Annex II

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

Scientific conclusions

Overall summary of the scientific evaluation of Femara and associated names (see Annex I)

Femara contains letrozole, an aromatase inhibitor which inhibits the conversion of androgens to oestrogens. 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. Femara was included in the list of products for Summary of Product Characteristics (SmPC) harmonisation, due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product. A referral under Article 30(2) of Directive 2001/83/EC, as amended was therefore triggered to resolve these divergences and thus harmonise the product information (PI) across the EU.

Section 4.1 – Therapeutic Indications

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

The CHMP noted 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), which specifically excluded patients who did not have a confirmed diagnosis of invasive breast cancer. In addition, no studies on DCIS (ductal carcinoma *in situ*) or LCIS (lobular carcinoma *in situ*) patients have been performed. The CHMP also noted that the wording was consistent with the wording in most nationally approved SmPCs.

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 CHMP considered the term "*hormone-dependent*" to be justified, as letrozole has no efficacy in hormone receptor negative breast cancer. The CHMP also considered information on the treatment duration with tamoxifen to be justified, based on studies in which letrozole was administered after 5 years of adjuvant tamoxifen. Regarding "*invasive*", it is not common practice to prescribe aromatase inhibitors to patients with no invasive component. No studies have been performed in DCIS or LCIS on the use of extended adjuvant aromatase inhibitors after tamoxifen and there is no reason to suggest a different mechanism of action in the extended adjuvant setting compared with the adjuvant setting. The CHMP therefore considered it justified to qualify the indication with "*invasive*". The CHMP also noted that the wording was consistent with the wording in most nationally approved SmPCs.

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

The CHMP considered this indication to be well-established and noted that the wording was consistent with the wording in the nationally approved SmPCs.

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 CHMP considered the indication to be well-established and that confirmation of postmenopausal endocrine status of women before initiation of treatment is justified for both efficacy and safety reasons, as studies have shown that women with induced menopausal status may not be of postmenopausal endocrine status. As a result, 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. In addition, it is essential to avoid pregnancy during letrozole therapy because of the risk of embryotoxicity and foetotoxicity. The CHMP also noted that the wording was largely consistent with the nationally approved SmPCs.

5) 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.

The neoadjuvant (pre-operative) treatment indication represented the major deviation across the nationally approved SmPCs, as it was approved in some member states in 2001 but the application was withdrawn in others, primarily because neoadjuvant endocrine treatment was not a validated concept at the time and because the results of the pivotal adjuvant study were not yet available. The CHMP reviewed all available data and considered that letrozole has shown significant superiority to tamoxifen in clinical response rate, mammographic response rate, breast ultrasound response rate and rate of breast-conserving surgery (BCS). The CHMP therefore concluded that the current data, 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 or to allow inoperable tumours to become operable. The CHMP defined the target patient population as women of established postmenopausal status and patients with ER-positive tumours, patients whose tumours are HER-2 (Human Epidermal Growth Factor Receptor 2) negative and patients who are unable to tolerate or who refuse to take neoadjuvant chemotherapy as well as patient for whom immediate surgery is not an option.

In conclusion, the following harmonised indications were adopted 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

The CHMP endorsed the 2.5 mg daily dose in adults, based on several dose-finding studies. Regarding use in elderly, the CHMP did not consider dose adjustment to be required, based on analyses of efficacy and safety conducted for all pivotal studies with Femara. Regarding duration of treatment, the CHMP considered that studies show that Femara treatment should be continued until further progression of disease becomes evident. Regarding adjuvant and extended adjuvant treatment, studies show that efficacy was sustained over the median duration of 5 years of treatment. Regarding neoadjuvant treatment, recent studies investigating duration of therapy show higher response rates and more patients becoming suitable for BCS at 4-8 months, with very little incremental benefit beyond that and that the minimum duration is 4-6 months. Regarding children, invasive breast cancer is extremely rare in children and adolescents but has been reported. In the absence of clinical trials, the CHMP therefore concluded that the safety and efficacy of Femara in this population is not established. Regarding renal impairment, the CHMP noted the available pharmacokinetics report and observed that letrozole is mainly cleared by the hepatic metabolism, with renal clearance reported to be less than 5%. The CHMP noted that while elimination of metabolites is expected to be slower in patients with renal impairment, the available data show that this did not affect the safety profile and did not alter pharmacokinetics in patients with severe renal impairment. The CHMP concluded that no specific warnings or dose adjustments recommendations are needed for patients with CrCl $\geq$ 10 ml/min. Regarding hepatic impairment, the CHMP noted that studies have shown that Femara is safe in mild to moderate hepatic insufficiency but that 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. Because doubling the exposure to letrozole is not linked to safety concerns and because under-exposure should be avoided as efficacy has been shown to be dose dependent, the CHMP concluded that no dose adjustment is needed in patients with severe hepatic impairment, but that a warning should be inserted in section 4.4.

