22 May 2012
EMA/267448/2012

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

Femara and associated names

INN of the active substance: letrozole

Marketing authorisation holder: Novartis group of companies and associated companies

Procedure no: EMEA/H/A-30/1264

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

1.1. Background information on the basis of the grounds for referral

On 31 August, 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 (SmPC), labelling and package leaflet (PL) of Femara and associated names (see Annex I of CHMP opinion).

Further to consideration of the matter by the Committee for Medicinal Products for Human Use (CHMP), the referral procedure was initiated during its September 2010 meeting. The marketing authorisation holder (MAH) was informed of the start of the procedure.

The CHMP appointed Tomas Salmonson (Sweden) as rapporteur and Barbara van Zwieten-Boot (The Netherlands) as co-rapporteur.

Femara medicinal products are registered in all EU Member States as well as in Iceland and Norway.

2. Scientific discussion during the referral procedure

2.1. Introduction

Femara contains letrozole, an orally active non-steroidal competitive aromatase inhibitor which inhibits the conversion of androgens to oestrogens both *in vitro* and *in vivo*. Femara was first approved in the European Union (EU) in 1996 and is available as a 2.5 mg film-coated tablet. Femara is approved for a number of indications related to the treatment of breast cancer in postmenopausal women with disease progression. In the EU/European Economic Area (EEA), Femara is approved in 14 member states (MS) through the Mutual Recognition procedure (MRP) with France as Reference Member State (RMS) and the following Concerned Member States (CMS): Austria, Belgium, Denmark, Finland, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain and Sweden. Femara is approved through national approvals in the remaining EU/EEA member states.

Femara was included in the list of products for Summary of Product Characteristics (SmPC) harmonisation, as drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended, due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product (and its associated names). The European Commission (EC) therefore notified the CHMP/EMA Secretariat of an official referral under Article 30 of Directive 2001/83/EC, as amended in order to resolve these divergences and thus harmonise the product information (PI) across the EU.

The main areas of disharmony were Sections 4.1, 4.2, 4.3 and 4.4. Nevertheless, the MAH was asked to review all other sections of the nationally approved EU SmPCs and suggest appropriate changes in the text where divergences exist. As a consequence, the entire PI was reviewed and harmonised by the CHMP. Regarding Section 4.1, the CHMP noted that five indications were approved for Femara in the EU, although all indications were not approved in all member states. Acknowledging divergences in the exact wording, the general approved indications were the following:

1) *Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer*
2) *Extended adjuvant treatment of early breast cancer in postmenopausal women who have received 5 years of adjuvant tamoxifen therapy*
3) *First-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer*

4) *Treatment of advanced breast cancer in postmenopausal women with disease progression following anti-oestrogen therapy*
5) *Pre-operative therapy in postmenopausal women with localized hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for this type of surgery*

Regarding Section 4.2, the differences were mainly a result of the differences in the indications, including important differences in treatment duration. In addition, the use of Femara in renal and hepatic impairment was not harmonised**.** In response to the CHMP list of questions, the MAH provided proposals for a harmonised Product Information, a tabulated overview of the major differences between the current nationally authorised SmPCs and an updated clinical Expert Report with literature references.

2.2. Critical Evaluation

Section 4.1 – Therapeutic Indications

1) Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.

The MAH stated that the pivotal study for the adjuvant treatment indication, BIG 1-98, coordinated by the collaborative group IBCSG (International Breast Cancer Study Group) and the parent organization BIG (Breast International Group), specifically excluded patients who did not have a confirmed diagnosis of invasive breast cancer. Both organisations did not consider non-invasive contralateral or ipsilateral breast cancers as disease-free survival events. The MAH therefore considered it appropriate to include "invasive breast cancer" in the indication wording.

The CHMP noted that the proposed wording was consistent with the wording in the nationally approved SmPCs, with the exception of the term "*invasive*", which is only present in two MSs. However, the CHMP agreed that the data was obtained from a study which excluded all non invasive breast cancer patients (BIG 1-98) and that no studies on DCIS (ductal carcinoma *in situ*) or LCIS (lobular carcinoma *in situ*) patients have been performed (*Dixon et al*. J Steroid Biochem Mol Biol. 2007 Aug-Sep;106(1-5):173-9. Epub 2007 May 24. DCIS and aromatase inhibitors). The CHMP therefore agreed to include the term 'invasive'. In conclusion, the CHMP adopted the following harmonised indication:

"Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer."

2) Extended adjuvant treatment of hormone-dependent-invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years.

The MAH stated that it is unlikely that patients who have completed 5 years of adjuvant therapy with tamoxifen would not have hormone-dependent breast cancer. Nevertheless, the MAH considered that the MRP wording including "*hormone-dependent*" is relevant. To avoid confusion with sequencing of endocrine therapies, or administration of 2 to 3 years of tamoxifen followed by an aromatase inhibitor, the MAH considered it necessary to state clearly that adjuvant therapy with tamoxifen should have been given for 5 years and proposed to add the qualifier *"... for 5 years (i.e. at least 4.5 years)"*. The MAH considered that the word "*invasive*" early breast cancer was not justified for the extended adjuvant treatment setting (in contrast to the initial adjuvant setting). The MA-17 study, on which the extended adjuvant treatment setting was based, included a small number of cases with ductal carcinoma *in situ* (DCIS) and of lobular carcinoma *in situ* (LCIS), which responded successfully to Femara.

The CHMP noted that the proposed wording was consistent with the wording in the majority of the nationally approved SmPCs, including those where Femara was approved through MRP, with the exception of 4 MSs where the information "*for 5 years*" is not included, one MS where the clarification "*invasive*" is included and one MS where "*hormone-dependent*'' is not mentioned. The CHMP considered that the inclusion of the term "*hormone-dependent*" was justified, as letrozole has no efficacy in hormone receptor negative breast cancer. The CHMP also considered that providing information on the treatment duration with tamoxifen is justified, based on studies in which letrozole

was administered after 5 years of adjuvant tamoxifen. Regarding "*invasive*", the CHMP did not consider it common practice to prescribe aromatase inhibitors to patients with no invasive component. It is known that anti-hormonal therapy with tamoxifen in DCIS can decrease cancer recurrence by about 30% (*Cohen and Ward*. J Natl Compr Canc Netw. 2010 Oct;8(10):1211-7. Risk reduction strategies for ductal carcinoma *in situ*). No studies have been performed in DCIS or LCIS on the use of extended adjuvant aromatase inhibitors after tamoxifen. In the publication of the MA-17 study by Goss (2003, NEJM), no information on DCIS and or LCIS patients is provided. One of the inclusion criteria was histologically confirmed primary breast cancer. The results of this study did show less new DCIS and LCIS lesions in the aromatase inhibitor treated group compared to the placebo group. However, since the studies performed did not include significant numbers of DCIS and LCIS patients and there is no reason to suggest a different mechanism of action in the extended adjuvant setting compared with the adjuvant setting, the CHMP considered it justified to qualify the indication with "*invasive"*. In conclusion, the CHMP adopted the following harmonised indication:

"Extended adjuvant treatment of hormone-dependent-invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years."

3) First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.

The MAH stated that the indication was well-established and that most MSs had wording similar to that of the MRP SmPC.

The CHMP agreed that this indication is well-established and that the proposed wording was consistent with the nationally approved SmPCs, including the MRP SmPCs. Only two MSs did not mention the wording "*hormone-dependen*t" but the CHMP considered the inclusion to be justified, as letrozole has no efficacy in hormone receptor negative breast cancer. In conclusion, the CHMP adopted the following harmonised indication:

"First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer."

4) Advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status, who have previously been treated with anti-oestrogens.

The MAH stated that since the initial marketing authorisation as second-line endocrine treatment of metastatic breast cancer, the importance of confirming the postmenopausal endocrine status of women before initiation of treatment has been recognised for both efficacy and safety reasons. It has been shown that women with induced menopausal status, particularly by chemotherapy, may not be of postmenopausal endocrine status. In many cases, efficacy was suboptimal and high rates of menopausal symptoms such as hot flushes occurred, as their perimenopausal status was insufficient to suppress the feedback loop of oestrogen synthesis. The MAH proposed to add supportive text in the Section 4.4, to emphasise that postmenopausal endocrine status is a pre-requisite for use of Femara.

The CHMP was of the opinion that the indication is well-established and that the proposed wording was largely consistent with the nationally approved SmPCs, including the MRP SmPCs. Only three MSs had a slightly different wording. The CHMP noted that the MAH justification focused on the postmenopausal status. The CHMP agreed that the endocrine status of patients with unclear menopausal status should be checked, which is already suggested in section 4.4 of the proposed harmonised SmPC: '*In patients whose menopausal status is unclear, LH, FSH and/or oestradiol levels should be measured before initiating treatment with Femara. Only women of postmenopausal endocrine status should receive Femara*'. In conclusion, the CHMP adopted the following harmonised indication:

"Advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status, who have previously been treated with anti-oestrogens."

