

Part VI – Summary of the risk management plan

This is a summary of the risk management plan (RMP) for *Saccharomyces boulardii* CNCM I-745. The RMP details important risks of *Saccharomyces boulardii* CNCM I-745, how these risks can be minimised, and how more information will be obtained about *Saccharomyces boulardii* CNCM I-745's risks and uncertainties (missing information).

Saccharomyces boulardii CNCM I-745's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how *Saccharomyces boulardii* CNCM I-745 should be used.

I. The medicine and what it is used for

Saccharomyces boulardii CNCM I-745 is authorised for the following main indications: acute infectious (viral or bacterial) diarrhoea, Antibiotic-Associated Diarrhoea (AAD) and colitis, digestive side effects during *Helicobacter Pylori* (HP) eradication therapy, and recurrence of *Clostridium difficile* Disease (CDD) in addition to vancomycin (VAN), metronidazole (MTZ), etc. (see SmPC for the full indication). It contains lyophilized *Saccharomyces boulardii* CNCM I-745 as the active substance and it is given by oral route.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of *Saccharomyces boulardii* CNCM I-745, together with measures to minimise such risks and the proposed studies for learning more about *Saccharomyces boulardii* CNCM I-745's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II. A. List of important risks and missing information

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Important risks of *Saccharomyces boulardii* CNCM I-745 are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of *Saccharomyces boulardii* CNCM I-745. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Fungemia and sepsis in patients with a central venous catheter (CVC), in critically ill patients or in immunocompromised patients
Important potential risks	None
Missing information	None

II. B. Summary of important risks

Important identified risk: Fungemia and sepsis in patients with a CVC, in critically ill patients or in immunocompromised patients	
Evidence for linking the risk to the medicine	The analysis of cases with reported fungaemia and sepsis associated with the use of <i>Saccharomyces boulardii</i> CNCM I-745 showed that patients with identified severe weakness such as critically ill or immunocompromised patients, majored by a context of hospital stay and central or peripheral access for the yeast to penetrate the blood, are at risk of experiencing fungaemia. The risk of experiencing fungaemia has also been highlighted in patients not treated with <i>Saccharomyces boulardii</i> CNCM I-745 but hospitalized in the same room as treated patients.
Risk factors and risk groups	Risk factors well identified as a condition for the occurrence of fungaemia are: - patients in a context of hospital stay, - patients with identified weakness such as major surgery, prematurity, ongoing severe infection, chemotherapy or known to be immunocompromised, e.g. the use of immunosuppressive treatments could aggravate the intestinal mucosa condition and increase the risk¹⁵,

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	- patients with a CVC, - patients with a peripheral access for the yeast to penetrate the blood such as a nutrition access, a dialysis or documented treatment with parenteral route drugs. Other risk factors can contribute to the occurrence of fungaemia: - patients with bowel diseases (ischemic or inflammatory), preexisting intestinal pathology including diarrhoea and short intestine and colonic ulceration, - probiotics with properties of high adherence to the intestinal mucosa, - patients having an unbalanced intestinal environment during and after a decontamination with multiple antibiotics, specially antibiotics active on anaerobic bacteria which suppress the barrier effect of these bacteria.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> CCDS Sections “contra-indications” and “undesirable effects”. CCDS Sections “mode of administration” and “warning” with specific recommendations for use: - not to open the product (capsule, sachet) in patient room to avoid air contamination, - healthcare providers to wear gloves during handling of probiotics for administration, then promptly discard the gloves and properly wash their hands, - special care when handling the product in the presence of patients with central or peripheral venous catheter to avoid any contamination by hands and/or spread over room air. <u>Additional risk minimisation measures:</u> None

II. C. Post-authorisation development plan

II. C. 1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of *Saccharomyces boulardii* CNCM I-745.

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II. C. 2. Other studies in post-authorisation development plan

There are no studies required for *Saccharomyces boulardii* CNCM I-745.

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