COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Anidulafungine Accord 100 mg powder for concentrate for solution for infusion (anidulafungin)

NL/H/4543/001/DC

Date: 2 March 2023

This module reflects the scientific discussion for the approval Anidulafungine Accord 100 mg powder for concentrate for solution for infusion. The procedure was finalised in the United Kingdom (UK/H/6626/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Anidulafungin 100mg Powder for Concentrate for Solution for Infusion

(Anidulafungin)

Procedure No: UK/H/6626/001/DC

UK Licence No: PL 20075/0539

Accord Healthcare Limited

LAY SUMMARY

Anidulafungin 100mg Powder for Concentrate for Solution for Infusion (Anidulafungin)

This is a summary of the Public Assessment Report (PAR) Anidulafungin 100mg Powder for Concentrate for Solution for Infusion (PL 20075/0539; UK/H/6626/001/DC). It explains how the application for Anidulafungin 100mg Powder for Concentrate for Solution for Infusion was assessed and its authorisation recommended, as well as its condition of use. It is not intended to provide practical advice on how to use this product.

The product may be referred to as Anidulafungin solution for infusion in this Lay Summary.

For practical information about using Anidulafungin solution for infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is Anidulafungin solution for infusion and what is it used for?

Anidulafungin solution for infusion is a "generic medicine". This means that this product is similar to a 'reference medicine' already authorised in the UK called Ecalta 100 mg powder for concentrate for solution for infusion (Pfizer Limited; EU/1/07/416/002).

Anidulafungin solution for infusion is prescribed in adults to treat a type of fungal infection of the blood or other internal organs called invasive candidiasis. The infection is caused by fungal cells (yeasts) called Candida.

How does Anidulafungin solution for infusion work?

Anidulafungin solution for infusion contains the active substance anidulafungin, which belongs to a group of medicines called echinocandins. These medicines are used to treat serious fungal infections.

Anidulafungin solution for infusion prevents normal development of fungal cell walls. In the presence of Anidulafungin Powder, fungal cells have incomplete or defective cell walls, making them fragile or unable to grow.

How is Anidulafungin solution for infusion used?

Anidulafungin solution for infusion is prepared and given by a doctor or a healthcare professional, by slow infusion (a drip) into the vein. This will take at least 1.5 hours for the maintenance dose and 3 hours for the loading dose.

The treatment starts with 200mg on the first day (loading dose). This will be followed by a daily dose of 100mg (maintenance dose).

A doctor will determine the duration of the treatment and how much Anidulafungin Powder a patient will receive each day and will monitor the response and condition. In general, the treatment should continue for at least 14 days after the last day Candida was found in the blood.

Anidulafungin solution for infusion can only be obtained with a prescription from a doctor.

For further information on how Anidulafungin solution for infusion is used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

What are the benefits and risks of Anidulafungin solution for infusion?

As Anidulafungin solution for infusion is a generic medicine and is comparable to the reference

medicine, Ecalta 100 mg powder for concentrate for solution for infusion, its benefits and risks are taken as being the same as those for the reference medicine.

Why is Anidulafungin solution for infusion approved?
No new or unexpected safety concerns arose from this application. It was, therefore, concluded that the benefits of Anidulafungin solution for infusion outweigh the risks; and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Anidulafungin solution for infusion?
A risk management plan has been developed to ensure that Anidulafungin solution for infusion is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Anidulafungin solution for infusion, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Anidulafungin solution for infusion
Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, Germany, Greece, Italy, Norway, Poland, Portugal, Republic of Ireland, Romania, Slovenia, Spain, Sweden, The Netherlands and the UK agreed to grant a Marketing Authorisation for Anidulafungin solution for infusion on 30 October 2018. A Marketing Authorisation was granted in the UK on 26 November 2018.

The full PAR for Anidulafungin solution for infusion follows this summary.

This summary was last updated in January 2019.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMS) considered that the application for Anidulafungin 100mg Powder for Concentrate for Solution for Infusion (PL 20075/0539; UK/H/6626/001/DC), is approvable.

Anidulafungin 100mg Powder for Concentrate for Solution for Infusion is indicated for the treatment of invasive candidiasis in adult patients.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, Germany, Greece, Italy, Norway, Poland, Portugal, Republic of Ireland, Romania, Slovenia, Spain, Sweden and The Netherlands as Concerned Member States (CMS). This application was submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The applicant has cross-referred to Ecalta 100 mg powder for concentrate for solution for infusion, which was originally authorised to Pfizer Limited on 20 September 2007 through a Centralised Procedure (EU/1/07/416/002).

Anidulafungin is a semi-synthetic echinocandin, a lipopeptide synthesised from a fermentation product of *Aspergillus nidulans*.

