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 glatiramer, the scientific conclusions are as follows:

In view of available data on 'Long latency anaphylaxis' from clinical trials, the literature, spontaneous reports, including cases with a plausible temporal relationship, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between glatiramer and 'Long latency anaphylaxis' is at least a reasonable possibility. The PRAC concluded that the product information of products containing glatiramer 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 glatiramer the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing glatiramer 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~~)

Summary of Product Characteristics

[Applicable for glatiramer acetate 20 mg/ml and 40 mg/ml products]

- Section 4.4

A warning should be amended as follows:

[Product name] should only be administered subcutaneously. [Product name] should not be administered by intravenous or intramuscular routes.

Glatiramer acetate can cause post-injection reactions as well as anaphylactic reactions (see section 4.8):

Post-injection reactions

The treating physician should explain to the patient that a reaction associated with at least one of the following symptoms may occur within minutes of a [product name] injection: vasodilatation (flushing), chest pain, dyspnoea, palpitations or tachycardia (see section 4.8). The majority of these symptoms is short-lived and resolves spontaneously without any sequelae. Should a severe adverse event occur, the patient must immediately stop [product name] treatment and contact his/her physician or any emergency doctor. Symptomatic treatment may be instituted at the discretion of the physician.
There is no evidence to suggest that any particular patient groups are at special risk for these reactions. Nevertheless, caution should be exercised when administering [product name] to patients with pre-existing cardiac disorders. These patients should be followed up regularly during treatment.

~~Convulsions and/or anaphylactoid or allergic reactions have been reported rarely.~~

Anaphylactic reactions

~~Serious hypersensitivity reactions (e.g. bronchospasm, anaphylaxis~~ **Anaphylactic reactions** ~~or urticaria)~~ may ~~rarely~~ occur **shortly following administration of glatiramer acetate, even months up to years after initiation of treatment (see section 4.8). Cases with fatal outcome have been reported. Some signs and symptoms of anaphylactic reactions may overlap with post-injection reactions.** ~~If reactions are severe, appropriate treatment should be instituted and [product name] should be discontinued.~~

All patients receiving treatment with [product name] and caregivers should be informed about the signs and symptoms specific for anaphylactic reactions and that they should seek immediate emergency medical care in case of experiencing such symptoms (see section 4.8).

If an anaphylactic reaction occurs, treatment with [product name] must be discontinued (see section 4.3).

[Applicable for glatiramer acetate 20 mg/ml products]

- Section 4.8

The following adverse reaction should be added under the SOC Immune system disorders with a frequency uncommon:

Anaphylactic reaction

[..]

The description of selected adverse reactions below the tabulated list of adverse reactions should be

amended as follows:

~~The following adverse reaction reports were collected from MS patients treated with Copaxone in uncontrolled clinical trials and from post-marketing experience with Copaxone: hypersensitivity reactions (including rare occurrence of anaphylaxis, >1/10000, < 1/1000).~~

Description of selected adverse reactions

Anaphylactic reactions may occur shortly following administration of glatiramer acetate, even months up to years after initiation of treatment (see section 4.4).

[Applicable for glatiramer acetate 40 mg/ml products]

- Section 4.8

The following adverse reaction should be added under the SOC Immune system disorders with a frequency uncommon:

Anaphylactic reaction

[…]

The description of selected adverse reactions below the tabulated list of adverse reactions should be amended as follows:

~~Rare (≥1/10,000 to <1/1,000) reports of anaphylactoid reactions were collected from MS patients treated with Copaxone in uncontrolled clinical trials and from post-marketing experience with Copaxone.~~

[…]

A few specific adverse reactions are noted:

- ~~Anaphylactic response was seen rarely (≥1/10,000, <1/1,000) in MS patients treated with glatiramer acetate 20 mg/ml in uncontrolled clinical trials and from post-marketing experience. It was reported by 0.3% of the patients on glatiramer acetate 40 mg/ml (Uncommon: ⩾1/1,000 to < 1/100)~~ **Anaphylactic reactions may occur shortly following administration of glatiramer acetate, even months up to years after initiation of treatment (see section 4.4).**

Package Leaflet

[Applicable for glatiramer acetate 20 mg/ml and 40 mg/ml products]

2. What you need to know before you use [product name]

Warnings and precautions

[Product name] can cause severe allergic reactions, some of which may be life-threatening. These reactions may occur shortly after administration, even months up to years after starting treatment and even if previous administrations were without allergic reactions.
The signs and symptoms of allergic reactions may overlap with post-injection reactions. Your doctor will inform you on the signs of an allergic reaction.

[Applicable for glatiramer acetate 20 mg/ml products]

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic Reactions (hypersensitivity, **anaphylactic reaction**)
You may ~~rarely~~ develop a serious allergic reaction to this medicine **shortly after administration**. **This is an uncommon side effect. These reactions may occur months up to years after starting treatment with [product name], even if previous administrations were without allergic reactions.**

Stop using [product name] and contact your doctor immediately or go to the ~~casualty~~ **emergency** department at your nearest hospital, if you notice any **sudden** sign of these side effects:

- **widespread** rash (red spots or nettle rash)
- swelling of the eyelids, face**,** ~~or~~ lips**, mouth, throat or tongue**
- sudden shortness of breath**, difficulty breathing or wheezing**
- convulsions (fits)
- **trouble swallowing or speaking**
- fainting**, feeling dizzy or faint**
- **collapse**

[Applicable for glatiramer acetate 40 mg/ml products]

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic Reactions (hypersensitivity, **anaphylactic reaction**)
You may develop a serious allergic reaction to this medicine **shortly after administration.** ~~but it~~ **This** is **an** uncommon **side effect. These reactions may occur months up to years after starting treatment with [product name], even if previous administrations were without allergic reactions.**

Stop using [product name] and contact your doctor immediately or go to the ~~casualty~~ **emergency** department at your nearest hospital, if you notice any **sudden** sign of these side effects:

- **widespread** rash (red spots or nettle rash)
- swelling of the eyelids, face**,** ~~or~~ lips**, mouth, throat or tongue**
- sudden shortness of breath**, difficulty breathing or wheezing**
- convulsions (fits)
- **trouble swallowing or speaking**
- fainting**, feeling dizzy or faint**
- **collapse**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	08 September 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	07 November 2024