LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Precosa Neutral
(Saccharomyces boulardii, strain CNCM I-745)

Asp no: 2022-0723

This module reflects the scientific discussion for the approval of Precosa Neutral. The procedure was finalised on 2024-02-22. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Precosa Neutral, 250 mg, Powder for oral suspension in sachet.

The active substance is Saccharomyces boulardii, strain CNCM I-745, freeze dried. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The MPA has been assured that acceptable standards of GMP are in place for these product types at the site responsible for the manufacture and assembly of this product.
The manufacturing site within the European Community, the MPA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
The manufacturer of the active substance is the same as the manufacturer of the finished product. Satisfactory GMP status has been confirmed by the Swedish Drug Inspectorate.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology
A comprehensive set of literature studies on the mode of action and pharmacological effects of *S. boulardii* on various pathogenic bacteria and viruses and on the intestinal mucosa were provided. It indicates that *S. boulardii* CNCM I-745 can act on bacterial toxins, on the pathogen and on the intestinal mucosa of the host and modulate the response to infection, e.g., by creating a favourable growth environment for the beneficial intestinal microbiota. The protective action of *S. boulardii* CNCM I-745 to adverse effects induced by an infection is expected to result from complementary effect of several mechanisms.

Pharmacokinetics
No standard pharmacokinetic analysis was presented for *S. boulardii* CNCM I-745 250 mg, powder for oral suspension, which is acceptable. *S. boulardii* yest cells have local effect in the gastro-intestinal tract and there are no indications that they cross the gastrointestinal wall and reach the systemic circulation after oral administration. The cells are introduced in the gastrointestinal tract compartment and transferred to and eliminated in the feces compartment, mainly as dead cells or digested dead cells. Pharmacokinetic interactions with other drugs are considered less likely. The half-life for live cells could not be obtained but was estimated to be shorter than 3 hours.

Toxicology
S. boulardii CNCM I-745
Studies on acute and repeated dose toxicity of *S. boulardii* in rats did not reveal any treatment-related effects on weight, clinical signs (including changes in respiratory, circulatory, autonomic and central nervous system, behavioural pattern), haematology or biochemical parameters, food intake and gross pathology. Furthermore, other repeated dose toxicity studies of high doses in rats, mice, rabbits and dogs showed no abnormalities. No significant risk of *S. boulardii* for humans is thus indicated when the product is used according to the recommendations. Possible adverse effects in humans noted during the well-established use of *S. boulardii* are described below (see Clinical aspects).

Except for a negative Ames test no data of the genotoxic potential of *S. boulardii* were provided. Lack of results from a standard battery of tests of genotoxic effects of *S. boulardii* is considered acceptable for cells of *S. boulardii*. No relevant literature studies of the carcinogenic potential of *S. boulardii* were found or provided. This is considered acceptable for a product with *S. boulardii* cells intended for treatment up to 4 weeks.

No relevant literature studies of the potential of S. *boulardii* to induce reproductive or developmental toxicity were found or provided. This is considered acceptable for *S. boulardii* cells that are not absorbed from the gastro-intestinal tract and not excreted into milk. As *S. boulardii* is neither absorbed from the gastro-intestinal tract nor excreted into milk it will not reach the foetus or a breastfed child during treatment with Precosa Neutral. Precosa Neutral can be used during pregnancy and breastfeeding.

Maltodextrin
As maltodextrin is of pharmacopoeia grade (Ph. Eur. monograph 1542) no safety information was provided for this excipient. The appropriateness of the formulation has been justified in line with applicable guidelines for pediatric use.

Environmental Risk Assessment (ERA)
As the active ingredient *S. boulardii* CNCM I-745 are yeast cells naturally occurring in the environment and are excreted as dead or degraded cells following oral administration, Precosa Neutral 250 mg, powder for oral suspension is unlikely to result in a significant risk to the

environment. Furthermore, this new formulation of Precosa Neutral is expected to replace other products on the market and will not lead to an increased exposure to the environment. In conclusion, the use of Precosa Neutral 250 mg, powder for oral suspension is not expected to pose a significant risk to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics

No new pharmacokinetic studies have been submitted. The applied product is for children and include maltodextrine as excipient. No difference in terms of pharmacokinetics is expected for the applied product compared to previously approved Precosa Neutral products including another sweetener (fructose) and flavours.

Because of its fungal nature, Precosa Neutral must not be administered with oral or systemic antifungal drugs.

Saccharomyces boulardii has local effect in the gastro-intestinal tract and concentrations in faeces are presented in the literature. In conclusion, if Precosa Neutral is administered, steady-state concentrations of *Saccharomyces boulardii* is achieved in the colon within 3 days and is cleared from the stools 2-5 days after discontinuation.

Pharmacodynamics

A thorough review of the literature has been provided, describing the various mechanisms of action for S. boulardii in the treatment and prevention of diarrhoea of various etiologies.

