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 tamoxifen, the scientific conclusions are as follows:

In view of available data on toxic epidermal necrolysis from the literature and spontaneous reports including in some cases a close temporal relationship and in view of a plausible mechanism of action, the Lead Member State considers a causal relationship between tamoxifen and toxic epidermal necrolysis is at least a reasonable possibility. The Lead Member State concluded that the product information of products containing tamoxifen should be amended accordingly.

Update of section 4.4 of the SmPC with the inclusion of a warning on the risk of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome and toxic epidermal necrolysis with tamoxifen. Update of section 4.8 of the SmPC to add the adverse reaction 'toxic epidermal necrolysis' with a frequency of rare. The Package leaflet is updated accordingly.

In view of available data on the exacerbation of angioedema from the literature and spontaneous reports, including evidence of a close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, the Lead Member State considers a causal relationship between tamoxifen and the exacerbation of hereditary angioedema is at least a reasonable possibility. The Lead Member State concluded that the product information of products containing tamoxifen should be amended accordingly.

Update of section 4.4 of the SmPC to add a warning on the risk of exacerbation of hereditary angioedema with tamoxifen. Update of section 4.8 of the SmPC to add the adverse reaction "exacerbation of hereditary angioedema" with a frequency of not known. The Package leaflet is updated accordingly.

In view of available data on the excretion and accumulation of tamoxifen and its active metabolites in breastmilk from the literature the Lead Member State considers the product information of products containing tamoxifen should be amended accordingly.

Update of section 4.6 of the SmPC to amend the warning on use of tamoxifen in breastfeeding.

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 tamoxifen the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing tamoxifen 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 tamoxifen 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~~)

Toxic epidermal necrolysis

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows (where a warning on the risk of SCARs is not already included in section 4.4 of the SmPC):

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with <medicine> treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, <medicine> should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed a serious reaction such as SJS or TEN with the use of <medicine>, treatment with <medicine> must not be restarted in this patient at any time.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Skin and subcutaneous tissue disorders with a frequency of rare:

"Toxic epidermal necrolysis[a]"

Package Leaflet

- Section 2 "What you need to know before you take <medicine>"

Warnings and precautions - Take special care with <medicine>:

Serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in association with <medicine> treatment. Stop using <medicine> and

seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

- Section 4 "Possible side effects"

'Stop using <medicine> and seek medical attention immediately if you notice any of the following symptoms:'

Reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms [Stevens-Johnson syndrome, toxic epidermal necrolysis] – these side effects occur rarely.

Reference to Stevens Johnson syndrome currently included under the subsection 'Rare (may affect up to 1 in 1,000 people) should be deleted as follows:

- ~~A severe rash with blisters or peeling of the skin and possibly blisters in the mouth and nose (Stevens-Johnson syndrome).~~

Exacerbation of hereditary angioedema

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

In patients with hereditary angioedema, tamoxifen may induce or exacerbate symptoms of angioedema.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Skin and subcutaneous tissue disorders with a frequency of "not known":

"Exacerbation of hereditary angioedema"

Package Leaflet

- Section 2 "What you need to know before you take <medicine>"

Warnings and precautions

Talk to your doctor or pharmacist before you take <medicine>

- **If you have a history of hereditary angioedema as <Medicine> may cause or worsen symptoms of hereditary angioedema. If you experience symptoms such as swelling of the face, lips, tongue and/or throat with difficulty in swallowing or breathing, contact a doctor immediately.**

- Section 4 "Possible side effects"

Stop taking<medicine> and tell your doctor straight away if you notice any of the following side effects – you may need urgent medical treatment

Swelling of the face, lips, tongue or throat, difficulty in swallowing or breathing (angioedema). <Medicine> may cause or worsen symptoms of hereditary angioedema.

Tamoxifen excretion and accumulation in breastmilk

Summary of Product Characteristics

- Section 4.6

The warning should be amended as follows:

Breast-feeding

Limited data suggest that ~~It is not known if~~ <medicine> **and its active metabolites are** excreted **and accumulate over time** in human milk, therefore the drug is not recommended during breast-feeding. The decision either to discontinue nursing or discontinue <medicine> should take into account the importance of the drug to the mother.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	15 March 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	13 May 2021