# 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 levosimendan, the scientific conclusions are as follows:

**BREASTFEEDING**

In view of available data from the literature concerning case reports on excretion of active metabolites of levosimendan in human milk, the PRAC considers that the recommendations for use of levosimendan during breastfeeding should be revised in order to specify that women who receive levosimendan should not breastfeed to avoid potential cardiovascular adverse events in the infant. The PRAC concluded that the product information of products containing levosimendan should be amended accordingly.

**OPALESCENCE/PRECIPITATION IN HIGH CONCENTRATION**

In view of available data from case reports of medication errors in post-marketing, in which opalescence and precipitation were reported after levosimendan was diluted to a higher concentration than the maximum 0.05mg/mL concentration, the PRAC considers that the consequences of levosimendan being poorly soluble in water, when diluted to a higher than recommended concentration should be included in the product information under the special precautions for disposal and other handling.

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 levosimendan the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing levosimendan 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 levosimendan 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**

**BREASTFEEDING**

- Section 4.6

Update of section 4.6 of the SmPC to revise the existing information regarding lactation and recommendation for use during breastfeeding.

Lactation:

~~It is not known whether levosimendan is excreted in human milk. Studies in rats have shown excretion of levosimendan in breast milk, therefore women receiving levosimendan should not breastfeed.~~ **Information from post marketing use in breast feeding women indicates that the active metabolites of levosimendan OR-1896 and OR-1855 are excreted in breast milk and were detected in milk for at least 14 days after the start of the 24-h levosimendan infusion. Women receiving levosimendan should not breastfeed in order to avoid potential cardiovascular adverse effects in the infant.**

**Package Leaflet**

Section 2

Pregnancy and breast-feeding

The information regarding breast-feeding should be amended as follows:

~~It is not known if~~ **There are indications that** Simdax passes into human breast milk. ~~Therefore, y~~ **Y**ou should not breast-feed while using Simdax **in order to avoid potential cardiovascular side-effects in the infant.** ~~Ask your doctor or pharmacist for advice before taking any medicine.~~

**OPALESCENCE/PRECIPITATION IN HIGH CONCENTRATION**

**Summary of Product Characteristics**

- Section 6.6

A statement should be included to inform on the occurrence of opalescence and precipitation if levosimendan is diluted to a higher concentration than the maximum 0.05 mg/mL concentration:

**<Product name> 2.5 mg/ml concentrate for solution for infusion should not be diluted into a higher concentration than 0.05mg/ml as instructed below, otherwise opalescence and precipitation may occur.**

## Annex III

## Timetable for the implementation of this position

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|---|---|
| Adoption of CMDh position: | May 2020 CMDh meeting |
| Transmission to National Competent Authorities of the translations of the annexes to the position: | 12/07/2020 |
| Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder): | 10/09/2020 |