Anidulafungin selectively inhibits 1,3-β-D glucan synthase, an enzyme present in fungal, but not mammalian cells. This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall. Anidulafungin has shown fungicidal activity against *Candida* species and activity against regions of active cell growth of the hyphae of *Aspergillus fumigatus*.

No new non-clinical or clinical studies were conducted, which is acceptable given that this is a generic application of an originator product that has been in clinical use for over 10 years.

A bioequivalence study was not necessary to support this application for a parenteral product, containing the same active substance as the reference product.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS 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.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 30 October 2018). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 20075/0539) for this product on 26 November 2018.

II QUALITY ASPECTS

II.1 Introduction

This product is a powder for concentrate for solution for infusion and each vial contains 100 mg anidulafungin, as the active ingredient. The excipients present are fructose, mannitol, polysorbate 80, lactic acid, sodium hydroxide and hydrochloric acid.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

The finished product is filled in a 30 mL type I colourless glass vial with bromobutyl rubber stopper and aluminium flip-off cap with plastic button with a pack size of 1 vial.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 DRUG SUBSTANCE

Anidulafungin

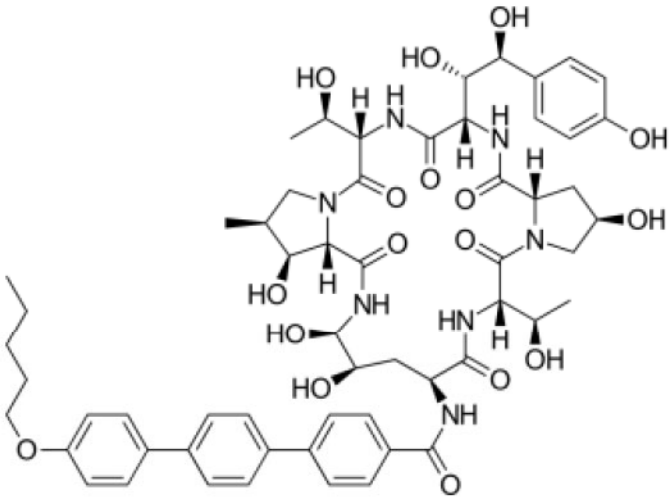
INN: Anidulafungin

Chemical Name:

N-[(3S,6S,9S,11R,15S,18S,20R,21R,24S,25S,26S)-6-[(1S,2R)-1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl]-11,20,21,25-tetrahydroxy-3,15-bis[(1R)-1-hydroxyethyl]-26-methyl-2,5,8,14,17,23-hexaoxo-1,4,7,13,16,22-hexaazatricyclo[22.3.0.09,13]heptacosan-18-yl]-4-{4-[4(pentyloxy)phenyl]phenyl}benzamide

Molecular formula: $C_{58}H_{73}N_7O_{17}$

Structure:



Molecular mass: 1140.2 g/mol

Appearance: White or off-white powder.

Solubility: Anidulafungin is slightly soluble in methanol and practically insoluble in water or acetonitrile.

Anidulafungin is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis. No materials of animal or human origin are used in the production of the active substance.

Appropriate proof-of-structure data have been supplied for the active substance. All potential impurities have been identified and monitored appropriately.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been provided supporting a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the pharmaceutical development programme was to obtain a stable product containing anidulafungin which could be considered as a generic medicinal product of Ecalta 100 mg powder for concentrate for solution for infusion (Pfizer Limited; EU/1/07/416/002).

Suitable pharmaceutical development data have been provided for this application.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on three commercial scale batches have been provided. The results are satisfactory.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the products

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 30 months for the unopened vial with special storage conditions "Store in a refrigerator (2 C – 8 C) and "Do not freeze" are set. This is satisfactory.

Excursions for 96 hours up to 25°C are permitted, and the powder can be returned to refrigerated storage.

Reconstituted solution

The reconstituted solution may be stored at up to 25°C for up to 24 hours.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25ºC.

From a microbiological point of view the product should be used immediately. If not used immediately, the in-use storage times and conditions prior to use are the responsibility of the user.

Solution for infusion
The infusion solution may be stored at 25ºC for 48 hours or stored frozen for 72 hours.

Chemical and physical in-use stability of the infusion solution has been demonstrated for 48 hours at 25ºC.

From a microbiological point of view the product should be used immediately. If not used immediately, the in-use storage times and conditions prior to use are the responsibility of the user and would normally not longer than 24 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a Marketing Authorisation is recommended.

III.1 NON-CLINICAL ASPECTS

Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of anidulafungin are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.1 Pharmacology

Not applicable, see Section III.1 Introduction, above.

III.2 Pharmacokinetics

Not applicable, see Section III.1 Introduction, above.

