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 (except for centrally authorised products), the scientific conclusions are as follows:

In view of available data on iatrogenic botulism from the literature and spontaneous reports and in view of a plausible mechanism of action, the PRAC concluded that the product information of products containing botulinum toxin A (except for centrally authorised products) should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for botulinum toxin a (except for centrally authorised products) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing botulinum toxin a (except for centrally authorised products) is unchanged subject to the proposed changes to the product information

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

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~~)

BOTOX

Summary of Product Characteristics

Section 4.4

Side effects related to spread of toxin distant from the site of administration have been reported (see section 4.8), sometimes resulting in death, which in some cases were associated with dysphagia, pneumonia and/or significant debility. The symptoms are consistent with the mechanism of action of botulinum toxin and have been reported hours to weeks after injection.

Cases of iatrogenic botulism have been reported following injection of botulinum toxin products. Patients and caregivers should be advised to seek immediate medical advice if they experience any signs or symptoms consistent with the spread of botulinum toxin effect or if swallowing, speech or respiratory disorders arise (see section 4.9).

The risk of symptoms **from toxin spread** is probably greatest in patients who have underlying conditions and comorbidities that would predispose them to these symptoms, including children and adults treated for spasticity, and are treated with high doses.

Patients treated with therapeutic doses may also experience exaggerated muscle weakness.

Section 4.9

Signs of overdose are not apparent immediately post-injection. Should accidental injection or ingestion occur, or overdose **or spread of toxin** be suspected, the patient should be medically supervised for several days for signs and symptoms of general weakness or muscle paralysis. Admission to hospital should be considered in patients presenting with symptoms of botulinum toxin type A poisoning (generalised weakness, ptosis, diplopia, swallowing and speech disorders, or paresis of the respiratory muscles).

Package Leaflet

Section 2

You or your caregiver should contact your doctor and seek medical attention immediately if you experience any of the following:
• difficulty in breathing, swallowing, or speaking

[…]

Adverse reactions possibly related to the spread of toxin distant from the site of administration **and botulism** have been reported with botulinum toxin (e.g. **double vision, blurred vision and/or drooping eyelids, trouble breathing or speaking, excessive** muscle weakness, difficulty swallowing, or unwanted food or liquid in the airways). These side effects can be mild to severe, may require treatment and in some cases may be fatal. This is a particular risk for patients with an underlying illness that makes them susceptible to these symptoms.

BOTOX COSMETIC

Summary of Product Characteristics

Section 4.4

Adverse reactions possibly related to the spread of toxin distant from the site of administration have been reported very rarely with botulinum toxin (see section 4.8). Patients treated with therapeutic doses may experience exaggerated muscle weakness. Swallowing and breathing difficulties are serious and can result in death. Injection of VISTABEL is not recommended in patients with a history of dysphagia and aspiration. **Cases of iatrogenic botulism have been reported following injection of botulinum toxin products.** Patients should be advised to seek immediate medical care if **they experience any signs or symptoms consistent with the spread of botulinum toxin effect or if** swallowing, speech or respiratory disorders arise **(see section 4.9).**

Section 4.9

Signs of overdose are not apparent immediately post-injection. Should accidental injection or ingestion occur**, or overdose or spread of toxin be suspected**, the patient should be medically supervised for several days for signs and symptoms of general weakness or muscle paralysis. Admission to hospital should be considered in patients presenting with symptoms of botulinum toxin type A poisoning (generalised weakness, ptosis, diplopia, swallowing and speech disorders, or paresis of the respiratory muscles).

Package Leaflet

Section 2

Warnings and precautions

A warning should be amended as follows:

Adverse reactions possibly related to the spread of toxin distant from the site of administration **and botulism** have been reported very rarely with botulinum toxin (e.g. **double vision, blurred vision and/or drooping eyelids, trouble breathing or speaking, excessive** muscle weakness, difficulty swallowing, or unwanted food or liquid in the airways). Patients receiving recommended doses may experience exaggerated muscle weakness.

Visit your doctor immediately:
- If you find it difficult to swallow, to speak or to breathe after treatment.

Letybo

Summary of Product Characteristics

Section 4.4

Local or distant spread of toxin effects

Adverse reactions possibly related to the spread of toxin distant from the site of administration have been reported very rarely with botulinum toxin (see section 4.8). Patients treated with therapeutic doses may experience exaggerated muscle weakness.
Swallowing and breathing difficulties are serious and can result in death. Injection of Letybo is not recommended in patients with a history of dysphagia and aspiration.

Cases of iatrogenic botulism have been reported following injection of botulinum toxin products.
Patients should be advised to seek immediate medical care if **they experience any signs or symptoms**

consistent with the spread of botulinum toxin effect or if swallowing, speech or respiratory disorders arise **(see section 4.9)**.

Section 4.9

Management of overdose

Should accidental injection or ingestion occur, **or overdose or spread of toxin be suspected,** the patient should be medically monitored for signs and symptoms of general weakness or muscle paralysis. Admission to hospital should be considered in patients presenting with symptoms of botulinum toxin type A poisoning (generalised weakness, ptosis, diplopia, swallowing and speech disorders, or paresis of the respiratory muscles).

Package Leaflet

Section 2

Warnings and precautions

A warning should be amended as follows:

Side effects due to botulinum toxin's spread away from the injection site **and botulism** have been reported very rarely **with botulinum toxin**~~, such as~~ **(e.g. double vision, blurred vision and/or drooping eyelids, trouble breathing or speaking,** excessive muscle weakness**, difficulty swallowing, or unwanted food or liquid in the airways)**. Swallowing and breathing difficulties are serious and can result in death. If you have problems with your swallowing, speech or breathing, seek medical help immediately.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2025 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	2 November 2025
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	1 January 2026