Its action is based on multiple mechanisms, including immunological effects, pathogen-binding and anti-toxin effects, as well as effects on digestive enzymes. Correlated with these effects, but also due to its inherent properties, S. boulardii is able to create a favourable growth environment for the beneficial intestinal microbiota, while constituting extra protection to the host mucus layer and mucosa.

Clinical efficacy

The efficacy of S. boulardii in preventing AAD has been reviewed in several publications. A number of studies from published literature have been submitted to support the efficacy of S. boulardii in prevention of AAD in adults. All presented data showed a reduction of the numbers of patients that got diarrhoea in the S. boulardii group compared to the placebo group. The number of participants was between 151 and 477 in the various studies and the dose received was 200-1000 mg/day for different periods of time up to 7 days after antibiotic discontinuation.

The meta-analyses provided show a similar result as the single studies with a reduction of AAD in the S. boulardii groups compared to the placebo group. In some of the studies included in the meta analysis children were also included, with a similar result.

The dose, 1000 mg/day, as proposed in the SmPC for adults is supported by data.
For the duration of treatment, it is agreed that a maximum duration of 4 weeks is appropriate. Different literature studies recommend different dosing regimens regarding treatment after antibiotic treatment is terminated, but the proposal to continue 3 days is supported by literature and is consistent with the already approved Precosa Neutral.

The data from the literature provided in support of the efficacy for prevention of recurrence of CDD is not consistent. Some studies show a reduced risk of recurrent CDD in the S. boulardii group compared

to placebo, while others did not. Some studies also had both primary and secondary CDD in the same study. In the studies showing a positive effect the dosing regimen was the same as proposed in the SmPC, 1000 mg/day for 4 weeks.

Clinical safety
From the reviews and meta-analyses it can be concluded that *S. Boulardii* has a safety profile with few adverse events, and mostly mild to moderate. Examples are constipation, rash and allergic reactions. The more serious adverse event, fungaemia in critically ill patients and/or patients with central venous cathether, has been handled by a DHPC letter and an insertion of a contraindication in the SmPC.

Pharmacovigilance system
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the MPA considers the Summary acceptable.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Precosa Neutral.

Safety specification

Summary of safety concerns

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

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Important identified risks		
Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Fungemia and sepsis in patients with a central venous catheter (CVC), in critically ill patients or in immunocompromised patients	Routine: CCDS Sections “Mode of administration”, “contraindications”, “warning” and “undesirable effects”	Only routine activities – adverse reactions reporting and signal detection

Summary of the RMP
The submitted Risk Management Plan, version 2.1 signed 17/02/2023 is acceptable.

When accepted, the MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the Swedish MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Precosa 500 mg powder for oral suspension, sachet (MA no 60586) leaflet which was assessed and accepted in Dnr. 5.4.1-2020-29579.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

From a quality point of view, acceptable information has been provided regarding manufacture and control of drug substance and drug product. Acceptable stability data has also been provided for both drug substance and drug product, justifying the claimed shelf-life. Acceptable GMP status has also been confirmed for all manufacturing sites involved in the production and control of Precosa Neutral.

Based on non-clinical literature data the protective action of *S. boulardii* to adverse effects induced by an infection is expected to result from complementary effects of several mechanisms, e.g., effects on bacterial toxins, on the pathogen and on the intestinal mucosa of the host. Furthermore, non-clinical literature data do not indicate any significant risks for patients (including pregnant and breastfeeding women) or the environment, when Precosa Neutral is used according to the recommendations in the SmPC.

The use of *S. boulardii* as a therapeutic probiotic is supported by its mechanisms of action, pharmacokinetics, and efficacy from animal models. Administration of *S. boulardii* during antibiotic therapy has certain advantage over bacterial probiotics, because due to its fungal natural properties, it is intrinsically resistant to the antibiotics and cannot promote the spread of antimicrobial resistance.

Meta-analyses confirm that *S. boulardii* is effective in reducing the risk of AAD in adults and children. *S. boulardii* administration, concomitantly with antibiotics, compared with placebo or no intervention, reduces the risk of AAD in adults and children treated with antibiotics for any reason.

For prevention of recurrence of CDD the supportive data is not as strong and there are only limited studies to show a decrease in CDD with probiotics.

The use of *S. boulardii* is accepted to be safe and well tolerated. The adverse events are rare and mostly mild to moderate.
Rare cases of fungaemia have occurred in patients with central venous catheters and serious com-morbidities. A contraindication has been included in the SmPC to mitigate the risk.

In conclusion, the quality is found adequate and there are no objections to approval of Precosa Neutral from a quality, non-clinical and clinical point of view. The benefit/risk of this product is positive when used in accordance with the recommendations in the SmPC.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Precosa Neutral, 250 mg, Powder for oral suspension in sachet was approved in the national procedure on 2024-02-22.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se