Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for letrozole, the scientific conclusions are as follows:

Cumulatively, 117 cases of jaundice / hyperbilirubinemia were retrieved from the marketing authorisation holder's safety database. Although majority of 117 cases were confounded by different factors, for six cases a causal role of letrozole in increased bilirubin levels and/or jaundice could not be excluded, considering the close temporal association, positive de-challenge and lack of alternative explanation. Hyperbilirubinemia/jaundice were reported with "uncommon" frequency in all four datasets of the clinical trials conducted with letrozole in the adjuvant/extended adjuvant treatment setting. Therefore, section 4.8 of product information should be updated with the adverse drug reactions "jaundice" and "hyperbilirubinemia" with the frequency "uncommon" under the SOC "Hepatobiliary disorders".

Cumulatively, 357 cases of chest pain have been reported post marketing. For 62 out of 356 cases a complete recovery/improvement (dechallenge) was observed upon letrozole discontinuation or interruption. A suspected causality was reported for 78 out of the 356 cases. Chest pain was reported with "common" frequency in three out of the four datasets of the clinical trials conducted with letrozole. Therefore, section 4.8 of product information should be updated to include "chest pain" with the frequency "common" under "General disorders and administration site conditions".

Upon review of cumulative data from the clinical trials, the frequency of adverse drug reactions "arthritis" and "palpitations", already listed in section 4.8 of product information, should be upgrade from "uncommon" to "common".

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for letrozole the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing letrozole is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing letrozole are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.8

"**Hyperbilirubinemia**" and "**jaundice**" should be added under the SOC "Hepatobiliary disorders" with a frequency "uncommon".

"**Chest pain**" should be added under the SOC "General disorders and administration site conditions" with a frequency "common".

The frequency of the adverse reaction "arthritis" should be changed to "**common"**.

The frequency of the adverse reaction "palpitations" should be changed to "**common"**.

Package Leaflet

- 4. Possible side effects

…//…

Common side effects

- **Palpitations, rapid heart rate**
- **Joint stiffness (arthritis)**
- **Chest pain**

Uncommon side effects

(…)

- ~~Palpitations, rapid heart rate~~

(…)

- ~~Joint stiffness (arthritis)~~

(…)

- **Yellowing of the skin and eyes**
- **High blood levels of bilirubin (a breakdown product of red blood cells)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	5 August 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	4 October 2017