5) Neoadjuvant treatment of postmenopausal women with hormone receptor positive, HER-2 negative breast cancer where chemotherapy is not suitable and immediate surgery not indicated.

The MAH stated that the neoadjuvant (pre-operative) treatment indication represents the major deviation in the EU Femara SmPCs. The application for the neoadjuvant treatment indication was submitted in 2000 in both MRP and non-MRP MSs. While it was approved nationally in 5 MSs in 2001,

the application was withdrawn in the MRP MSs based on the preliminary assessment report, prior to the final RMS variation assessment report. In the preliminary variation assessment report, the RMS indicated that the neoadjuvant indication could not be approved, primarily because neoadjuvant endocrine treatment was not a validated concept at the time and because the results of the pivotal adjuvant study, BIG 1-98, were not available, especially for disease-free survival and overall survival. The MAH is of the view that there is now sufficient information available to justify the neoadjuvant (pre-operative) treatment indication for Femara and that the situation across Europe regarding neoadjuvant therapy, in particular neoadjuvant endocrine therapy, has changed dramatically since 2000-2001. Although some current guidelines still propose that women have surgery within two weeks of diagnosis of breast cancer, few regions (within a country or across countries) have the available resources, facilities or cost coverage to comply with such recommendations. In clinical practice, neoadjuvant (pre-operative) therapy for some months may successfully down-size the breast tumour to allow breast-conserving surgery (BCS), or to allow inoperable tumours to become operable. Neoadjuvant therapy may reduce tumour volume to such an extent that BCS becomes possible even in women with small breasts, by reducing the tumour-breast ratio to preserve a satisfactory cosmetic effect. BCS is associated with less morbidity and less mortality than mastectomy, which is an important consideration in elderly and/or frail women, many of whom are likely to have concomitant debilitating medical conditions. Regardless of whether or not the patient was originally considered suitable for BCS, there are other advantages of neoadjuvant therapy, well documented over the past decade. Neoadjuvant therapy will provide information in a relatively short period of one to two months on whether the patient is likely to benefit from adjuvant therapy, and if so, whether the adjuvant therapy should be endocrine or chemotherapeutic. Sufficient evidence is now available with respect to tumour biomarkers examined in the pre-operative phase to allow individually-tailored therapy after surgery.

The MAH clarified that although the therapeutic intent of neoadjuvant therapy may be to allow BCS, the word "*neoadjuvant*" covers the situation in which surgery is not possible for various reasons (e.g. age, medical condition/status, availability of surgery and post-surgical care, patient refusal). In order to convey this intent, "*neoadjuvant*" is qualified by stating "*pre-operative*". Regarding the duration of treatment, the MAH stated that while early studies in the neoadjuvant treatment setting proposed 3 to 4 months of therapy, based on the duration of the preceding neoadjuvant chemotherapy, new evidence has become available from recent studies investigating the duration of neoadjuvant therapy. Although some studies have used Femara in the neoadjuvant indication for 12 months or more, maximum/optimum benefit appears to be gained at 4-8 months, with very little incremental benefit beyond that. There appears to be consensus in most studies investigating duration of neoadjuvant therapy that the minimum is 4-6 months. Monthly breast sonograms or magnetic resonance imaging as well as monthly clinical examinations are recommended, in order to alert the physician to progression of disease as soon as possible. The MAH also proposed that "*primary*" should be added, to reflect that the primary breast tumour should not have been resected and should not have been treated before initiation of neoadjuvant therapy. The MAH provided evidence from clinical studies to further support the neoadjuvant treatment indication, as summarised below.

The pilot study AR/ET1 was performed in a single UK centre and initially included 12 postmenopausal women, with a mean age of 78 years (61-87 years). Seven were expected to undergo mastectomy, five were suitable for breast conserving therapy. An additional 12 patients, with a mean age of 72 years (52-84 years) were enrolled, of which eight were expected to undergo mastectomy. Patients received letrozole 2.5 mg once daily for 3 months prior to surgery. Overall, clinical responses were seen in 88% of the patients. Imaging gave one complete response, nine partial responses and two with no change. Median duration (in 24 patients) of adjuvant treatment was 52 months. In total, 10 (42%) patients relapsed (3 loco-regional recurrences, 7 distant relapses). Eight patients died, 6 with metastatic disease and 2 from a non-cancer cause.

Study P024 was a pivotal study enrolling 337 patients from 55 centres in 16 countries. The study was double-blinded, with equal randomisation using permuted blocks. No stratification on baseline characteristics was performed. Patients received letrozole 2.5 mg or tamoxifen 20 mg once daily for 4 months prior to surgery. All patients enrolled had oestrogen receptor (ER) positive and/or progesterone receptor (PgR) positive tumours. Median age was 68 and 67 years in the letrozole and tamoxifen group respectively. 86% of the patients were considered to be suitable for mastectomy, 14% considered inoperable. Overall clinical response was significantly higher in the letrozole arm (55%) than in the tamoxifen arm (36%), leading to BCS in 45% and 35% respectively. Following surgery, most (> 80%) patients received tamoxifen adjuvant therapy which was the approved standard therapy. Median follow-up of patients was 5 years. There were no significant differences between the original treatment arms in disease-free survival or overall survival at the end of adjuvant treatment. Approximately 40% of the patients in both treatment arms had a recurrence/relapse. Distant

metastasis as site of first recurrence/relapse occurred in just under 20% of patients in each treatment arm, with a further 9% of patients in each treatment arm having loco-regional recurrence as first site of treatment failure. Approximately a quarter of all patients had died by the end of 5 years of follow-up, with progression of the underlying breast cancer being considered the main cause of death in about half of all deaths. Significantly higher response rates to letrozole (88%) than to tamoxifen (21%) were found for HER-1/ HER-2 (Human Epidermal Growth Factor Receptor 1/2) over-expressing tumours, and tumours with intermediate ER expression were responsive to letrozole but not to tamoxifen. Tumours with high ER expression responded to both endocrine agents.

FEM-D-1 was a pilot study in which letrozole 2.5 mg was given as pre-operative treatment for 4 to 8 months to investigate the effects of the duration of neoadjuvant treatment. A total of 33 postmenopausal women with ER-positive breast cancer, expected to undergo mastectomy, were enrolled. Tumour response was assessable in 29 patients, with duration of letrozole neoadjuvant therapy of 4 months in 14 patients and longer than 4 months (median 7 months) in 15 patients. Compared with baseline, median tumour volume was reduced by over 60% at 4 months and by almost 70% at the “final visit” (median 7 months). Most patients had responded within 4 months. Breast-conserving surgery was performed in 22 of the 29 assessable patients (76%). In this study, there was some evidence suggesting that greater tumour regression occurred when pre-operative neoadjuvant treatment with letrozole was longer than 4 months.

CFEM345E GB07 was a single-arm multicenter phase IV study conducted to determine the optimal treatment duration of neoadjuvant treatment with letrozole 2.5 mg once daily given pre-operatively, to allow BCS in postmenopausal women who were initially assessed as suitable only for mastectomy. Trial subjects were postmenopausal women with ER positive and/or PgR positive tumours, classified as T2 (2-5 cm and no lymph node involvement) or greater and not suitable for BCS. Because letrozole had already been demonstrated to be superior to tamoxifen (Study P024, *Eiermann et al* 2001), it was considered unethical to use tamoxifen as comparator. As no endocrine agent other than letrozole was approved for neoadjuvant use in the UK, a single arm study design was decided upon. Tumour assessments were conducted at baseline and at 2-monthly intervals for up to 12 months, based on clinical palpation and breast ultrasound measurements of tumour diameter. Supplementary mammography and/or magnetic resonance imaging was conducted in most centres (*Forouhi et al* 1994). Following surgery, patients were to be followed for 5 years. Treatment beyond 12 months was at the discretion of the treating investigator. The primary endpoint was time until the patient became suitable for BCS. Secondary endpoints included RECIST (Response Evaluation Criteria In Solid Tumours) response rate, reduction in tumour volume, long-term (at 5 years) local recurrence rate and general safety. Interim results (*Carpenter et al* 2009) showed that most patients had responded by 8 months of treatment with letrozole. Patients were likely not to have sufficiently additional tumour shrinkage to qualify for BCS after 8 months of treatment if their tumour had not already regressed by then. As accrual was slower than expected, it was decided to terminate the study early on ethical grounds. In total, 146 patients median age 74 years (46-95) were enrolled at 20 sites in the UK. The majority had T2 tumours. No information is yet available on long-term local recurrence rates. Median duration of letrozole treatment was 6.6 months and median time until the patient became eligible for BCS was 7.5 months (95% CI 6.3, 8.5 months). Lumpectomy and quadrantectomy was performed in 53.2% and 4.6% of patients, respectively. Surgery was not performed in 24.4%, one patient was not operable, 13 patients had insufficient tumour response, 7 had progressive disease.

