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:

-Tachycardia: 21 ADRs including 3 serious ones which led to hospitalisation were reported by the MAH Santen cumulatively. 18 ADRs all non-serious of heart rate increased were also reported. 1 non-serious ADR was reported by another MAH cumulatively. Based on the analysis of cases provided by the MAHs, while some cases are poorly documented and confounding factors reported in other cases, suggestive elements regarding chronology and outcome were retrieved. Finally, 11 cases were considered as possibly related with a positive dechallenge reported in 10 cases and a positive rechallenge in 3 cases with dorzolamide alone.

-Hypertension: 37 ADRs including 3 serious ones (2 hospitalisation, 1 life-threatening) were reported by the MAH Santen cumulatively. 51 ADRs of blood pressure increase including 3 serious ones (1 hospitalisation) were also reported. 9 ADRs (1 serious and 8 non serious) were retrieved by other MAHs cumulatively. Based on the analysis of cases provided by the MAHs, while some cases are poorly documented and confounding factors reported in other cases, suggestive elements regarding chronology and outcome were retrieved. Finally, 19 cases were considered as possibly related with positive dechallenge reported in 17 cases and a positive rechallenge in 4 cases with dorzolamide alone.

Considering plausible pharmacological mechanism, absorption of dorzolamide into the systemic circulation after local administration and known AE of brinzolamide eye drops, another carbonic anhydrase inhibitor, the PRAC recommends adding tachycardia and hypertension to the product information of dorzolamide.

In this context, addition a step of eye drops administration which consists of pressing the inner corner of the eye for about two minutes after administration to reduce the systemic passage of dorzolamide remains necessary in section 4.2 of the SmpC in line with recommendations of PhVWP of June 2011 related to risk of systemic adverse reactions for beta-blokers for ophthalmic use. This information has been included in the Product Information of the innovator Trusopt® during the review period and should be implemented by all MAHs, if similar wording is not already implemented.

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 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 4.2

Method of administration

[…]

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

- Section 4.8

The following adverse reaction should be added under the **SOC Cardiac disorders** with a frequency unknown:

Tachycardia

The following adverse reaction should be added under the **SOC Vascular disorders** with a frequency unknown:

Hypertension

Package Leaflet

- Section 3

Instruction for use

[…]

Close your eye and press the inner corner of the eye with your finger for about two minutes. This helps to stop the medicine from getting into the rest of the body.

- Section 4

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

Increased heart rate

Increased blood pressure

<Annex III>

<Conditions to the Marketing Authorisation(s)>

Timetable for the implementation of this position

Adoption of CMDh position:	October 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	27 November 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	26 January 2023