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 fexofenadine, the scientific conclusions are as follows:

In view of available data on the drug-drug interaction between fexofenadine and apalutamide from a clinical trial published in the literature and in view of a plausible mechanism of action, the PRAC considers that the drug-drug interaction between fexofenadine and apalutamide is at least a reasonable possibility. In addition, in view of available data on blurred vision from spontaneous reports including many cases with a close temporal relationship, a positive de-challenge and/or re-challenge, the PRAC considers a causal relationship between fexofenadine and blurred vision is at least a reasonable possibility.

The PRAC concluded that the product information of products containing fexofenadine should be amended accordingly.

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 fexofenadine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing fexofenadine 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 fexofenadine are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that 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 4.5

A warning should be amended and an interaction should be added as follows:

Fexofenadine is a **P-glycoprotein (**P-gp**)** and **organic-anion-transporting polypeptide (**OATP**)** substrate. **Concomitant use of fexofenadine with P-gp inhibitors or inducers can affect the exposure to fexofenadine.** Co-administration of fexofenadine hydrochloride with **P-gp inhibitors** erythromycin or ketoconazole has been found to result in a 2-3 times increase in the level of fexofenadine in plasma. The changes were not accompanied by any effects on the QT interval and were not associated with any increase in adverse reactions compared to the medicinal products given singly. ~~Animal studies have shown that the increase in plasma levels of fexofenadine observed after co-administration of erythromycin or ketoconazole, appears to be due to an increase in gastrointestinal absorption and either a decrease in biliary excretion or gastrointestinal secretion, respectively.~~

A clinical drug-drug interaction study showed that co-administration of apalutamide (a weak inducer of P-gp) and a single oral dose of 30 mg fexofenadine resulted in a 30 % decrease in AUC of fexofenadine.

No interaction between fexofenadine and omeprazole was observed. However, the administration of an antacid containing aluminium and magnesium hydroxide gels 15 minutes prior to fexofenadine hydrochloride caused a reduction in bioavailability, most likely due to binding in the gastrointestinal tract. It is advisable to leave 2 hours between administration of fexofenadine hydrochloride and aluminium and magnesium hydroxide containing antacids.

- Section 4.8

The following adverse reaction should be added under the SOC Eye disorders with a frequency not known:

Vision blurred

Package Leaflet

What you need to know before you take <product name>

Other medicines and <product name>

Tell your doctor if you are taking, have recently taken or might take any other medicines.

If you are taking apalutamide (a medicine to treat prostate cancer), as the effect of fexofenadine may be decreased.

4. Possible side effects

Not known: frequency cannot be estimated from the available data

Blurred vision

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position :	04 January 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	23 February 2023