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 neurotoxin type a (150 kD) free from complexing proteins, the scientific conclusions are as follows:

A battery of publications provide strong hints that injections of *Botulinum* neurotoxin type A exert a considerable influence on the properties of muscles in animals and humans, thereby resulting in their structural and mechanical changes. Moreover, published systematic reviews revealed that the available evidence indicates a post-injection muscle atrophy, which may last for a period ranging from months to years following the *Botulinum* neurotoxin type A. Additionally, a study in healthy volunteers revealed a high degree of neurogenic atrophy even after 12 months following the injection of the medicinal product concerned, that is *Xeomin.* Histopathology confirmed neurogenic muscle fiber atrophy with some compensatory fiber hypertrophy in the injected muscle. Similar changes were not observed in the contralateral control muscle. Furthermore, the 'hourglass deformity', which is the consequence of the temporalis muscle atrophy, secondary to *Botulinum* neurotoxin type A treatment, have been described in the literature. Likewise, those findings published in the scientific literature are supported by data in the product information of other preparations containing botulinum toxin.
Recent investigations demonstrated that owing to the identical mechanism of action of the available *Botulinum* neurotoxin type A preparations, the observed phenomena within the muscle are not likely to be specific for a particular preparation. The intensity, duration, and reversibility of muscle atrophy following *Botulinum* neurotoxin type A injections remain not fully understood. Consequently, the neurogenic atrophy can go undetected in clinical trials and post-marketing owing to possible compensating mechanisms, underlying muscle disorders, or its uncharted clinical relevance. In conclusion, the inclusion of *'muscle atrophy'* in the product information is deemed warranted based on the evaluation of the available evidence.

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 neurotoxin type a (150 kD) free from complexing proteins the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing botulinum neurotoxin type a (150 kD) free from complexing proteins 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 neurotoxin type a (150 kD) free from complexing proteins 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 should be added under the SOC Musculoskeletal and connective tissue disorders with a frequency not known:

muscle atrophy

Package Leaflet

- 4. Possible side effects

shrinkage of injected muscle

A tabulated list of adverse reactions (*i. e.* presented by SOC and frequency) needs to be implemented for the section Post-Marketing Experience in the Summary of Product Characteristics.

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