

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of Arimidex

Arimidex (anastrozole) is a 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.

Arimidex was first approved in 1995 in the UK and via a MRP procedure in Austria, Germany, Italy, Portugal and Spain. In all other EU-countries, approval has been granted through national procedures.

Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product, the European Commission notified the CHMP/European Medicines Agency of an official referral under Article 30 of Directive 2001/83/EC as amended, in order to resolve divergences amongst the nationally authorised SPCs and thus to harmonise its divergent SPCs across the EU.

Quality aspects

The Quality Modules of Arimidex Tablet Marketing Authorisation Application have been harmonised and updated from Notice to Applicant (NTA) format to Common Technical Document (CTD) format.

Specifications

The active substance specification has been harmonised and includes the following tests: description, identification, clarity of solution, sulphated ash, water content, strength, related substances, residual solvent, heavy metals, specific surface area and microscopy.

The applicant will have to ensure compliance with the relevant Ph. Eur. monograph of anastrozole which is currently under revision.

The active substance specification complies with all relevant guidelines and standards.

The drug product specification has been harmonised and includes the following tests: description, average weight, identity, dissolution, content, uniformity of content, water content, degradation products, identification of titanium dioxide and microbial quality.

The drug product specification complies with all relevant guidelines and standards.

Stability

Stability data from production scale batches of the active substance and drug product which was already approved in some member states was presented. In all cases the results were within the approved specifications.

The active substance is stable under the conditions specified in the dossier.

Arimidex tablets are very stable under the conditions recommended in the product information, i.e. "store under 30°C"

Manufacturer

The list of manufacturers in the harmonised version of the dossier has been updated and the sites no longer in use have not been included.

Clinical aspects

Summary of Product Characteristics

Section 4.1 Therapeutic indications

The indications were essentially the same but worded differently in the various countries. In order to harmonise the SPCs for Arimidex, the following therapeutic indications were agreed upon:

- ***Treatment of hormone receptor-positive advanced breast cancer in postmenopausal women.***

In its initial proposal the MAH suggested the following wording: *Treatment of advanced breast cancer in postmenopausal women. Efficacy has not been demonstrated in estrogen receptor-negative patients unless they had a previous positive clinical response to tamoxifen.* However, CHMP considered that this could be misinterpreted as implying an effect in hormone receptor negative patients, when in fact it merely reflects the inclusion criteria of clinical studies. Aromatase inhibitors have demonstrated efficacy in estrogen receptor positive patients, and has shown to have little efficacy in hormone receptor negative patients as could be anticipated by the mechanism of action.

- ***Adjuvant treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women.***

The majority of the Member States currently have the same wording or wording within the same meaning with respect of this indication. The inclusion of the term '*invasive*' is supported by data from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) study in which 9366 patients were evaluated from 381 centres worldwide (3125 randomised to anastrozole 1 mg alone, 3116 randomised to tamoxifen 20 mg alone and 3125 randomised to anastrozole plus tamoxifen). One of the main inclusion criteria for this study was histologically proven operable *invasive* breast cancer.

In a small number of countries the indication includes reference to the reduction in incidence of contra lateral breast cancer, based on a secondary endpoint of the previously mentioned ATAC study. The CHMP noted that the MAH did not suggest its inclusion as part of the harmonised indication, and agreed to this. A reference to reduction in incidence of contra lateral breast cancer would not add to the patient population and should therefore be included only in section 5.1 of the SPC.

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

Identical wording for this indication exists in 19 out of the 29 countries where Arimidex is approved. The remaining 10 countries do not currently have wording to this effect. The proposed indication is supported by a phase III trial (Austrian Breast and Colorectal Cancer Study Group [ABCSSG] 8) conducted in postmenopausal women with hormone receptor positive early breast cancer. Patients who switched to Arimidex after 2 years of adjuvant treatment with tamoxifen had a significant improvement in disease free survival compared to patients who remained on tamoxifen.

Section 4.2 Posology and method of administration

The CHMP noted the MAH's proposal for section 4.2. A recommended duration of treatment of 5 years is justified by the results of the ATAC study, in which the efficacy of adjuvant treatment with Arimidex was compared to adjuvant treatment with tamoxifen. The wording on posology did not differ significantly across Member States, but recommendations on use in renal and hepatic impairment were not harmonised. The final adopted wording on use in renal and hepatic impairment is as follows:

Renal impairment

No dose change is recommended in patients with mild or moderate renal impairment. In patients with severe renal impairment, administration of Arimidex 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).

Section 4.3 Contraindications

The MAH presented a proposal for section 4.3 which was based on the currently existing contraindications in the different countries. The Committee considered that most of the contraindications proposed were not appropriate as such, given that they reflected the lack of relevant data rather than absolute contraindications. ‘Premenopausal women’ and ‘patients with concomitant tamoxifen therapy’ were deleted from this section and information moved to section 4.4. Information on severe renal impairment and moderate or severe hepatic impairment was also moved to section 4.4, as based on the latest studies a significant increase in exposure is not expected with renal impairment, and only a modest increase in exposure was observed in patients with hepatic impairment. The CHMP adopted the following wording for this section:

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.*

Section 4.4 Special warnings and precautions for use

The CHMP noted the MAH’s proposal for section 4.4 and agreed with the majority of the content. Revised warnings were suggested regarding renal and 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. Therefore the proposed warning on renal impairment was revised, at the request of the CHMP, to reflect that exposure to anastrozole is not increased in patients with severe renal impairment, but still in these patients administration should be performed with caution.