The ongoing REAL study, conducted in postmenopausal women with hormone receptor positive tumours larger than 2 cm, by the Danish Breast Cancer Group (DBCG), was also presented. The study is expected to enrol around 1500 patients, with equal randomisation to immediate surgery followed by adjuvant treatment for 5 years with letrozole or to neoadjuvant therapy with letrozole for 4 months, followed by surgery and then adjuvant treatment for 56 months with letrozole. Patients whose disease relapsed during the neoadjuvant treatment phase would receive chemotherapy following surgery. To date, no further information is available.

Regarding guidelines, the MAH also stated that in the past decade, several cancer organizations have specifically included neoadjuvant (pre-operative) endocrine treatment, especially with aromatase inhibitors, in treatment or practice guidelines (e.g. NICE 2009; St Gallen Consensus 2009; *Blohmer and Huober* on behalf of AGO 2010; *Kataja and Castiglione* on behalf of ESMO 2010). Endocrine neoadjuvant (preoperative) treatment is recommended for postmenopausal women with hormone receptor positive breast cancer. The St Gallen guidelines suggest that neoadjuvant endocrine therapy be used for “postmenopausal women with strongly receptor-positive disease” and recommend that, if such therapy is used, it should be given for “5-8 months or until maximum tumour response” (*Goldhirsch et al* 2009).

The MAH concluded that the current information on the effects (efficacy and tolerability) of letrozole in the neoadjuvant treatment setting, including long-term follow-up information, is sufficient to support the neoadjuvant (pre-operative) treatment indication for Femara, in particular with the aim to down-size hormone receptor-positive tumours to allow BCS. The optimal duration of neoadjuvant treatment with letrozole appears to be 4-8 months. Regular monitoring, especially by multi-modal evaluation, reveals progression of disease relatively early (generally within the first two months of treatment).

The CHMP noted that the neoadjuvant (preoperative) indication was applied for in 2000 in the majority of the MSs (both MRP and non-MRP) but was withdrawn in the MRP countries after the preliminary assessment report from the RMS, France and is now only approved in 5 MSs. The CHMP therefore reviewed the considerable new data available on the neoadjuvant indication, including the studies submitted by the MAH, noting that the MAH provided a complete and adequate Clinical Expert Statement on neoadjuvant Femara treatment.

The CHMP agreed that there is a large body of data for letrozole in the neoadjuvant indication suggestive of a positive benefit-risk balance. However, the CHMP was concerned that the studies presented did not compare neoadjuvant letrozole with relevant alternative treatment options for the sought indication (enabling BCS in locally advanced breast cancer (LABC) such as primary radical mastectomy or neoadjuvant poly-chemotherapy). Furthermore, the MAH referred to a population of frail, elderly patients where poly-chemotherapy is not an option; however, there are no restrictions to specific patient groups in the proposed indication. Finally, the intent of the proposed neoadjuvant therapy indication is to enable breast conserving therapy. However, in locally advanced breast cancer (LABC) which is the proposed diagnosis for this indication, the primary goal of neoadjuvant therapy is to achieve operability, and in the pivotal study the majority of the patients did not have a locally advanced breast cancer. The CHMP also questioned the divergence between the wording of the nationally approved indication, in which “localised breast cancer” is the target, and the wording proposed by the MAH where “locally advanced breast cancer” is targeted. The MAH was therefore requested to further justify the neoadjuvant indication.

The MAH responded that regarding the comparison with relevant treatment options, the pilot study AR/ET1 was conducted with letrozole alone to determine whether letrozole had an effect in the primary treatment of oestrogen receptor positive breast cancer prior to surgical intervention. The resulting overall clinical response rate of 88% justified the planning of the pivotal study P024. After taking advice from leading external clinicians, tamoxifen was chosen as the comparator, primarily because it was the only available and approved endocrine treatment in the neoadjuvant treatment of breast cancer and secondarily because it was considered important to conduct the study under double-blind conditions, given possible biases. A comparative study against chemotherapy was rejected for several reasons. Many women, especially those with no nodal involvement, will not require chemotherapy. No standard chemotherapy was approved worldwide for neoadjuvant use and a double-blind study involving “placebo chemotherapy” was precluded on ethical grounds. Additionally, chemotherapy (especially at the standards available at the time of application) tends not to be well-tolerated, particularly in elderly women. More than a decade ago, when the pivotal neoadjuvant study was being planned, the only widespread neoadjuvant treatment choice was either tamoxifen or an aromatase inhibitor, leading to letrozole being compared with tamoxifen in study P024. The results of study P024 showed that letrozole was significantly superior to tamoxifen in clinical response rate, mammographic response rate, breast ultrasound response rate and rate of BCS (*Eiermann et al* 2001). Study D01 was the pilot study for determining optimal duration of treatment. Study GB07 evolved from both P024 and D01 and because letrozole was the only approved endocrine treatment for neoadjuvant treatment of primary breast cancer in the UK and because P024 had shown that tamoxifen was significantly inferior to letrozole in the neoadjuvant setting, GB07 was designed as a single-arm study (with letrozole) on ethical grounds.

Non-MAH studies have generally not used a direct comparator. *Dixon et al* have examined several series of patients indirectly comparing letrozole with anastrozole and exemestane in the neoadjuvant setting. The results of study Z1031 by the American College of Surgeons Oncology Group, recently published, showed that letrozole and anastrozole have been selected for further consideration on the basis of their clinical response rates. Although the clinical response rates were not statistically significantly different, the response rate to letrozole was numerically higher (ITT analysis: letrozole, 75%; anastrozole, 69%; exemestane, 63%) (*Ellis et a*l 2011) and significant effects were demonstrated on Ki-67 index, a validated marker of proliferation. Thus, the reduction in tumour size/volume induced by neoadjuvant treatment with letrozole is demonstrably a real anti-tumour effect.

One of the main benefits of neoadjuvant treatment with letrozole has been the increase in BCS, an obvious benefit enhancing quality of life in a life-threatening disease. Studies in the adjuvant treatment

setting, based on disease-free survival and/or overall survival endpoints require several thousands of patients followed over several years of treatment and even longer follow-up. Studies designed to show superiority in the neoadjuvant setting, based on clinical response and/or surgical endpoints require hundreds of patients and can never be sufficiently powerful to provide conclusive evidence of improvements in disease-free survival or overall survival. Nevertheless, study P024 was predictive of the superiority of letrozole over tamoxifen in disease-free survival, distant metastasis, and indeed overall survival in the adjuvant study, BIG 1-98 (*Eiermann et al* 2001; *Colleoni et al* 2011).

Regarding the wording of the indication, the MAH proposed "*locally advanced breast cancer*" because P024 was conducted in postmenopausal women with locally advanced breast cancer and AR/ET1 was conducted in postmenopausal women with untreated locally advanced or large operable breast cancer. In both studies, clinically significant tumour downsizing occurred, including in T4 tumours and including large tumours that shrank sufficiently to allow BCS. From a review of the literature, "localised breast cancer" can be confused with or understood as DCIS (ductal carcinoma *in situ*). "Locally advanced breast cancer" (may be large tumours greater than 5 cm, may have spread to axillary or mammary lymph nodes, may have spread to regional tissues around the breast, e.g. skin or muscles) covers much more severe disease for which the prognosis is significantly poorer than that for women with "localized breast cancer" (restricted to the breast and has not spread to surrounding tissues or organs). However, the MAH agreed to remove the statement on diagnosis to avoid confusion.

The CHMP noted the study data comparing neoadjuvant endocrine therapy with an aromatase inhibitor (exemestane or anastrozole) to neoadjuvant chemotherapy, in women with receptor positive breast cancer. The study showed no statistically significant difference between aromatase inhibitors and chemotherapy, in objective response (complete response plus partial response) determined by clinical examination (palpation) and mammography according to WHO criteria, rates of BCS and the incidence of local recurrence (*Semiglazov et al* Cancer, 2007, 110:244-254). Recent reports on comparisons in similar groups of patients treated in the neoadjuvant setting with aromatase inhibitors have shown that the efficacies of anastrozole, letrozole and exemestane are broadly similar. (*Ellis et al* J Clin Oncol 2011; 29: 2342-2349). Clinical trial data comparing follow-up results on progress-free survival after neoadjuvant endocrine therapy with adjuvant endocrine therapy is not available nor are there data on progress-free survival after neoadjuvant hormonal therapy compared with neoadjuvant applied chemotherapy. Neoadjuvant chemotherapy is commonly preferred to neoadjuvant endocrine therapy, however patients for whom adjuvant chemotherapy is not indicated whereas adjuvant endocrine therapy is indicated or for older frail women who are not able to receive chemotherapy, neoadjuvant endocrine therapy should be a treatment option. The CHMP concluded that aromatase inhibitors are effective as neoadjuvant hormonal therapies. As a direct comparison with the efficacy of neoadjuvant chemotherapy is yet lacking, letrozole can be indicated as neoadjuvant treatment for patients who are not indicated to receive chemotherapy or for whom chemotherapy is not suitable. The CHMP concluded that there is sufficient data to support the neoadjuvant indication for letrozole, including considerable amounts of new data in the neoadjuvant setting, such as the Immediate Preoperative Anastrozole, Tamoxifen or Combined with Tamoxifen (IMPACT) trial (*Smith IE et al* 2005, J Clin Oncol 23:5108-5116) and the Preoperative 'Arimidex' Compared to Tamoxifen (PROACT) trial (*Cataliotti et al* 2006), in addition to data submitted by the MAH. However, the CHMP considered that the proposed indication was too broad, and requested the MAH to further define the target patient population, in particular with regard to the type of cancer, as the population described in the proposed indication could include women for whom alternative treatment or surgery would be preferred. Without further restriction, there is a risk that patients could receive neoadjuvant endocrine therapy that could delay a potentially curative treatment.

