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 botulinum toxin a, the scientific conclusions are as follows:

The MAH provided a review for eyelid oedema in the chronic migraine indication. The MAH have identified a number of cases in the chronic migraine indication where eyelid oedema developed within a temporal association to BOTOX administration and furthermore a number of cases of positive rechallenge have also been identified where there was reoccurrence of oedema following a subsequent BOTOX treatment. The MAH have argued that of the 44 non-serious cases reported during the interval that 11 were confounded as they appeared to occur with concomitant administration of medications known to cause peri-orbital or facial oedema however the MAH have not discussed the timing of administration of the co-suspect medications (patients may have been on these long-term) and therefore it is not possible to determine if they are true confounders in the context of the ADR under evaluation. For the remaining 33 cases the MAH have argued that there is insufficient information for assessment. Whilst acknowledging that eyelid oedema is already listed as an ADR for the 'blepharospasm, hemifacial spasm and associated dystonias' indication and for glabellar lines the MAH consider that the lower recommended doses into the corrugator muscle for the chronic migraine indication would not be supportive of a causal association. However, although information on doses to specific sites is not known the total reported administration in the above cases does fall within the overall recommended dose for the chronic migraine indication of '155 to 195 units administered intramuscularly as 0.1 ml injections to 31 and up to 39 sites'. For BOTOX, Eyelid oedema is currently only listed under the 'Blepharospasm' indication as mentioned. Overall, given the four reported cases of rechallenge, and the fact that this is a labelled ADR for other indications with similar injection sites the MAH is requested to reflect 'Eyelid oedema' as an ADR for the chronic migraine indication and within the table of ADRs reflecting cases received from post-marketing sources.

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 botulinum toxin a, the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing botulinum toxin a 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 botulinum toxin a 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 4.8

The following adverse reaction(s) should be added under the SOC Eye Disorders and should be included under the 'Additional information' reflecting ADRs received from post-marketing sources.

- **Eyelid Oedema**

Package Leaflet

The package leaflet should be updated accordingly to reflect **'Swelling of the eyelid'**.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	03/11/2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	02/01/2020