In study 1033IL/0014, the apparent clearance (CL/F) of anastrozole, following oral administration, was approximately 30% lower in volunteers with stable hepatic cirrhosis, although plasma anastrozole concentrations in the volunteers with hepatic cirrhosis were within the range of concentrations seen in normal subjects in other trials. Therefore, the CHMP concluded that the lack of data in moderate to severe hepatic impairment should be highlighted, but that considering the fact that the product is a potentially life-saving treatment, a warning rather than a contraindication was appropriate. Administration of Arimidex in patients with hepatic impairment should be performed with caution.

In one country the SPC contained the warning ‘*slight increases in total cholesterol have been observed in patients treated with Arimidex. Patients-presenting with confirmed coronary disease or risk factors should undergo lipid monitoring and should be treated according to the guidelines in force*’. The CHMP supported the proposal from the MAH not to include this warning in the harmonised wording, as the published clinical studies do not indicate a significant increase in total cholesterol or LDL-C, or a decrease in HDL-C after Arimidex use.

The final adopted wording for this section is the following:

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 ($GRF < 30 \text{ ml/min}$, 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.

Section 4.5 Interaction with other medicinal products and other forms of interaction

The CHMP noted the wording proposed by the MAH for the harmonisation of this section, which included a statement to the fact that antipyrine and cimetidine clinical interaction studies indicate that significant drug interactions mediated by cytochrome P450 are unlikely. The Committee considered that available study results and current scientific knowledge allow for more detailed and informative wording on the potential for cytochrome P450 interactions. Given that cimetidine is currently known to be a weak, unspecific cytochrome P450 inhibitor, it was considered more relevant to include reference to existing data on warfarin. The final adopted wording for this section is as follows:

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).

Section 4.6 Fertility, pregnancy and lactation

In most countries the SPCs contained only a contraindication for the use of anastrozole in pregnancy and lactation with no additional information. The CHMP noted the proposal from the MAH to contraindicate use in pregnancy and lactation but considered that reference should be made to the lack of data in humans and a reference to reproductive toxicity in animals should be included. In addition, the Committee considered that the contraindication would be more appropriate for breastfeeding women rather than lactating women. A subheading on fertility was also introduced. The final agreed wording for this section is as follows:

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).

Section 4.7 Effects on ability to drive and use machines

There were no significant differences between the SPC of different countries for this section. The CHMP noted and agreed with the MAH proposal for this section:

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.

Section 4.8 Undesirable effects

In section 4.8, the MAH proposed to align the System Organ Class terms with the MedDRA dictionary, including the frequency groupings, harmonising several adverse reaction frequencies that varied between Member States, and updating the frequency of events such as Stevens-Johnson syndrome and angioedema from 'not known' to 'very rare', based on data from the ATAC study 5-year analysis. The CHMP considered also that a summary of the safety profile needed to be included in the beginning of the section in accordance to the SPC guideline. The CHMP further asked the MAH to include information present in the SPC of some countries on the occurrence of carpal tunnel syndrome in clinical trials. Bone density decrease and Henoch-Schönlein purpura were added to section 4.8 as adverse events.

Section 4.9 Overdose

The wording for this section of the SPC was similar in most countries. The CHMP agreed with the following wording proposed by the MAH:

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.

Section 5.1 Pharmacodynamic properties

The CHMP noted the wording suggested by the MAH for this section and proposed a few revisions. One statement proposed in relation to the SABRE study mentioned a neutral effect of Arimidex on plasma lipids in patients concomitantly treated with risendronate. The CHMP requested for this statement to be deleted as it is contradictory with the inclusion of hypercholesterolaemia as a common adverse event in section 4.8. The MAH also proposed to include a summary of the paediatric studies on gynaecomastia and McCune-Albright syndrome, which had already been approved in a number of countries. This was accepted but may need to be revised in the future as a consequence of an ongoing procedure under Art. 45 of Regulation 1901/2006 as amended specifically to assess this data. Other changes were introduced in the description of the clinical trials supporting the indication to clarify and streamline the information for the prescriber.

Section 5.2 Pharmacokinetic properties

The wording for this section did not significantly differ between countries. The CHMP noted the proposal from the MAH and asked for a revision of the wording on the pharmacokinetics on the paediatric population, to clarify the exact characteristics of the population studied and its potential impact on the results obtained. As mentioned above, the wording of this paragraph may need to be

revised in the future as a consequence of an ongoing procedure under Art. 45 of Regulation 1901/2006 as amended specifically to assess this set of paediatric data.

Section 5.3 Preclinical safety data

The majority of the European countries had identical wording included in this section. The CHMP adopted the MAH's proposal with only minor amendments.

Labelling and Package Leaflet

Harmonised versions of the labelling and of the package leaflet were adopted. The changes to the SPC, when relevant, were also reflected in the package leaflet.

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas

- the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet
- the summary of products characteristics, labelling and package leaflet proposed by the marketing authorisation holders have been assessed based on the documentation submitted and the scientific discussion within the Committee

the CHMP has recommended the amendment of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Arimidex.