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 *Saccharomyces boulardii*, the scientific conclusions are as follows:
In view of available data on the risk of sepsis from spontaneous reports including 12 cases where causal association was concluded as possible, three fatal cases with positive blood cultures and cases with positive de-challenge following the use of corrective treatment and in view of a plausible mechanism of onset, the PRAC considers a causal relationship between *Saccharomyces boulardii* and sepsis is at least a reasonable possibility. The PRAC concluded that the product information of products containing *Saccharomyces boulardii* should be amended accordingly.

Update of the existing warning in section 4.4 of the SmPC to add possible complications of sepsis related to *Saccharomyces boulardii* systemic fungaemia in fragilized patients, i.e. immunocompromised, with central venous catheter or severely ill. Update of section 4.8 to add “Sepsis in critically ill or immunocompromised patients” (frequency not known) and a cross-reference to section 4.4 on the risk of sepsis. Package Leaflet is to be updated accordingly in section 4.
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 *Saccharomyces boulardii* the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing *Saccharomyces boulardii* 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 *Saccharomyces boulardii* 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 4.4

There have been very rare cases of fungaemia (and blood cultures positive for Saccharomyces strains) **and sepsis** reported mostly in patients with central venous catheter, critically ill or immunocompromised patients, most often resulting in pyrexia. In most cases, the outcome has been satisfactory after cessation of treatment by *Saccharomyces boulardii*, administration of antifungal treatment and removal of the catheter when necessary. However, the outcome was fatal in some critically ill patients (see sections 4.3 and 4.8).

- Section 4.8

The following adverse reaction should be added under the SOC lnfections and infestations with a frequency ´not known´:
Sepsis in critically ill or immunocompromised patients (see section 4.4)

Package Leaflet

- Section 4

Unknown frequencies side effects:
- **Serious blood infection (sepsis)**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	10/2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	29/11/2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	20/01/2021