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:

In view of the available data from the literature and spontaneous reports regarding iatrogenic Botulism and a plausible mechanism of action, the PRAC concluded that the product information of products containing botulinum neurotoxin type a (150 kD) free from complexing proteins 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 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 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~~)

XEOMIN/BOCOUTURE

Summary of Product Characteristics

Section 4.4

Local and distant spread of toxin effect

Undesirable effects may occur from misplaced injections of Botulinum neurotoxin type A that temporarily paralyse nearby muscle groups. Large doses may cause paralysis in muscles distant from the injection site.
There have been reports of undesirable effects that might be related to the spread of Botulinum toxin type A to sites distant from the injection site (see section 4.8). Some of these can be life threatening and there have been reports of death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.

Patients treated with therapeutic doses may experience excessive muscle weakness. **Cases of iatrogenic botulism have been reported following injection of botulinum toxin products.** Patients or caregivers 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 occur **(see section 4.9)**.

Dysphagia has also been reported following injection to sites other than the cervical musculature.

Section 4.9

Symptoms of overdose

Increased doses of Botulinum neurotoxin type A may result in pronounced neuromuscular paralysis distant from the injection site with a variety of symptoms. Symptoms may include general weakness, ptosis, diplopia, breathing difficulties, speech difficulties, paralysis of the respiratory muscles or swallowing difficulties which may result in aspiration pneumonia.

Measures in cases of overdose

In the event of overdose **or spread of toxin** the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment may be necessary. Respiratory support may be required if paralysis of the respiratory muscles occurs.

Package Leaflet

Section 2

Warnings and precautions

Side effects may occur from misplaced injections of Botulinum neurotoxin type A temporarily paralysing nearby muscle groups. There have been very rare reports of side effects that may be related to the spread of toxin distant from the injection site **and botulism** to produce symptoms consistent to Botulinum toxin type A effects (e.g. **double vision, blurred vision and/or drooping eyelids, trouble speaking or breathing**, excessive muscle weakness, swallowing difficulties or accidental swallowing

of food or drink into the airways). Patients who receive the recommended doses may experience excessive muscle weakness.

[…]

Contact your doctor and seek medical attention immediately if you experience any of the following:
- Difficulty in breathing, swallowing or speaking

Relfydess

Summary of Product Characteristics

Section 4.4

Spread of Toxin effect

Post-marketing safety data from other approved botulinum toxin products suggest that botulinum toxin effects (such as diplopia, blurred vision and ptosis) may be observed beyond the site of local injection (see section 4.8). **Cases of iatrogenic botulism have been reported following injection of botulinum toxin products.** In addition, adverse reactions possibly related to the spread of toxin effect distant from the site of injection have been reported very rarely with botulinum toxin-and may include asthenia, generalised muscle weakness, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms are consistent with the mechanism of action of botulinum toxins and have been reported hours to weeks after injection.

Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. More specifically, following treatment with botulinum toxin, very rare cases of death have been reported in the context of patients who have dysphagia, pneumopathy, or significant asthenia. Therefore, Relfydess is not recommended in such patients. Patients or caregivers 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

Overdose

Excessive doses may produce distant and profound neuromuscular paralysis with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose **or spread of toxin**, the patient should be medically monitored for several weeks for any signs and/or symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment may be necessary. Symptoms of overdose may not be present immediately post-injection. Admission to hospital should be considered for patients with symptoms of botulinum toxin overdose (e.g. a combination of muscle weakness, ptosis, diplopia, swallowing and speech disorders, or paresis of the respiratory muscle.

Package Leaflet

Section 2

Special warnings

Side effects possibly related to the spread of toxin effect away from the site of injection **and botulism** have been reported very rarely with botulinum toxin (e.g. **double vision, blurred vision and/or drooping eyelids**, **excessive muscle weakness,** difficulty swallowing, coughing and choking when swallowing, difficulty speaking or breathing). These symptoms have been reported hours to weeks after the injection. Seek immediate medical attention if you experience difficulties in swallowing, speaking or breathing.

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:	02/11/2025
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	01/01/2026