The MAH submitted responses discussing the individual qualifying statements of the proposed indication.

Postmenopausal status

Regarding "postmenopausal status", the MAH stated that Femara should only be used by women of established postmenopausal status, as there is a concern of reduced efficacy of letrozole in premenopausal or perimenopausal women, because of physiologic feedback mechanisms that result in stimulation of ovarian oestrogen production in women with active ovarian function. There are also reports of perimenopausal women regaining ovarian function during treatment with aromatase inhibitors, particularly letrozole (*Burstein et al* 2006; *Smith et al* 2006). It is very important to avoid pregnancy during letrozole therapy because of the risk of embryotoxicity and foetotoxicity.

Hormone receptor positivity

In patients with weakly ER-positive tumours, letrozole has demonstrated superior efficacy over tamoxifen (*Ellis et al* 2001) as well as over anastrozole (*Murray et al* 2009). However, published

evidence supports higher response rates with neoadjuvant letrozole therapy in patients with strongly ER-positive tumours than in patients with weakly ER-positive tumours (*Dixon et al* 2001; *Ellis et al* 2001). Therefore neoadjuvant letrozole therapy is most effective in patients with strongly ER-positive tumours.

Neoadjuvant chemotherapy
The MAH considered that neoadjuvant chemotherapy is an established treatment modality to improve operability and downsize the tumour to enable less radical surgery than mastectomy. The MAH also maintained that neoadjuvant letrozole therapy improves operability and enhances the ability of patients with ER-positive tumours to undergo BCS. The pilot neoadjuvant study AR/ET1 showed an average reduction of 81% in tumour volume, enabling BCS in all 24 enrolled women (*Dixon et al* 2001). Similarly, the pivotal study P024 on neoadjuvant treatment showed a downsizing of tumour in the letrozole arm, enabling patients to undergo breast-conserving surgery, despite initially not being regarded as suitable for such surgery (*Eiermann et al* 2001; E*llis et al* 2001).

Duration of neoadjuvant endocrine therapy
The MAH stated that high clinical response rates to neoadjuvant endocrine therapy in patients with ER-positive tumours – similar to rates obtained with neoadjuvant chemotherapy – are common. Several investigators have shown that extending neoadjuvant treatment with letrozole induces higher clinical response rates. One study showed rates of clinical complete response of 9.5% at 3 months, 29% at 6 months and 36% at 12 months (*Renshaw et al* 2004). Other investigators have proposed that maximum tumour response is obtained with neoadjuvant letrozole after around 8 months (*Krainick-Strobel et al* 2008; *Dixon et al* 2009; *Carpenter et al* 2010). The MAH considered that the duration of neoadjuvant therapy with letrozole should be 4-8 months or until maximum tumour response.

Further description of target population
In agreement with the CHMP suggestions as well as with European treatment guidelines (*Kaufmann et al* 2006; *Minckwitz* 2008; *Goldhirsch et al* 2011; *Kataja and Castglione* 2009; *Goldhirsch et al* 2011), the MAH proposes that neoadjuvant treatment with letrozole be restricted to patients with (strongly) ER-positive tumours (for which chemotherapy has been reported to have lower response rates than for ER-negative tumours); patients whose tumours are HER-2 negative; and patients who are unable to tolerate or who refuse to take neoadjuvant chemotherapy.

The CHMP agreed with the MAH justifications with regard to postmenopausal status, HER-2 status and duration of treatment, however the wording was shortened and information that immediate surgery is not an option was added. In conclusion, the CHMP adopted the following harmonised indication:

"Neoadjuvant treatment of postmenopausal women with hormone receptor positive, HER-2 negative breast cancer where chemotherapy is not suitable and immediate surgery not indicated."

The MAH also proposed a statement under Section 4.1 to state that the efficacy of Femara has not been demonstrated in patients with hormone receptor negative breast cancer. The MAH stated that while much information on hormone receptor status has been obtained after 1996, when Femara was first authorised, Femara is most efficacious in patients whose tumours were both oestrogen receptor (ER) positive and progesterone receptor (PgR) positive. At minimum, overall positivity (ER or PgR) is required. The CHMP noted that this was in line with the majority of the nationally approved SmPCs and agreed with the statement.

In conclusion, the CHMP adopted the following harmonised indications for Femara:

"Section 4.1 - Therapeutic indications

- *Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.*
- *Extended adjuvant treatment of hormone-dependent invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years.*
- *First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.*
- *Advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status, who have previously been treated with anti-oestrogens.*
- *Neo-adjuvant treatment of postmenopausal women with hormone receptor positive, HER-2 negative breast cancer where chemotherapy is not suitable and immediate surgery not indicated.*

Efficacy has not been demonstrated in patients with hormone receptor negative breast cancer."

Section 4.2 - Posology and Method of Administration

Adults and elderly patients

Regarding the daily dose in adults, the MAH stated that 2.5 mg is recommended in all national SmPCs, based on several dose-finding studies, particularly the two pivotal studies AR/BC2 (versus megestrol acetate) and AR/BC3 (versus aminoglutethimide) in metastatic breast cancer. The 2.5 mg daily dose was superior to 0.5 mg daily and/or to the comparator in several study endpoints including time to progression and objective response rate. In earlier dose-finding studies (e.g. P03, AR/BC1, AR/ST1 and AR/ES1, as well as AR/BC2 and AR/BC3), 2.5 mg daily was selected as the dose yielding maximum oestrogen suppression and aromatase inhibition, without negative influences on tolerability. In studies AR/BC2 and AR/BC3, trough levels of letrozole were significantly positively correlated with time to progression. The 2.5 mg daily dose yielded sufficiently high letrozole trough levels to prolong time to progression, which the 0.5 mg daily dose did not. In study AR/BC2, the 2.5 mg daily dose of letrozole was significantly more effective than the 0.5 mg daily dose with respect to time to progression, time to treatment failure, overall objective response and overall survival (*Dombernowsky et al* 1998). In study AR/BC3, the 2.5 mg daily dose of letrozole was significantly more effective than the 0.5 mg daily dose with respect to overall survival (*Gershanovich et al* 1998).

Regarding the use in elderly, the MAH did not consider dose adjustment to be required, based on analyses of efficacy and safety conducted for all pivotal studies with Femara (AR/BC2, AR/BC3, P025, P024, MA-17, BIG 1-98). With respect to efficacy parameters, the efficacy of Femara for the main endpoints was at least as good for elderly patients (defined as ≥ 70 years at enrolment in studies in advanced or metastatic breast cancer and in the neoadjuvant setting, and as ≥ 65 years at enrolment in studies in the adjuvant and extended adjuvant treatment settings) as for younger patients. Various factors can be hypothesized as having a role in such a finding – disease tends to be more indolent in elderly than in younger postmenopausal women, hormone receptor status is more likely than not to be strongly positive, and symptoms that may affect quality of life such as hot flushes and arthralgia tend to be less problematic in the older patients. The efficacy of first-line letrozole and of adjuvant letrozole in elderly patients has been published (*Mouridsen et al* 2004; *Crivellari et al* 2008). With respect to safety, older patients experienced more osteoporosis and bone fractures than younger patients. In all pivotal studies, this was a consistent finding and was irrespective of study treatment, i.e. older patients in general were more susceptible to adverse skeletal events (osteoporosis and fractures). Particularly in studies MA-17 and BIG 1-98, each with 5 years of treatment, older patients, irrespective of study treatment (letrozole, placebo or tamoxifen), but especially women with a history of bone fractures and/or of osteoporosis, experienced more skeletal events than younger postmenopausal women. The higher rates of skeletal events can be attributed to advanced age itself (i.e., age ≥ 65 years), which is an independent risk factor for osteoporosis and fractures. In addition, low oestrogen levels have been correlated with the risk of fracture in elderly women (*Cummings et al* 1998). A prior history of bone fracture is a strong independent risk factor for the risk of having another fracture (*Kanis et al* 2004). The contrary applied regarding symptoms linked with short-term oestrogen deficiency – older patients experienced fewer and less severe hot flushes, nausea and headache than younger postmenopausal women. A pharmacokinetic study, AR/PK1, conducted in two distinct age groups (≥ 50 and ≤ 65 years, and ≥ 70 years) showed no significant differences in total drug exposure or terminal half-life between the two age groups, either after a single dose of letrozole 2.5 mg or at steady state (*Pfister et al* 2001).

