# 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 ethanol extracts of: Iberis amara L., planta tota recens / Angelica archangelica L., radix / Matricaria recutita L., flos / Carum carvi L., fructus / Silybum marianum (L.) Gaertn., fructus / Melissa officinalis L., folium / Mentha piperita L., folium / Chelidonium majus L., herba / Glycyrrhiza glabra L., radix, the scientific conclusions are as follows:

In view of the available data on drug induced liver injury from the literature as well as 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 Iberogast and drug induced liver injury (DILI) is at least a reasonable possibility. The PRAC concluded that the product information of products containing ethanol extracts of: Iberis amara L., planta tota recens / Angelica archangelica L., radix / Matricaria recutita L., flos / Carum carvi L., fructus / Silybum marianum (L.) Gaertn., fructus / Melissa officinalis L., folium / Mentha piperita L., folium / Chelidonium majus L., herba / Glycyrrhiza glabra L., radix 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 ethanol extracts of: Iberis amara L., planta tota recens / Angelica archangelica L., radix / Matricaria recutita L., flos / Carum carvi L., fructus / Silybum marianum (L.) Gaertn., fructus / Melissa officinalis L., folium / Mentha piperita L., folium / Chelidonium majus L., herba / Glycyrrhiza glabra L., radix the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing ethanol extracts of: Iberis amara L., planta tota recens / Angelica archangelica L., radix / Matricaria recutita L., flos / Carum carvi L., fructus / Silybum marianum (L.) Gaertn., fructus / Melissa officinalis L., folium / Mentha piperita L., folium / Chelidonium majus L., herba / Glycyrrhiza glabra L., radix 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 ethanol extracts of: Iberis amara L., planta tota recens / Angelica archangelica L., radix / Matricaria recutita L., flos / Carum carvi L., fructus / Silybum marianum (L.) Gaertn., fructus / Melissa officinalis L., folium / Mentha piperita L., folium / Chelidonium majus L., herba / Glycyrrhiza glabra L., radix 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 4.3

The contraindication should be added as follows:

**In existing or previous liver disease or concomitant use of medicines containing liver damaging properties the medicinal product must not be taken.**

- Section 4.4

A warning should be amended/added as follows:

**Cases of drug induced liver injury including liver failure have been reported with the use of [medicinal product] (see also section 4.8).**

**If signs of liver damage occur (yellowing of the skin or eyes, dark urine, discoloured stool, pain in the upper abdomen), treatment should immediately be discontinued and a physician consulted.**

To be added after paragraph on children:

**Patients should also be advised to consult a physician if their symptoms persist or if the success expected from the administration is not achieved within 7 days.**

- Section 4.8

The following adverse reaction(s) should be added under the SOC Hepatobiliary disorders with a frequency not known: **Drug induced liver injury***

***With the use of [medicinal product] cases of drug induced liver injury (increase in liver enzymes and bilirubin up to drug-related jaundice and cases of liver failure) have been reported.**

**Package Leaflet**

- Section 2. What you need to know before you use [medicinal product]

  Do not use [medicinal product]

  **- if you have or have had a liver disease or if you are taking medicines with a side effect of liver damage included in the package leaflet. If you are in doubt, ask your doctor or pharmacist.**

  Warnings and precautions

  **- If you notice yellowing of the skin or eyes, dark urine, discoloured stool, pain in the upper abdomen, you should immediately stop taking [medicinal product] and consult a physician. These can be symptoms of liver damage.**

  To be added after paragraph on children:

**- If your symptoms do not get better within 7 days or even get worse visit your physician so that other serious diseases can be excluded.**

- Section 4. Possible side effects

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

  **- Frequency unknown: Liver damage (increase in liver values, drug related jaundice, hepatitis and liver failure); if you notice symptoms like yellowing of the skin or eyes, dark urine, discoloured stool, you should immediately stop taking [medicinal product] and consult a physician.**

## Annex III

## Timetable for the implementation of this position

**Timetable for the implementation of this position**

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|---|---|
| Adoption of CMDh position: | July 2021 CMDh meeting |
| Transmission to National Competent Authorities of the translations of the annexes to the position: | 5 September 2021 |
| Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder): | 4 November 2021 |