Section 4.3 – Contraindications

Regarding premenopausal endocrine status, the CHMP noted that although no clinical trials testing the safety or efficacy of Femara in premenopausal women have been conducted, there are safety reasons

for not treating premenopausal or even perimenopausal women with letrozole. Letrozole inhibits the enzyme involved in the synthesis of oestrogens, which are required for proper embryo and foetal development. Letrozole is thus predicted to have a potential for adverse effects on the embryo-foetus, as confirmed by studies in pregnant rats and rabbits. The CHMP concluded that there are significant safety concerns warranting a contraindication in premenopausal women, specifically in women of premenopausal endocrine status.

Regarding hepatic impairment, the CHMP considered that a strict contraindication 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.

Regarding the pre-operative use of letrozole if receptor status is negative or unknown, the CHMP considered a contraindication to be unnecessary, as this is already sufficiently explained in Section 4.4.

The CHMP also clarified the contraindications for pregnancy and breast-feeding, making the information more visible and included a contraindication for known hypersensitivity to letrozole or to any of the excipients.

Section 4.4 - Special Warnings and Precautions for Use

The CHMP introduced a warning regarding postmenopausal endocrine status, as studies have shown sub-optimal efficacy and increased frequency and severity of adverse events in women with perimenopausal status. Regarding renal impairment, the CHMP noted that there is very limited information about patients whose creatinine clearance is below 10 ml/min and therefore agreed on a precaution for these patients. Regarding hepatic impairment, the CHMP noted that no signal was raised regarding the safety of Femara in patients with severe impairment of hepatic function. While a contraindication in these patients was not warranted, the CHMP inserted a precaution.

Regarding bone effects, the CHMP reviewed data from studies showing 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 therefore added a statement regarding bone effects associated with the use of Femara.

Regarding male breast cancer, the CHMP noted the absence of clinical trials or specific systematic investigation on the use of Femara in male breast cancer. The CHMP moved the statement from Section 4.4 to Section 5.1. The CHMP also added a warning that oestrogens and/or tamoxifen may reduce letrozole plasma levels, thus reducing its pharmacological action, and that co-administration should therefore be avoided. A statement recommending against the use of Femara for patients with problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption was also added.

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

The CHMP reviewed 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 CHMP considered that reviews of clinical databases are poorly suited to assess the risk for interactions or to assess reports of lack of interaction and therefore removed references to these reviews. Finally, the CHMP inserted a statement advising against the co-administration of Femara with tamoxifen, other anti-oestrogens or oestrogens.

Section 4.6 - Pregnancy and Lactation

The CHMP noted the absence of adequate clinical trials in pregnant women and that isolated cases of birth defects have been reported in pregnant women exposed to Femara, while nonclinical studies have shown that letrozole is embryotoxic and foetotoxic. The CHMP was also of the opinion that there is a concern of reduced efficacy of letrozole in premenopausal or perimenopausal women. The CHMP also noted the limitations of the pregnancy prevention tools and therefore considered that postmenopausal status must 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.

Other sections

For the remaining sections, the CHMP adopted a harmonised wording in line with the nationally approved SmPCs, although minor revisions were made. In particular, for Section 4.8 - Undesirable Effects, the wording was significantly shortened and condensed. The adverse drug reactions table was structured according to the SmPC guideline and several ADRs were relocated under more appropriate system organ class. Regarding the description of selected adverse reactions, the CHMP agreed to separate the metastatic, adjuvant and extended adjuvant indications. For Section 5.1 - Pharmacodynamic Properties, the wording was substantially shortened to focus on information relevant to the prescriber for the approved indications. A statement on the absence of studies on the use of Femara in male breast cancer was also added.

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

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.

Whereas

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

the CHMP has recommended the amendment of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Femara and associated names (see Annex I).