Duration of treatment

Regarding the duration of treatment, the MAH submitted an overview of the nationally approved SmPCs. The MAH considered that in patients with advanced or metastatic breast cancer, the pivotal studies (AR/BC2, AR/BC3 and P025) all provided strong evidence that Femara treatment should be continued until further progression of disease becomes evident. Median progression-free survival varied according to line of treatment (first-line longer than second-line) and dominant site of disease (e.g. median 12 months in patients with only soft tissue disease in study P025 but around 6 months in patients with visceral and/or bone involvement in the same study). Regarding adjuvant treatment, the pivotal studies BIG 1-98 (adjuvant treatment) and MA-17 (extended adjuvant after adjuvant treatment with tamoxifen) both showed that efficacy was sustained over the median duration of 5 years of treatment. Regarding neoadjuvant treatment, although the pivotal study (P024) used a 4-month treatment period, more recent studies (including GB07) conducted specifically to investigate the optimum duration of neoadjuvant treatment with letrozole, have shown that 4 months should be the minimum planned treatment duration but that higher response rates and more patients becoming suitable for BCS are gained around 8 months treatment. On the other hand, these recent studies have

shown that there is little incremental gain in either response rate or proportion of patients becoming suitable for BCS beyond 8 months.

The CHMP noted that the proposed daily dose for adults, including elderly patients and the duration of treatment recommendation is in line with the majority of the nationally approved SmPCs. The CHMP therefore adopted the following harmonised recommendations:

"Adult and elderly patients
The recommended dose of Femara is 2.5 mg once daily. No dose adjustment is required for elderly patients.

In patients with advanced or metastatic breast cancer, treatment with Femara should continue until tumour progression is evident.

In the adjuvant and extended adjuvant setting, treatment with Femara should continue for 5 years or until tumour relapse occurs, whichever is first.

In the adjuvant setting a sequential treatment schedule (letrozole 2 years followed by tamoxifen 3 years) could also be considered (see sections 4.4 and 5.1).

In the neoadjuvant setting, treatment with Femara could be continued for 4 to 8 months in order to establish optimal tumour volume reduction. If the response is not adequate, treatment with Femara should be discontinued and surgery scheduled and/or further treatment options discussed with the patient."

Children
Regarding recommendations for use in children, the MAH stated that invasive breast cancer is extremely rare in children and adolescents, but that it has been reported (*Corpron et al* 1995; *Longo et al* 1999; *Tea et al* 2009). In a report from the Surveillance Epidemiology and End Results (SEER) program, the incidence of invasive breast cancer was estimated to be 0.2/100,000 for females between 15 and 19 years (SEER Cancer Statistics Review, 1975-2005, National Cancer Institute. Bethesda, MD). In view of the extremely rare occurrence of invasive breast cancer in the paediatric population, the MAH considered that the indications approved for Femara are not applicable to this population. The MAH stated that it has not conducted clinical trials in children or adolescents and did therefore not recommend the use of Femara in paediatric patients below 18 years. The CHMP noted the absence of clinical trials in patients below 18 years and therefore concluded that the safety and efficacy of Femara in this population is not established. The CHMP adopted the following harmonised recommendation:

"Paediatric population
Femara is not recommended for use in children and adolescents. The safety and efficacy of Femara in children and adolescents aged up to 17 years has not been established. Limited data are available and no recommendation on a posology can be made."

Renal impairment
The MAH provided an overview of the nationally approved texts and stated that because letrozole is mainly cleared by the hepatic metabolism into its major carbinol metabolite, which is pharmacologically inactive, renal clearance is reported to be less than 5%. The MAH provided the pharmacokinetic report for AR/BC2, a phase IIb/III trial comparing two doses of letrozole (0.5 mg and 2.5 mg once daily) with megestrol acetate (160 mg total daily dose). In this study, calculated creatinine clearance was obtained in 347 postmenopausal women with metastatic breast cancer, with values ranging from around 19 to 187 ml/min. Approximately half of the 347 patients received 0.5 mg letrozole daily and half 2.5 mg daily, for up to 12 months. There was no statistically significant effect of creatinine clearance levels on letrozole trough levels (P=0.95), or tumour response (including time to progression) or severity or occurrence of adverse events (Pharmacokinetic report – Module VII – in AR/BC2 Clinical Trial Report, Ciba-Geigy Ltd, February 1996). Irrespective of letrozole concentration, there was a statistically significant but small effect of creatinine clearance on the severity of adverse events (odds ratio 1.06; P=0.04), with patients with higher creatinine clearance levels tending to have less severe adverse events.

The MAH also provided the pharmacokinetics report for AR/BC3, a phase IIb/III trial comparing two doses of letrozole (0.5 mg and 2.5 mg once daily) with aminoglutethimide 500 mg daily with corticoid supplementation in postmenopausal women with metastatic breast cancer. Calculated creatinine

clearance was obtained in 314 postmenopausal women with metastatic breast cancer, with baseline values ranging from around 10 to 180 ml/min. Approximately half of the 314 women were treated with 0.5 mg/day letrozole and half with 2.5 mg/day for up to 12 months. Plasma trough levels showed no statistically significant correlation with mild impairment of renal function (defined as creatinine clearance of 20-50 ml/min), and no significant effects of creatinine clearance on the severity of adverse events, although there was a statistically significant effect on letrozole trough levels, with increased creatinine clearance (above 120 ml/min) being associated with lower levels of letrozole (Pharmacokinetics report No. BPK (CH) 1996/158, Ciba-Geigy Ltd, January 1997).

Finally, the MAH provided the study report from Study 06, a single dose study in 19 postmenopausal women without breast cancer with varying degrees of renal insufficiency (normal renal function (n=3), mild renal impairment (CrCl >60-90 ml/min; n=2), moderate renal impairment (>30-60 ml/min; n=11) and severe renal impairment (CrCl ≤ 30 ml/min; n=3)). A single dose of 2.5 mg letrozole was administered and blood sampling was performed up to 336 hr post-dose. Urine sampling was performed up to 168 hr post-dose. Plasma and urine samples were analysed for letrozole concentrations using validated HPLC assays (with fluorescence detection for urine). The results of this study were the basis for the Basic Prescribing Information on renal insufficiency. In this study, no effect of renal function, based on 24-hour creatinine clearance (ranging from 9 to 116 ml/min) was found on the pharmacokinetics of single doses of 2.5 mg of Femara (Human Pharmacokinetics Report of Protocol 2026701006, 1996). The MAH concluded that given the elimination pathway of letrozole and the results of the investigation of calculated creatinine clearance on letrozole trough levels, time to progression and severity of adverse events, there is sufficient support for a change in creatinine clearance level from 30 ml/min to 10 ml/min.

The CHMP noted that while the total body clearance of letrozole is reported to be 2.21 l/h, renal clearance only accounts for 0.08 l/h. Elimination half-life is long, with a mean of 82 hours. Approximately 90% of a single radio-labelled dose was recovered in urine, with >75% as a glucuronide of the major carbinol metabolite, 9% as two unidentified metabolites, and 6% as unchanged drug. In plasma, unchanged compound accounts for about 82% of the total drug material after a single dose. In the nationally approved SmPCs, a creatinine clearance of < 30 ml/min is suggested to be the limit for where insufficient data is available but the CHMP noted that the MAH proposed to lower the limit to < 10 ml/min. Elimination of metabolites is expected to be slower in patients with renal impairment, but the safety data presented by the MAH indicates that this does not appear to affect the safety profile of the product. The CHMP noted the results from study AR/BC2, AR/BC3 and Study 06. The CHMP agreed that there was no apparent trend towards higher letrozole plasma trough levels in patients with severe renal impairment (CrCl of 20-30 ml/min) compared with patients with mild/moderate renal impairment and also agreed that the statistically significant negative correlation could be due to the low concentrations seen in patients with extremely high calculated CrCl. The CHMP acknowledged the results recorded for the three subjects with severe renal impairment in Study 06 (baseline creatinine clearance values of 9 ml/min, 11 ml/min and 13 ml/min, respectively, i.e. they were all within the low <20 ml/min range that is not covered by studies AR/BC2 and AR/BC3). Although the number of subjects was low and the variability high in this study, the CHMP concluded that the data did not indicate any signal of altered pharmacokinetics in patients with severe renal impairment and that given that letrozole is eliminated mainly via metabolism and given the results form the submitted studies, no specific warnings or dose adjustments recommendations are needed for patients with CrCl ≥ 10 ml/min. The CHMP inserted appropriate warnings that data is missing for patients with CrCl < 10 ml/min. The CHMP adopted the following harmonised recommendation:

"Renal impairment
No dosage adjustment of Femara is required for patients with renal insufficiency with creatinine clearance ≥ 10 ml/min. Insufficient data are available in cases of renal insufficiency with creatinine clearance lower than 10 ml/min (see sections 4.4 and 5.2)."

