/day by the intraperitoneal route. In an oral acute toxicity study in the dog the median lethal dose was greater than 45mg/kg/day.

Chronic Toxicity
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 (1mg/kg/day) and mid-doses (dog 3mg/kg/day; rat 5mg/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 400mg/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 1mg/kg/day and increased pre-implantation loss at 0.02mg/kg/day. These effects were related to the pharmacology of the compound and were completely reversed after a 5-week compound withdrawal period.

The survival of litters born to rats given anastrozole at 0.02mg/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 the 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 (25mg/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

Lactose monohydrate
Povidone
Sodium Starch Glycolate
Magnesium Stearate
Hypromellose
Macrogol 300
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the blister and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC blister/aluminium foil pack of 28 tablets contained in a carton.

6.6 Special precautions for disposal

No special requirments.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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UK

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1328/155/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd June 2011

10 DATE OF REVISION OF THE TEXT