III.3 Toxicology

Not applicable, see Section III.1 Introduction, above.

III.4 Ecotoxicity/Environmental Risk Assessment (ERA)

A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with a product that is already marketed, no increase in environmental exposure to anidulafungin is anticipated. Thus, the justification for not submitting an Environmental Risk Assessment is accepted.

III.5 Discussion of the non-clinical aspects

There are no objections to the approval of this product from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

The applicant did not conduct any clinical study to support this application. In accordance with the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), a bioequivalence study is not required if the test product is a solution containing the

same active substance as the reference product. As this product is a solution at the time of administration, no bioequivalence studies have been submitted and none are required.

Anidulafungin 100 mg powder for concentrate for solution for infusion is administered as an aqueous parenteral solution and contains the same concentration of the same active substance and very similar excipients as those of the reference product, ECALTA 100 mg powder for concentrate for solution for infusion (Pfizer Limited). The only difference in the composition of the generic anidulafungin product is lactic acid instead of tartaric acid which is present in the reference medicinal product. Both these excipients are organic acids and perform the same function (i.e., are used as antioxidants or preservatives to prevent degradation of the active ingredient). No influence of the lactic acid on the pharmacokinetics is expected.

Based on the comparative studies performed on micelle characterisation, the biowaiver is now sufficiently justified (see also section III.1). Taking into account the Guideline on Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev.1, Corr) and the Reflecting Paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems, satisfactory further data has now been provided by the applicant.

No new data have been submitted and none are required for applications of this type.

IV.1 Pharmacokinetics

The clinical pharmacokinetic properties of anidulafungin are well-known. No new pharmacokinetic data are provided or required for this application.

IV.2 Pharmacodynamics

The clinical pharmacodynamics properties of anidulafungin are well-known. No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.3 Clinical Efficacy

The clinical efficacy of anidulafungin is well-known. No new efficacy data are presented or are required for applications of this type.

IV.4 Clinical Safety

No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application. Anidulafungin has a well-established safety profile and an acceptable level of safety in the proposed indication.

IV.5 Risk Management Plan (RMP)

The Marketing Authorisation Holder (MAH) has submitted a RMP, 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 Anidulafungin 100mg Powder for Concentrate for Solution for Infusion.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Important identified risks	• Infusion-associated AEs • Hepatobiliary AEs • Convulsions
Important potential risks	• Anesthetic exacerbation of infusion-associated AEs • QT Prolongation/*Torsade de Pointes*
Missing information	• Use in children and adolescents • Use during pregnancy and lactation • Use in elderly • Resistance to anidulafungin

IV.6 Discussion of the clinical aspects

The grant of a Marketing Authorisation is recommended.

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 patient information leaflet (PIL) was English.

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*.

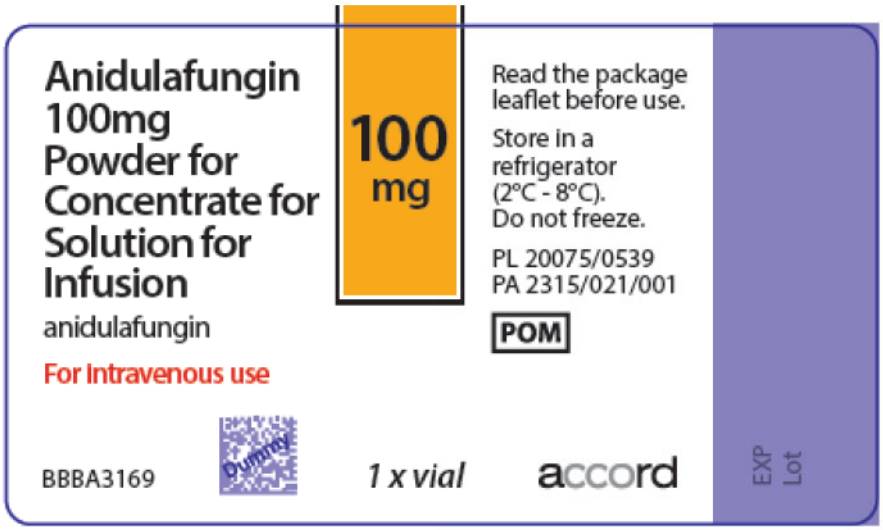
VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with anidulafungin is considered to have demonstrated the therapeutic value of the compound. The benefit risk assessment is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:

The approved labelling for Anidulafungin 100mg Powder for Concentrate for Solution for Infusion is presented below:



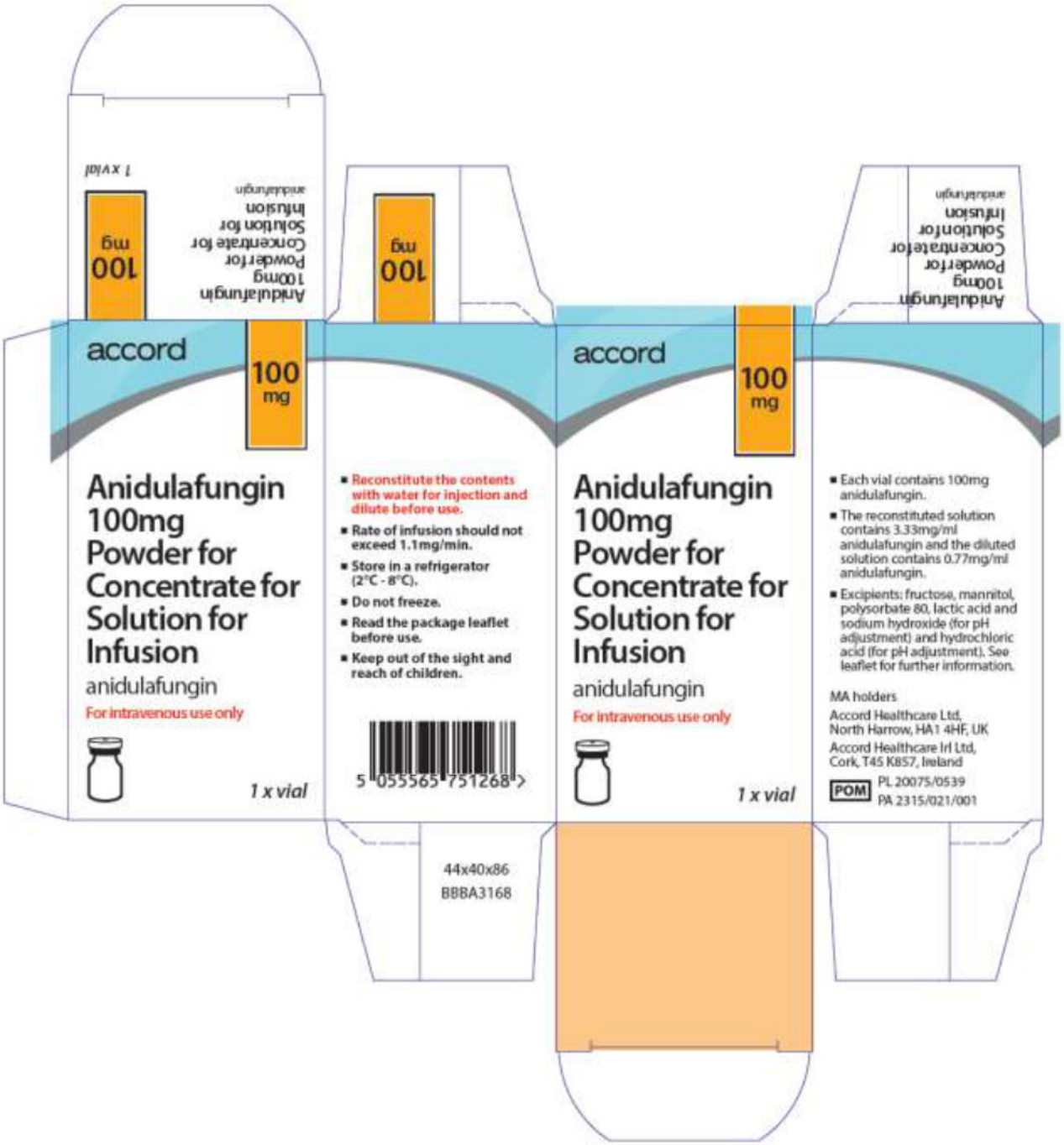

accord
100 mg
Anidulafungin 100mg Powder for Concentrate for Solution for Infusion
anidulafungin
For intravenous use only
1 x vial
• Reconstitute the contents with water for injection and dilute before use.
• Rate of infusion should not exceed 1.1mg/min.
• Store in a refrigerator (2°C - 8°C).
• Do not freeze.
• Read the package leaflet before use.
• Keep out of the sight and reach of children.
5 055565 751268
44x40x86
BBBA3168
• Each vial contains 100mg anidulafungin.
• The reconstituted solution contains 3.33mg/ml anidulafungin and the diluted solution contains 0.77mg/ml anidulafungin.
• Excipients: fructose, mannitol, polysorbate 80, lactic acid and sodium hydroxide (for pH adjustment) and hydrochloric acid (for pH adjustment). See leaflet for further information.
MA holders
Accord Healthcare Ltd, North Harrow, HA1 4HF, UK
Accord Healthcare Irl Ltd, Cork, T45 K857, Ireland
POM
PL 20075/0539
PA 2315/021/001

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)