Hepatic impairment
The MAH provided an overview of the nationally approved SmPCs and stated that studies have shown that Femara is safe in mild to moderate hepatic insufficiency (i.e. in Child-Pugh stages A or B), however, there is limited experience of use in patients with severely impaired hepatic function, non-cancer patients with liver cirrhosis and/or Child-Pugh stage C liver insufficiency. A small pharmacokinetic study indicated that total drug exposure might be approximately doubled in patients with severe hepatic impairment. Supportive data in postmenopausal women with metastatic breast cancer, including liver metastases (particularly in studies AR/BC2 and AR/BC3) did not raise safety concerns. Repeated liver function tests in these studies did not give rise to any finding warranting a contraindication for severely impaired liver function. The MAH acknowledged, however, that the duration of treatment in patients with liver metastases tends to be relatively short (median around 3-4

months) compared to patients with metastases confined to soft tissue sites (median 12 months or more). In conclusion, the MAH considered that it is not justified to contraindicate Femara in patients with severe hepatic impairment (Child-Pugh C) but did consider that such patients should be kept under close supervision.

The CHMP noted that in a study (available as abstract only) including 8 patients with severe hepatic impairment (Child Pugh Score C), the total exposure to letrozole was increased to 6 nM*h/ml, compared with 3.6 nM*h/ml in 8 healthy volunteers (no variability measures available). Terminal half-life was increased approximately 3-fold, oral clearance decreased to about half and urinary metabolite/parent ratio to a third of the values in healthy subjects. The effect is likely variable between patients, depending on the type of impairment. As discussed by the MAH under section 4.4 (see below) a doubling of the exposure to letrozole is not considered a safety problem, while the efficacy of letrozole has been shown to be dose dependent and under-exposure should therefore be avoided. The CHMP agreed that no dose adjustment is needed in severe hepatic impairment, but that a warning that patients with severe hepatic impairment should be kept under close supervision should be inserted in section 4.4. The CHMP adopted the following harmonised recommendation:

"Hepatic impairment
No dose adjustment of Femara is required for patients with mild to moderate hepatic insufficiency (Child-Pugh A or B). Insufficient data are available for patients with severe hepatic impairment. Patients with severe hepatic impairment (Child-Pugh C) require close supervision (see sections 4.4 and 5.2)."

Method of administration
The CHMP added information on the method of administration, in line with the SmPC guideline:

"*Femara should be taken orally and can be taken with or without food."*

Section 4.3 – Contraindications

Premenopausal endocrine status
The MAH stated that although no clinical trials testing the safety or efficacy of Femara in premenopausal women have been conducted, there are safety reasons for why letrozole should not be used by premenopausal or even perimenopausal women. Letrozole is an inhibitor of aromatase, an enzyme involved in the synthesis of oestrogens by converting androgens into oestrogens. Oestrogens are known to be required for proper embryo and foetal development. Inhibition of aromatase would thus be predicted to have a potential for adverse effects on the embryo-foetus and this has been shown in studies using pregnant rats and rabbits administered letrozole. Letrozole was tested in three embryo-foetal development studies. At the exposures in the pilot rat study 956165 (CGS 20 267: Pilot pre- and postnatal development study in rats by oral administration), none of the treated animals delivered viable newborns, demonstrating embryo/foetal lethality. At the exposures in the follow-up rat study 954027 (CGS 20267: An oral study for effects on embryo and foetal development in rats), embryotoxic and foetotoxic effects were observed, including increased mean numbers of early, late, and total resorptions with resultant increases in mean number and percent post-implantation losses, decreased mean number of live foetuses and increased mean number of dead foetuses. At the exposures in this study, live foetuses were available for examination and external malformation of domed head and skeletal malformation of fused centrum/vertebrae were observed. In the rabbit study 954025 (CGS 20267: An oral study for effects on embryo and foetal development in rabbits), treatment-related embryotoxicity and foetotoxiciy was observed including an increased numbers of early, late, and total resorptions with resultant increases in mean and percent post-implantation loss and a decreased number of live foetuses. In the live rabbit foetuses, there was no evidence of teratogenicity at any dose level tested. In addition, *Tiboni et al* 2009 reported that letrozole administered to pregnant rats produced embryolethality for 41% of conceptuses and minor axial skeletal anomalies in 51% of live foetuses. They also demonstrated that co-administration of oestradiol cyclopentylpropionate prevented the embryolethality but failed to reduce the incidence of axial skeletal alterations. The authors concluded that inhibition of oestrogen biosynthesis is a critical determinant of letrozole-induced embryonic death while the production of skeletal anomalies appears to involve a different mechanism. Based on these results, sufficiently high doses of an aromatase inhibitor would be expected to produce adverse effects on embryo-foetal development via a reduction in oestrogens as well as by another mechanism. The MAH therefore concluded that Femara should not be given to any woman who could potentially become pregnant. In addition, in study no. 91-6010 (CGS20267: 6/12 month oral toxicity study in rats), absence of large corpora lutea and stromal hyperplasia in the ovary were the most prominent findings in all female dose groups. Based on these preclinical findings,

Femara was not recommended in premenopausal or pregnant women in the initial Femara prescribing information. The MAH concluded that there are significant safety concerns with the potential use of Femara in pre- or perimenopausal women and there is no evidence available to justify loosening the recommendation for the contraindication in premenopausal women. The Femara SmPC, in line with the company Core Data Sheet (CDS), also recommends that treating physicians need to take adequate measures for women who have the potential to become pregnant, including women who are perimenopausal or who have recently become postmenopausal, until their postmenopausal status is fully established. Recently, the MAH amended the CDS to include information on cases of birth defects reported in pregnant women exposed to Femara and the submission of a variation to implement these changes in the Femara SmPC is under preparation. The MAH therefore concluded that letrozole should be contraindicated in premenopausal women, or rather specifically in women of premenopausal endocrine status, primarily for safety reasons. The CHMP agreed with the MAH justification and concluded that the contraindication present in the majority of nationally approved SmPCs should be reflected in the harmonised SmPC.

Hepatic impairment
The MAH considered that despite the strict contraindication currently present in certain MSs, the use of Femara should not be contraindicated in patients with severe hepatic impairment (Child-Pugh C), although such patients should be kept under close supervision. There are limited data available in non-cancer patients with liver cirrhosis and/or Child-Pugh C liver insufficiency and the supportive data from postmenopausal women with metastatic breast cancer, including liver metastases (particularly in studies AR/BC2 and AR/BC3), did not raise safety concerns. Repeated liver function tests in these studies did not give rise to any finding warranting a contraindication for severely impaired liver function. The MAH acknowledged, however, that the duration of treatment in patients with liver metastases tends to be relatively short (median 3-4 months) compared to patients with metastases confined to soft tissue sites (median 12 months or more). The CHMP agreed that a strict contraindication in hepatic impairment is not appropriate for letrozole, which is a potentially life-saving treatment with a relatively benign safety profile. In addition, letrozole is not considered to have a narrow therapeutic index. The CHMP instead included a warning in section 4.4 stating that safety data in patients with significant organ impairment are lacking, with a cross-reference to section 5.2.

Pre-operative use if the receptor status is negative or unknown
The MAH considered it unnecessary to include this contraindication, present in some nationally approved SmPCs, as it is covered by statements in Sections 4.1 and 4.2. The MAH considered that it is sufficient to emphasize in Section 4.1 that neoadjuvant (pre-operative) treatment with Femara should be restricted to “hormone receptor positive primary breast cancer”. The CHMP agreed that contraindicating the pre-operative use of letrozole if the receptor status is negative or unknown is unnecessary, as this is already sufficiently explained in the warning in section 4.4.

