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:

Tendonitis and tendon rupture:

The MAHs reviewed cases of tendon disorders [HLT], and most of the cases (66%) were tenosynovitis in hand (trigger finger), which is already listed in the SmPC and PL of letrozole.

From postmarketing, a total of 77 cases were retrieved cumulatively describing different tendinopathies other than tenosynovitis in hand (one case could be included in different PT; **tendonitis** (47), tenosynovitis (22), **Tendon rupture** (14), Tendon disorders (14)), Tendon pain (8), Epicondylitis/Tennis elbow (5), Tendon injury (3), Tendon calcification (2), Tendinous contracture (1)).

In summary, most of the tendinopathies identified (other than tenosynovitis of the hand) were **tendonitis** (47 cases, covering the narrow term tenosynovitis, which describe a specific condition of inflammation of the sheath (synovium) that surrounds the tendons), and tendon rupture (14 cases reported).

The commonly reported sites of tendonitis and associated terms were shoulder (24), Achilles tendon (12) elbow (7), other (<3) and unspecified (18). This differs substantially from the information available in the product information (finger only).

Based on the information collected in the clinical trials setting, 17 (0.7%) cases of tendonitis were reported (versus 2 in the placebo group, 0.2%), suggesting a difference between groups in the study MA17. Based on other results from clinical trials, in which patients were treated with letrozole versus anastrozole or tamoxifen (study BIG 1-98 and FACE), tendon disorders may be a class effect, with highest incidence reported with letrozole versus other hormonotherapies.

From literature, 8 articles reported tendon disorders (ref 45; 46; 50-55). In the article from Mitsimponas *et al.*, 3 cases of postmenopausal women with hormone receptor-positive breast cancer, who experienced tendinopathy or muscle tendon rupture (location Supraspinatus i.e. rotator cuff in all cases) under antihormonal treatment with letrozole. No other explanation or risk factors apart from letrozole were identified by authors. In the article from Kirchgesner et al., authors describe tendon toxicity of aromatase inhibitors as a class effect. They discussed the physiopathological mechanism with the presence of estrogen receptors within the intermediate layer of the pulleys and retinacula wich may explain the alterations of tendons observed.

Based on the available evidence, the PRAC concluded that an update to the product information (sections 4.4 and 4.8 of the SmPC, and sections 2 and 4 of the Package leaflet) is warranted with regards to the adverse drug reactions tendonitis (frequency uncommon) and tendon rupture (frequency rare) to inform healthcare professionals and patients about these risks.

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)

The following changes to the product information of medicinal products containing the active substance letrozole are recommended (new text **underlined and in bold**, deleted text ~~strike through~~):

SmPC

- Section 4.4

Tendonitis and tendon rupture

Tendonitis and tendon ruptures (rare) may occur. Close monitoring of the patients and appropriate measures (e.g. immobilisation) must be initiated for the affected tendon (see section 4.8).

- Section 4.8

Tabulated list of adverse reactions	
Musculoskeletal and connective tissue disorders	
Uncommon	**Tendonitis**
Rare	**Tendon rupture**

Package leaflet: Information for the patient

- Section 2

Letrozole may cause inflammation in tendons or tendon injury (see section 4). At any sign of tendon pain or swelling – rest the painful area and contact your doctor.

- Section 4

***Uncommon* - inflammation of a tendon or tendonitis (connective tissues that connect muscles to bones)**

***Rare* - rupture of a tendon (connective tissues that connect muscles to bones)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 August 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 October 2019