LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Precosa
(saccharomyces boulardii CNCM I-745 lyophilized)

Asp no: 2020-0363, 2020-0362

This module reflects the scientific discussion for the approval of Precosa. The procedure was finalised on 2021-05-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Biocodex S.A.S. has applied for a marketing authorisation for Precosa, Powder for oral suspension, sachet, 500 mg and Precosa, Powder and solvent for oral suspension, 250 mg. The active substance *saccharomyces boulardii* CNCM I-745 lyophilized is the same as in Precosa, 250 mg, powder for oral suspension, sachet, marketed by Biocodex since 1995.
There is no available public assessment report for the original product, Precosa, 250 mg, powder for oral suspension, sachet.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

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

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

III.1 Introduction

The non-clinical information is derived from the applicants Non-clinical Overview. No new non-clinical studies have been submitted for this procedure.

III.2 Pharmacology

Precosa has the yeast *Saccharomyces boulardii* CNCM I-745 as an active substance and lactose monohydrate as an excipient. The stated pharmacological mode of action of CNCM I-745 is to act as a probiotic agent that maintains and/or restores the natural flora in the large and small human intestine.

A number of pharmacological stipulations are made in the pharmacological dossier (although without specific references) including that the CNCM I-745 strain is stipulated to be resistant to 'several' antibiotic drugs in-vitro, gastric juice and tolerant to human body temperature of 37C. It is also stated that the CNCM I-745 strain can provide protection to animals from *Clostridium difficile* infection. The protection derives from the secretion of a 54 kDa protease inhibiting the enterotoxic and cytotoxic effects of *Clostridium difficile* toxins A and B and by the induction of immunoglobulins in mice immunized orally with a toxin A toxoid and by the dose-dependent inhibition of in vitro-cell adherence of *Clostridium difficile*. There is also a claim that the active substance provides protection in vivo in animals from *Vibrio cholerae* and *Escherichia coli* infection. The latter is stated to involve neutralizing the heat-labile (LT) and heat-stable (Sta) toxins of an enterotoxinogenic strain of *Escherichia coli* (ETEC). Other claimed protective functions are protection against other enteropathogenic bacteria such as *Shigella flexneri, Salmonella typhimurium* and *Citrobacter rodentium*. Animal intake of the active substance reduces the extent of the changes following disruption of flora homeostasis by clindamycin. There is also a claim of an anti-inflammatory effect on the intestinal mucosa which participate to its antidiarrhea action.

III.3 Pharmacokinetics

No non-clinical pharmacokinetic information is available for the oral intake of *Saccharomyces boulardii* CNCM I-745. This is considered acceptable as there is no systemic absorption of the active substance.

III.4 Toxicology

The toxicological dossier states that acute toxicity studies with CNCM I-745 in mouse and rats generated a NOAEL of 3000mg/kg (oral intake, maximum dose) and a NOAEL of 1500-2000mg/kg for intraperitoneal administration. Repeat-dose toxicity studies in rats, dogs and rabbits are stated to have not demonstrated any toxicity (macroscopic or microscopic) but experimental study details (e.g. formulation, exposure durations, dosage groups, observed endpoints) are missing. An Ames test genotoxicity assessment did not find any signs of genotoxicity. Based on that there is no systemic absorption, no in-vivo genotoxicity, in-vivo carcinogenicity or DART studies have been conducted. In combination with clinical experience since 1995, this is considered acceptable. No other toxicity study information has been provided.

III.5 Ecotoxicity/environmental risk assessment

The main environmental exposure route is considered to be via the waste-water treatment plants. Given a maximum dosage of 1000mg/d (DDD) and a Fpen of 0.0959, the ERA phase I surface water predicted environmental concentration (PECsw) is calculated to 0.0048ug/L (<0.01ug/L). No phase II assessment is triggered and CNCM I-745 is considered unlikely as an environmental risk.

III.6 Discussion on the non-clinical aspects

No additional non-clinical data supporting a new dose has been provided. While the non-clinical pharmacological, pharmacokinetic and toxicological dossier is lacking, as the product has a long historical clinical usage, the lack of information is not considered serious enough in this context for

further information requirements or that new non-clinical studies are necessary. Overall, this is not considered grounds for refusal/concerns from a regulatory point of view as the goal is not to conduct a reassessment of the dossier for the originator product.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Precosa with the *Saccharomyces boulardii* CNCMI-745 as an active substance is administered as an oral suspension. It is intended to act locally in the intestine and the active substance is not absorbed. The absence of pharmacokinetic studies is in line with the Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev.1 Corr.1*).

IV.2 Clinical efficacy and safety

No additional clinical data has been submitted which is agreeable. There are no updates in the SmPC regarding indication or posology.

IV.3 Risk Management Plans

The applicant has provided a justification for not providing an RMP as part of the application for the line extension. According to the CMDh recommendation on the summary of the pharmacovigilance system and risk management plan in the mutual recognition and decentralized procedures, this is acceptable.

Pharmacovigilance Plan

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

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

V. USER CONSULTATION

The user test of the Precosa leaflet was assessed and accepted in dnr 5.4.1-2020-29579.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

All issues raised in the quality parts have been resolved. There are no objections to approval from a non-clinical point of view. From a clinical point of view the benefit risk balance is in line with the previously approved Precosa products (i.e. positive). All issues regarding the product information has been resolved. The application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

Precosa, Powder for oral suspension, sachet, 500 mg and Precosa, Powder and solvent for oral suspension, 250 mg was approved in the national procedure on 2021-05-20.

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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)

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