In order to make the information more visible, the contraindications for pregnancy and breast-feeding were given separate bullet points. The CHMP also included a contraindication for known hypersensitivity to letrozole or to any of the excipients. In conclusion, the CHMP adopted the following harmonised contraindications:

- *Hypersensitivity to the active substance or to any of the excipients listed in section 6.1*
- *Premenopausal endocrine status*
- *Pregnancy (see section 4.6)*
- *Breast-feeding (see section 4.6)*

Section 4.4 - Special Warnings and Precautions for Use

Menopausal status
The MAH proposed the introduction of a statement about postmenopausal endocrine status. This warning is particularly relevant for adjuvant/extended adjuvant use but is also important in the first-line treatment setting, where treatment duration can be upwards of 12 months. Studies have shown that in women with perimenopausal status (e.g. following chemotherapy-induced or radiation-induced menopause), efficacy may be sub-optimal due to the feedback loop of oestrogen synthesis, and adverse events (especially of symptoms associated with menopause, such as hot flushes) may be more frequent and more severe. The use of aromatase inhibitors s in premenopausal or perimenopausal women could result in ovarian hyperstimulation due to elevated gonadotropin levels (LH, FSH). The CHMP agreed with the wording proposed by the MAH, although it disagreed with the justifications, as it considered postmenopausal status to be a prerequisite for aromatase inhibitor treatment of breast cancer.

Renal impairment
Regarding renal impairment, the MAH provided an overview of the nationally approved SmPCs and acknowledged that there is very limited information about patients whose creatinine clearance is below 10 ml/min. The MAH considered it appropriate that the harmonised SmPC contain a precaution for these patients. For patients whose creatinine clearance is ≥ 10 ml/min, the MAH considered that there is sufficient information to warrant safe administration of Femara, especially considering that excretion of Femara through the kidneys is less than 5%. The CHMP noted that no efficacy and safety nor pharmacokinetic data are available in patients with CrCl <10 ml/min and agreed with the overall wording proposed by the MAH. No effect of renal impairment (CrCl 9-116 ml/min) was observed on the PK of letrozole in a PK study and patients with renal impairment as low as CrCl 10 ml/min have been included in the pivotal clinical studies.

Hepatic impairment
Regarding hepatic impairment, the MAH provided an overview of the nationally approved SmPCs and stated that no signal was raised in the studies in metastatic disease regarding the safety of Femara in patients with severe impairment of hepatic function. Nevertheless, the MAH considered that due care should be exercised in administering Femara to such patients and proposed a precaution for the use of Femara in the harmonised SmPC. In early dose-finding studies, especially protocol 03, in which multiple doses of up to 10 mg letrozole daily were given for 6 weeks or longer to postmenopausal women with metastatic breast cancer, including extensive liver metastases, no findings suggested a safety problem in these patients. The safety of Femara has not been demonstrated to be dose-dependent, in contrast to efficacy, and a doubling of systemic exposure and terminal half-life are not considered grounds for a contraindication in patients with severe impairment of hepatic function. A precaution urging close supervision would be more appropriate. The CHMP agreed with the MAH proposal, which was in line with the majority of the nationally approved SmPCs.

Bone Effects
Regarding bone effects, the MAH stated that data from the close-out report of MA-17, including the bone substudy conducted over 5 years, and data from the 2009 report of BIG 1-98 with a median treatment of 5 years and median follow-up of over 6 years clearly shows that long-term use of Femara is associated with a significantly higher rate of osteoporosis and a significantly higher rate of bone fractures than tamoxifen (adjuvant setting) or placebo (extended adjuvant setting). Women with a history of fractures and/or osteoporosis experienced higher rates of bone fractures than women without such a history, irrespective of treatment. The CHMP noted that the majority of MSs have similar or less detailed information as in the nationally approved SmPCs and agreed that wording regarding bone effects associated with the use of Femara should be present in the harmonised SmPC. The CHMP also added a statement that in the adjuvant setting, a sequential treatment schedule (letrozole 2 years followed by tamoxifen 3 years) could also be considered depending on patient's safety profile.

Male breast cancer
Regarding male breast cancer, the MAH stated that it was unaware of clinical trials or specific systematic investigation (as opposed to isolated case reports) on the use of Femara in male breast cancer and that neither efficacy nor safety data exists. The CHMP noted that information regarding male breast cancer is included only in two nationally approved SmPCs and is limited to the statement "*Use of Femara in men with breast cancer has not been studied*". The CHMP therefore decided, based on the lack of data, to remove the statement from Section 4.4 and instead reflect it in Section 5.1.

Other warnings
At the request of the CHMP, the MAH proposed a statement warning that oestrogens and/or tamoxifen may reduce letrozole plasma levels, thus reducing its pharmacological action, and that co-administration should therefore be avoided. The MAH referred to a study by *Dowsett et al* 1999, which examined whether the addition of tamoxifen to the treatment regimen of patients with advanced breast cancer being treated with letrozole led to any pharmacokinetic or pharmacodynamic interaction. Twelve patients completed the core period of the trial in which 2.5 mg/day letrozole was administered alone for 6 weeks and in combination with 20 mg/day tamoxifen for the subsequent 6 weeks. Plasma levels of letrozole were measured at the end of the 6-week periods of treatment with letrozole alone and the combination and once more between 4 and 8 months on combination therapy. Plasma levels of letrozole were reduced by a mean 37.6% during combination therapy and this reduction persisted after 4–8 months of combination therapy. The authors suggested that the mechanism of the interaction is likely to be a consequence of an induction of letrozole-metabolizing enzymes by tamoxifen. Formation of the main metabolite of letrozole is catalysed by CYP3A4 and CYP2A6. The contribution of each

individual isoenzyme to this pathway is not known. The main metabolic transformation of tamoxifen to N-desmethyl-tamoxifen is mediated by CYP3A4 and probably also by CYP2C. The authors refer to animal experiments, where tamoxifen has been shown to induce the rat isoenzymes CYP2B1 and CYP3A1 and to increase 6-beta- and 16-alfa-hydroxylation of testosterone in the rat. Apart from single case reports, tamoxifen has not been described as a CYP inducer in the clinical literature, but there are few formal interaction studies with tamoxifen. The CHMP agreed that tamoxifen, other anti-oestrogens or oestrogen-containing therapies should not be co-administered with letrozole for pharmacological reasons, as these substances may diminish the pharmacological action of letrozole. However, the CHMP shortened and revised the text proposed by the MAH and also inserted the pharmacodynamic reasons for not recommending co-administration in Section 4.5. Finally, the CHMP also agreed with the MAH proposal to add a statement recommending against the use of Femara for patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption, as isolated reports of relevant adverse events have been reported in patients with such conditions.

In conclusion, the CHMP adopted a harmonised wording for Section 4.4.

Section 4.5 - Interaction with Other Medicinal Products and Other Forms of Interaction

The MAH presented a proposed wording for Section 4.5, addressing the potential for interaction of a number of substances, including cimetidine and anti-cancer agents, as well as the role played by CYP2A6 and CYP3A4 in the metabolism of letrozole. The MAH also proposed a statement regarding a review of the clinical database to identify clinically relevant interactions.

The CHMP raised a number of objections to the MAH proposal; in particular, the statement regarding the clinical database review was removed as it is generally considered very difficult to assess the risk for interactions based on safety-related clinical study data, and especially to assess reports of lack of interaction. Many factors important for the assessment of interactions are unknown, such as the dosage and the timing of dosing of the interacting drug, the number of patients receiving each combination, whether inhibitors of different potency were grouped together (grouping potent together with weak inhibitors might dilute effects of the potent inhibitors) etc. Such statements should therefore be avoided as they are considered insufficient to exclude the risk of interactions.

The proposed wording was updated in order to provide some more mechanistic information. Finally, the CHMP inserted a statement advising against the co-administration of Femara with tamoxifen, other anti-oestrogens or oestrogens, as discussed under Section 4.4.

In conclusion, the CHMP adopted a harmonised wording for Section 4.5.

Section 4.6 - Pregnancy and Lactation

Regarding pregnancy, the MAH proposed a harmonised wording and stated that Femara is contraindicated during pregnancy because there are no adequate and well controlled clinical trials of Femara in pregnant women. Isolated cases of birth defects (labial fusion, ambiguous genitalia) have been reported in pregnant women exposed to Femara and nonclinical studies have shown that letrozole is embryotoxic and foetotoxic. The MAH acknowledged the limitations of a single pregnancy test done just before initiation of letrozole therapy in perimenopausal/early postmenopausal women, as well as the limitations of the alternative approach in which the prescribing information is used to convey the importance of maintaining effective contraception in order to prevent pregnancy.

The CHMP noted the MAH proposal and the provided overview of nationally approved SmPCs and confirmed that Femara is contraindicated during pregnancy. However, the CHMP was of the opinion that there is a concern of reduced efficacy of letrozole in premenopausal or perimenopausal women because of physiologic feedback mechanisms that result in stimulation of ovarian oestrogen production in women with active ovarian function. There are also reports of perimenopausal women regaining ovarian function during treatment with aromatase inhibitors, particularly letrozole. The CHMP considered that the wording proposed by the MAH described a situation where women who are not deemed clearly postmenopausal are prescribed Femara, and gives the impression that Femara could be used in this situation. The CHMP also confirmed that the use of aromatase inhibitors is contraindicated in pregnancy and lactation and therefore deleted a proposed paragraph regarding contraception and pregnancy in “women of perimenopausal status or childbearing potential”. The CHMP also noted the limitations of the pregnancy prevention tools and therefore considered that a postmenopausal status

must therefore be fully established before initiation of and during treatment of Femara and that Femara should not be used in women when postmenopausal status is not fully established.

