EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Patient Health Protection

Assessment Report pursuant to Article 30 of Directive 2001/83/EC, as amended

Arimidex

INN of the active substance: anastrozole

Marketing authorisation holder: AstraZeneca group of companies

Procedure no: EMEA/H/A-30/1263

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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1. Background information on the procedure

On 22 July 2010 the European Commission presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, as amended, in order to harmonise the national summary of product characteristics, labelling and package leaflet of the medicinal products Arimidex (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the July 2010 meeting. The marketing authorisation holder was informed of the start of the procedure.

Arimidex medicinal products are registered in the following EU Members States: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Romania, Slovak Republik, Slovenia, Spain, Sweden and United Kingdom and also in Iceland and Norway.

2. Scientific discussion during the referral procedure

2.1. Introduction

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 1 mg film-coated tablets is in most EU-countries currently indicated for the treatment of advanced breast cancer in postmenopausal women, as adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer, and adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.

Arimidex was first approved on 11 August 1995 in the UK and via a MRP procedure in AT, DE, IT, PT and ES. 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, 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.

The harmonisation of the Quality documentation (Module 3) has been also included in this procedure at the request of the Marketing Authorisation Holder.

2.2. Critical Evaluation

Quality aspects

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

Some sections of the harmonised application were not presented in the original application and sections S.2.6 and S.6 for the drug substance and sections P.4.2-P.4.4, P.4.6, P.5. and P.6 for the drug product have been added for completeness.

Specifications
The drug substance specification includes: description, identification, clarity of solution, sulphated ash, water content, strength, related substances, residual solvent, heavy metals, specific surface area and microscopy.

The MAH was requested to update the drug substance specification limit of "any other impurity" to 0.10% to comply with current regulations. Additionally, as work on a Ph. Eur. monograph of anastrozole has been initiated (#2406) the applicant was required to adhere to the limits of the monograph, once it is published.

The harmonised specification proposed for Arimidex tablets is as approved in Mutual Recognition procedures, but differs in that the dissolution specification complies with the British Pharmacopoeia requirements, it includes an additional non routine test for microbial quality and a statement relating to a non routine test available for identity of titanium dioxide. The drug product specification includes: description, average weight, identity, dissolution, content, uniformity of content, water content, degradation products, identification of titanium dioxide and microbial quality.

Stability
Commercial stability data for drug substance and drug product which was already approved in some member states was presented.

The provided stability results are acceptable and within specification. The already approved re-test period of 5 years when stored below 30°C for anastrozole was substantiated by the additional commercial batches. No other special storage conditions for the active substance are necessary.

Storage
Although Arimidex tablets are very stable, the storage precaution statement "store under below 30°C" was applied. The applicant clarified that this was due to the fact the EU packs of Arimidex tablets are shared with countries outside of the EU, including some in zone III and IV markets.

Manufacturer
The applicant proposed not to include Cardinal Health as bulk testing site and packaging site and AstraZeneca, Destelbergen BE as batch release site, in the harmonised version of Module 3, as they are no longer used in the supply chain for Arimidex tablets.

Although the applicant initially proposed the addition of Brecon Pharmaceuticals, Brecon Road UK as batch release site, this was not accepted as this has not been approved in any of the MS and therefore could not be accepted in the scope of the harmonisation.

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 [ABCSG] 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. The wording on posology did not differ significantly across Member States, but recommendations on use in renal and hepatic impairment were not harmonised. The 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 final adopted wording is as follows:

Posology

The recommended dose of Arimidex 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.

Special populations

Paediatric population
Arimidex 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 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).

Method of administration

Arimidex should be taken orally.

Section 4.3 Contraindications

The MAH presented a proposal for section 4.3 which was based on the currently existing contra-indications 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<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.

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 antipyridine 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 anastrazole 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. The following harmonised wording was adopted for section 4.7:

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. The final agreed wording for this section is as follows:

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*
Nervous system disorders	*Very common*	*Headache*
	Common	*Somnolence* *Carpal Tunnel Syndrome**
Vascular disorders	*Very common*	*Hot flushes*
Gastrointestinal disorders	*Very common*	*Nausea*
	Common	*Diarrhoea* *Vomiting*

Table 1 Adverse reactions by System Organ Class and frequency

Adverse reactions by SOC and frequency		
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*
	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' (≥ 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 2 ATAC 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%)*

Table 2 ATAC study pre-specified adverse events

Adverse events	***Arimidex (N=3,092)***	***Tamoxifen (N=3,094)***
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.

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.

2.3. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Recommendation

In conclusion, the CHMP recommended the revision and harmonisation of the Product Information for Arimidex and adopted the following harmonised indications:

Arimidex is indicated for the:

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

2.5. Conclusions

The basis for this referral procedure was a harmonisation of the SPC, labelling and package leaflet. The CHMP having considered:

- the rapporteur and co-rapporteur assessment reports,
- scientific discussion within the Committee,
- comments from the marketing authorisation holder,

was of the opinion that the benefit/risk ratio of Arimidex is considered to be favourable. The CHMP adopted a positive opinion recommending the harmonisation of the SPC, labelling and package leaflet as set out in Annex III of the CHMP opinion for Arimidex.