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:

Based on the data presented within the periodic safety update report (PSUR) under review and based on the data in EudraVigilance database and available literature, the benefit-risk balance for use of Saccharomyces boulardii (S. boulardii) containing products in critically ill or immunocompromised patients is considered changed and an update of the product information is warranted.

There were 19 cases reported with preferred term (PT) fungaemia during the interval period and 61 cases cumulatively. The search in EudraVigilance database overall revealed 10 fatal cases of fungaemia/fungal infection and sepsis associated with administration of S. boulardii containing medicinal products where the causal association could not be ruled out. Moreover, there was also 1 fatal case of fungal infection and sepsis reported in a 48-year old patient, however no case narrative was provided, therefore the causality could not be established properly. Approximately half of the fatal fungaemia cases were reported in patients with central venous catheter (CVC) which has been already contraindicated. However, in rest of the fatal cases no CVC insertion was reported. In 1 fatal case of fungaemia insertion of CVC was explicitly ruled out by the reporter. Considering the known potential risk of fungaemia in critically ill patients and reported fatal cases in patients with no CVC insertion, the use of S. boulardii in critically ill or immunocompromised patients should be contraindicated and relevant sections of the SmPC (sections 4.2, 4.3, 4.4 and 4.8) and patient information leaflet (PIL) should be updated 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 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 4.2

Due to a risk of airborne contamination, sachets or capsules should not be opened in patient rooms. Healthcare providers should wear gloves during handling of probiotics for administration, then promptly discard the gloves and properly wash their hands (see section 4.4).

- Section 4.3

A contra-indication should be amended as follows:

Known hypersensitivity to one of the components; allergy to yeast, especially *Saccharomyces boulardii*; patients having a central venous catheter; **critically ill patients or immunocompromised patients due to a risk of fungaemia (see section 4.4).**

- Section 4.4

~~It is advisable not to open capsules or sachets in the surroundings of patients with a central venous catheter, to avoid any colonization, especially handborne, of the catheter. There have been reports in patients with a central venous catheter, even not treated with Saccharomyces boulardii, of very rare cases of fungemia (penetration of blood by yeast), most often resulting in pyrexia and blood cultures positive for Saccharomyces strains. The outcome in all these cases has been satisfactory after administration of antifungal treatment and, when necessary, removal of the catheter.~~

There have been very rare cases of fungaemia (and blood cultures positive for Saccharomyces strains) 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).

As with all medicines made from living micro-organisms, special attention must be paid to the handling of the product in the presence of patients mainly with central venous catheter but also with peripheral catheter, even not treated with Saccharomyces boulardii, in order to avoid any contamination by hands and/or the spread of microorganisms by air (see section 4.2).

- Section 4.8

The following adverse reaction should be added under the SOC Infections and infestations with a frequency ´very rare´:

System Organ Class	Rare	Very rare

Infections and infestations		Fungaemia in patients with a central venous catheter **and in critically ill or immunocompromised patients (see section 4.4)**

Package Leaflet

- Section 2
  - **Immunocompromised or hospitalised patients (due to serious illness or altered / weakened immune system)**

- Section 4

Very rare side effects:

- **Penetration of yeast into blood (fungaemia)**

Annex III

Timetable for the implementation of this position>

Timetable for the implementation of this position

Adoption of CMDh position:	October 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	25 November 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	24 January 2018