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:

Liver injury

In view of available data on severe liver injury from clinical trials and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge, the PRAC considers a causal relationship between glatiramer and severe liver injury is established. The PRAC concluded that the product information of products containing glatiramer should be amended accordingly.

Abortion

In view of available data on abortion from clinical trial(s), the literature and spontaneous reports, the PRAC considers the causal relationship between glatiramer and abortion is unlikely. The PRAC concluded that the product information of products containing glatiramer should be amended accordingly.

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 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 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 glatiramer 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

Applicable to 20 mg/ml and 40 mg/ml strengths:

- Section 4.4

A warning should be amended as follows:

Rare cases of severe liver injury have been observed (including hepatitis with jaundice, liver failure, and in isolated cases liver transplantation). Liver injury occurred from days to years after initiating treatment with <product>. **Most instances of severe liver injury resolved with discontinuation of treatment.** ~~Concomitant conditions reported in these cases included~~ **In some cases, these reactions have occurred in the presence of** excessive alcohol consumption, existing or history of liver injury and use of other potentially hepatotoxic medication. **Patients should be regularly monitored for signs of hepatic injury and instructed to seek immediate medical attention in case of symptoms of liver injury.** In case of clinically significant liver injury, discontinuation of <product> should be considered.

- Section 4.8

The section above the adverse reactions table should be amended as follows:

~~All adverse reactions, which were more frequently reported in <Copaxone> <glatiramer acetate 20 mg/ml> vs. placebo-treated patients~~, **Adverse reactions identified from clinical trials and post marketing experience** are presented in the table below. ~~This data~~ **Data from clinical trials** was derived from four pivotal, double-blind, placebo-controlled clinical trials with a total of 512 patients treated with glatiramer acetate 20 mg/day and 509 patients treated with placebo for up to 36 months. Three trials in relapsing-remitting MS (RRMS) included a total of 269 patients treated with glatiramer acetate 20 mg/day and 271 patients treated with placebo for up to 35 months. The fourth trial in patients who have experienced a first clinical episode and were determined to be at high risk of developing clinically definite MS included 243 patients treated with glatiramer acetate 20mg/day and 238 patients treated with placebo for up to 36 months.

The following adverse reaction(s) should be added under the SOC Hepatobiliary disorders with a frequency Rare:

Toxic hepatitis, Liver injury

The following adverse reaction(s) should be added under the SOC Hepatobiliary disorders with a frequency “not known”:

Hepatic failure*

A footnote should be added for the ADR Hepatic failure and placed under the tabulated list of adverse reactions with the following wording:

***Few cases were reported with liver transplantation.**

The following paragraph should be removed from section 4.8

~~Rare cases of severe liver injury (including hepatitis with jaundice, liver failure, and in isolated cases liver transplantation) have been reported with <product> in post-marketing experience. Most instances of severe liver injury resolved with discontinuation of treatment. Hepatic events have occurred from days to years after initiating treatment with <product>. In case of clinically significant liver injury, discontinuation of <product> should be considered.~~

Summary of Product Characteristics

Applicable to 20 mg/ml and 40 mg/ml formulations:

- Section 4.8

The following adverse reaction(s) should be removed:

~~Abortion~~

Package Leaflet

Section 4. Possible side effects

This section should be amended as follows:

Liver problems

Liver problems or worsening of liver problems, including liver failure **(some cases resulting in liver transplantation)**, can occur rarely with <product>.

Package Leaflet

Section 4. Possible side effects

The following adverse reaction(s) should be removed:

~~Abortion~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	6 September 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	4 November 2021