LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Micafungin Bioglan
(micafungin sodium dihydrate)

SE/H/2049/01-02/DC

This module reflects the scientific discussion for the approval of Micafungin Bioglan. The procedure was finalised on 2021-05-12. 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

The application for Micafungin Bioglan, 50 mg and 100 mg, powder for concentrate for solution for infusion is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Laboratorio Reig Jofré S.A., applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and FR, ES and PT as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Mycamine, 100 mg, powder for concentrate for solution for infusion, authorised in the Union since 2008, with Astellas Pharma Europe B.V. as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

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 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

No bioequivalence study has been submitted. The applicant claims that a bioequivalence study is not necessary according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) since the product is a parenteral solution.

Discussion and overall conclusion
The applied product is to be administered as an aqueous intravenous solution containing the same active substance as the currently authorised product. The applied product also has the same excipients as in the reference product and none of the excipients are known to interact with the drug substance. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1).

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 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 Micafungin Bioglan.

Safety specification
The MAH has submitted the version 0.1 RMP dated 31 January 2020, and proposed the following summary safety concerns:

Table 1. Summary of safety concerns

Important identified risks	• Haemolytic adverse events including disseminated intravascular coagulation (DIC) • Hepatic adverse events • Renal adverse events
Important potential risks	• Relevance in humans of the development of liver tumours in rats
Missing Information	• None

Summary of the RMP

The proposed RMP for Micafungin Bioglan is not completely in line with that of the reference product. The Important potential risk ”Development of resistant strains” is not included.

Development of resistant strains previously classified as important potential risk could be removed. As per the Infectious Diseases Working Party (IDWP) and EMA position taken in recent centralised procedure for antibiotics, Category 3 resistance surveillance studies are no longer being required as a pharmacovigilance measure in the RMP. Antibiotic resistance development constitutes an efficacy concern, not a safety concern. It is the responsibility of the MAH to adequately monitor trends in clinical resistance to their product and promptly report any emerging concern via the appropriate regulatory channels. It is expected that the MAH will monitor this as an efficacy issue in the PSURs.

The submitted Risk Management Plan, version 0.1 RMP dated 31 January 2020 is considered 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 a Prescriber Checklist is proposed as additional risk minimisation activity, which is endorsed.

The MAH shall ensure that prior to prescribing the product prescribers will receive the prescriber Checklist. Prescriber checklist reminds prescribers about the risks associated to the use of Micafungin Bioglan 50 mg and/or 100 mg to ensure the product is prescribed appropriately.

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 RMS;
- 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

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Micafungin Bioglan, is found adequate. There are no objections to approval of Micafungin Bioglan, from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk ratio is considered positive and 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

Additional risk minimisation measures
The MAH shall ensure that prior to prescribing of the product prescribers will receive the prescriber checklist.

The MAH should agree the final content, format and distribution modalities of the Prescriber checklist with the National Competent Authority in each Member State and ensure that the materials contain the key elements as described below.

Prescriber checklist
- The decision to use Micafungin Reig Jofre should take into account a potential risk for the development of liver tumours. Micafungin Reig Jofre should therefore only be used if other antifungals are not appropriate
- Caution must be demonstrated if the patient:
  - has severe liver function impairment
  - has chronic liver diseases known to represent preneoplastic conditions (e.g. advanced liver fibrosis, cirrhosis, viral hepatitis, neonatal liver disease or congenital enzyme defects)
  - is receiving a concomitant therapy including hepatotoxic and/or genotoxic properties
  - has history of haemolysis, haemolytic anaemia or renal impairment.
- Patients should be carefully monitored for liver damage and for worsening of renal function.
- To minimise the risk of adaptive regeneration and potentially subsequent liver tumour formation, early discontinuation in the presence of significant and persistent elevation of ALT/AST is recommended.
- Patients who develop clinical or laboratory evidence of haemolysis during micafungin therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the benefit/risk of continuing micafungin therapy.

VII. APPROVAL

The decentralised procedure for Micafungin Bioglan, 50 mg and 100 mg, powder for concentrate for solution for infusion was positively finalised on 2021-05-12.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/2049/01-02/IB/02	Update of RMP to align with the latest version of the innovator RMP (Mycamine RMP v23.2).	No	2023-11-24	Approval	List of safety concerns has been updated. Specific standardized follow-up questionnaire to address the important identified risk of haemolytic adverse events including disseminated intravascular coagulation (DIC) has been added. Prescriber's Checklist as an additional risk minimization activity has been removed. As a consequence, the condition pursuant to Article 21a of Directive 2001/83/EC is considered as fulfilled.

*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