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 dorzolamide, the scientific conclusions are as follows:

Isolated cases of *dyspnoea* were reported by most Marketing Authorisation Holders (MAHs). The originator reported 142 adverse events (AEs) cumulatively, including 31 during the review period. While limited information was provided on cases reported during the review period analysis of the cumulative data shows that despite some cases being poorly documented or having confounding factors, at least 41 cases have positive dechallenge (dorzolamide was the only medication stopped) and 8 cases have positive rechallenge. These data are indicative of a causal relationship between dorzolamide and dyspnoea.

A plausible pharmacological mechanism for this adverse drug reaction could be that dorzolamide is a carbonic anhydrase inhibitor and that a systemic absorption in case of eye administration is possible. Indeed, carbonic anhydrase blockers inhibit NaHCO3 reabsorption in the proximal tubule and thus induce bicarbonate excretion that may conduct to a metabolic acidosis by loss of base. Dyspnoea is one of the first sign of metabolic acidosis. Of note, dyspnoea is already listed in the summary of product characteristics (SmPC) of other carbonic anhydrase inhibitors.

Isolated cases of *foreign body sensation in eye* were reported by most MAHs. The originator reported cumulatively 43 AEs with the preferred term “sensation of foreign body” and 44 with the preferred term “foreign body sensation in eyes”, including 13 during the review period. While limited information was provided on cases reported during the review period analysis of the cumulative data shows that in half of the cases, the physician or pharmacist assessed the case as related to dorzolamide.

Foreign body sensation in eye is an adverse effect commonly reported for eye drops. Foreign body sensation in eyes can have multiple origins such as corneal disorders, allergic reaction, eye inflammation, or eye irritation. These three last alternative explanations are known to be induced by dorzolamide eye drops. Since in most cases reported with dorzolamide, adverse events of eye irritation or redness were associated, foreign body sensation in eyes could be symptoms of allergic reaction or eye irritation and are therefore indirectly related to dorzolamide use.

Therefore, in view of the data presented in the reviewed PSUR(s), the PRAC considered that changes to the product information of medicinal products containing dorzolamide were warranted.

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 dorzolamide the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing dorzolamide 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 dorzolamide are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that such marketing authorisations are varied accordingly.

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

The following adverse reaction(s) should be added under the SOC Respiratory, thoracic and mediastinal disorders with a frequency not known:

- **Dyspnoea**

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

- **Foreign body sensation in eye**

Package Leaflet

- Section 4

Not known (frequency cannot be estimated from the available data):

- Shortness of breath

- Foreign body sensation in eye (feeling that there is something in your eye)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2016 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	22 December 2016
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	22 February 2017