ARIMIDEX (Anastrazole)

Core Safety Profile

1. INTRODUCTION

The CSP for Arimidex has been developed following the assessment of the PSUR under the EU PSUR Synchronisation Scheme. The CSP has been generated based on an assessment by all Concerned Member States, with the UK Health Authority as the P-RMS. The assessment was based on a comparison of the MRP Summary of Product Characteristics (SmPC), and the Reference Safety Information (AstraZeneca Company Core Data Sheet). This is in accordance with the EU Notice to Applicants Vol 9A, 1.6, and the Guidance Document for Marketing Authorisation Holders on Submissions under the EU PSUR Synchronisation Scheme (July 2008).

1.1 ARIMIDEX Core Safety Profile

1.1.1 4.3 Contraindications

Arimidex is contraindicated in:

- Pregnant or breast-feeding women.
- Patients with known hypersensitivity to anastrozole or to any of the excipients as referenced in section 6.1

1.1.2 4.4 Special warnings and precautions for use

General

Arimidex 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 Arimidex with LHRH analogues.

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

Effect on bone mineral density

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

Hepatic impairment

Arimidex 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 Arimidex 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

Arimidex 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 Arimidex should be performed with caution (see section 4.2).

Paediatric population

Arimidex 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).

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.

Hypersensitivity to lactose

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.

1.1.3 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 Arimidex 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 Arimidex 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 estrogen-containing therapies with Arimidex should be avoided as this may diminish its pharmacological action (see section 4.4 and 5.1).

1.1.4 4.6 Fertility, pregnancy and lactation

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

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

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

1.1.5 4.7 Effects on ability to drive and use machines

Arimidex has no or negligible influence on the ability to drive and use machines. 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..

1.1.6 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 Arimidex, 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

Adverse reactions by SOC and frequency		
Metabolism and nutrition disorders	Common	Anorexia Hypercholesterolaemia
	Uncommon	Hypercalcaemia (with or without an increase in parathyroid hormone)
Nervous system disorders	Very common	Headache
	Common	Somnolence Carpal Tunnel Syndrome*
Vascular disorders	Very common	Hot flushes
Gastrointestinal disorders	Very common	Nausea

Table 1 Adverse reactions by System Organ Class and frequency

Adverse reactions by SOC and frequency		
	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 Arimidex 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 Arimidex. If bleeding persists, further evaluation should be considered.

The table 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 2ATAC study pre-specified adverse events

Adverse events	Arimidex (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%)
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 Arimidex and tamoxifen groups, respectively, after a median follow-up of 68 months. The observed fracture rate for Arimidex is similar to the range reported in age-matched postmenopausal populations. The incidence of osteoporosis was 10.5% in patients treated with Arimidex 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 Arimidex treatment reflect a protective effect of tamoxifen, a specific effect of Arimidex, or both.

1.1.7 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 Arimidex, 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 Arimidex 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 Arimidex is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.