The CHMP also added a statement on the potential regaining of ovarian function during treatment with Femara and the need to discuss adequate contraception when necessary. Finally, the CHMP inserted sub-headings for pregnancy, breast-feeding and fertility and cross-references to section 4.3.

In conclusion, the CHMP adopted a harmonised wording for Section 4.6.

Section 4.7 - Effects on Ability to Drive and Use Machines

The MAH stated that fatigue and dizziness have been observed with the use of Femara and somnolence has been reported uncommonly and therefore proposed that caution is advised when driving or using machines. The CHMP agreed with the wording proposed by the MAH, which was in line with all nationally approved SmPCs. In conclusion, the CHMP adopted a harmonised wording for Section 4.7.

Section 4.8 - Undesirable Effects

General
The MAH provided an overview of the nationally authorised SmPCs and submitted a proposed harmonised wording for this section. The MAH considered that the longer the study treatment duration, the more likely that a patient will experience at least one adverse reaction. Thus, the MAH considered that it is important to differentiate the treatment setting – at least metastatic or neoadjuvant from adjuvant/extended adjuvant. Regardless of treatment setting, however, the most commonly reported adverse reactions were similar in all clinical studies. Some (especially hot flushes, arthralgia, fatigue, increased sweating and nausea) were often associated with oestrogen deficiency and tended to occur within the first few weeks of initiating treatment with Femara. Others, such as hypercholesterolemia, appeared not to be related to the duration of exposure. Nearly all of the commonly reported adverse reactions were mild or moderate in severity. Adverse reactions of greater severity (cardiovascular, skeletal and endometrial events as well as second primary malignancies) were generally restricted to studies in the adjuvant (including extended adjuvant) setting. The MAH also significantly condensed the text under Section 4.8, as the previously proposed text was too detailed yet did not provide an adequate summary of the safety profile of Femara. Some information was also corrected.

Tabulated list of adverse reactions
The MAH considered that the revised tabulation of adverse reactions reflects the safety profile of Femara in all indications, including after 5 years of adjuvant or of extended adjuvant treatment, and including important additions from pharmacovigilance post-marketing data. Specific adverse drug reactions (ADRs) such as “tumour pain” and “bone pain” were reported only in the studies in metastatic breast cancer. The MAH stated that the frequency of ADRs based on post-marketing data cannot be estimated reliably as the size of the population treated fluctuates and cannot be estimated precisely. It is acknowledged that “Ischaemic cardiac events” is not a MedDRA preferred term. In the large clinical trials in the adjuvant and extended adjuvant treatment setting, “cardiovascular morbidity” constituted a specific module and included, in check-list format, specific cardiovascular events (including cerebrovascular and thromboembolic events) that were queried at each clinical visit (including after the patient had stopped or completed study treatment). In the extended adjuvant study MA-17, neither grade of severity nor suspected relationship with study drug was recorded for “cardiovascular morbidity”. Adverse events suspected as being related to study treatment were required to be noted, together with the grade of severity and suspected causality. Therefore, in section 4.8b, ADRs are presented while for section 4.8c, adverse events irrespective of causality are reported and not ADRs.

Description of selected ADRs
Cardiovascular events were seldom reported in studies in the metastatic treatment or the neoadjuvant treatment indication. Although the frequency of reporting of cardiovascular events in the adjuvant/extended adjuvant setting was low, the occurrence of a pre-printed list of cardiovascular events (including cerebrovascular and thromboembolic events) was specifically enquired about at each clinical visit. The list of terms was similar, but not identical in the two pivotal studies in the adjuvant/extended adjuvant setting. In study MA-17 (extended adjuvant after completion of standard adjuvant therapy with tamoxifen), visits were annual in contrast to study BIG 1-98 in which visits were conducted every 6 months. In study BIG 1-98, approximately a quarter of the patients in the tamoxifen arm selectively crossed over to Femara, mainly to complete their adjuvant treatment, when

the tamoxifen arm was unblinded. Patient-years under Femara, however, accounted for only around 7% of the total patient-years in the randomized tamoxifen arm. In contrast, in MA-17, fully 60% of the patients in the placebo arm selectively crossed over to Femara when the study was unblinded. Patient-years under Femara accounted for 64% of the total patient-years in the randomized placebo arm. In both studies, however, cardiovascular (and skeletal) events were reported with due cognizance of actual treatment received when the cardiovascular event occurred. In BIG 1-98, the impact of the selective crossover on treatment exposure was negligible with median duration of tamoxifen just short of 5 years. This differed greatly in MA-17 in which median duration of placebo was approximately 3 years instead of the planned 5 years (placebo was not dispensed after the study was unblinded). For these reasons, the MAH considered that cardiovascular events (including cerebrovascular and thromboembolic events) should be reported separately for the two studies. It should be noted that there were further limitations in the collection of events pre-printed in the "cardiovascular morbidity" module: In BIG 1-98, "MI" included myocardial ischemia as well as myocardial infarction while both cerebrovascular accident and transient ischemic attack were undistinguishable, captured in the term "CVA/TIA". Neither BIG 1-98 nor MA-17 distinguished amongst types of thromboembolic events (e.g. deep vein thrombosis and superficial venous thrombophlebitis were both recorded as "thromboembolic event"). Mouridsen and others have addressed cardiovascular safety in study BIG 1-98 (*Mouridsen et al 2007*).

Regarding skeletal adverse reactions, the MAH stated that although the rate of bone fractures during treatment with Femara or within 30 days of stopping treatment was similar for the two studies (adjuvant, 10.2%; extended adjuvant, 10.4%), the rate of osteoporosis was more than twice as high in MA-17 (12.2%) than in BIG 1-98 (5.1%). Therefore, the MAH considered it justified that skeletal events be summarised for the two studies separately.

The CHMP noted the MAH proposal and the MAH overview of the nationally approved SmPCs. The majority of SmPCs had the approved MRP wording. The CHMP considered that although the proposed text had been substantially condensed, it still provides a detailed and adequate summary of the safety profile of Femara. In general, with a number of minor revisions, the MAH proposal was agreed. Regarding the adverse drug reactions table, the CHMP considered it to be structured according to the SmPC guideline. The changes in frequencies were consistent with the frequencies in the majority of MSs and were accepted. Several ADRs have been relocated under more appropriate system organ class and no ADRs have been removed. In general, the MAH proposal was supported, with minor changes. Regarding the description of selected adverse reactions, the CHMP agreed to separate the metastatic, adjuvant and extended adjuvant indications.

In conclusion, following a number of revisions and the shortening of the text, the CHMP adopted a harmonised wording for Section 4.8.

Section 4.9 – Overdose

The CHMP agreed with the wording proposed by the MAH, which was consistent with previous approved data and in line with all nationally approved SmPCs. In conclusion, the CHMP adopted a harmonised wording for Section 4.9.

Section 5.1 - Pharmacodynamic Properties

The CHMP noted the MAH proposal and that there we no differences in the non-clinical part of section 5.1 in the nationally approved SmPCs. The CHMP agreed to the proposal from a non-clinical point of view, however a number of revisions were made and the text was substantially shortened to focus on information relevant to the prescriber. In conclusion, the CHMP adopted a harmonised wording for Section 5.1.

Section 5.2 - Pharmacokinetic Properties

The CHMP agreed with the wording proposed by the MAH, which was in line with most nationally approved SmPCs, with the exception of some minor revisions and re-arrangements of the text. In conclusion, the CHMP adopted a harmonised wording for Section 5.2.

Section 5.3 - Preclinical Safety Data

The CHMP noted the MAH proposal but made a number of revisions. In conclusion, the CHMP adopted a harmonised wording for Section 5.3.

Labelling and Package leaflet

The labelling and the package leaflet were revised and brought in line with the adopted harmonised SPC.

2.3. Risk Management Plan

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

2.4. Recommendation

Based on the assessment of the MAH responses and the total body of available data, the CHMP adopted a harmonised summary of product characteristics, labelling and package leaflet for Femara and associated names.

2.5. Conclusions

The basis for this referral procedure was a harmonisation of the summary of product characteristics, labelling and package leaflet.

Having considered:

- the data submitted by the Marketing Authorisation Holder,
- the rapporteur and co-rapporteur assessment reports,
- and the scientific discussions within the Committee,

the CHMP was of the opinion that the benefit-risk ratio of Femara and associated names is favourable. The CHMP adopted a positive opinion recommending the harmonisation of the SmPC, labelling and package leaflet as set out in Annex III of the CHMP opinion for Femara and associated names (see Annex I).