COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ertapenem Villerton, 1 g powder for concentrate for solution for infusion

(ertapenem sodium)

NL/H/4383/001/DC

Date: 17 October 2019

This module reflects the scientific discussion for the approval of Ertapenem Villerton, 1 g powder for concentrate for solution for infusion. The procedure was finalised on 14 May 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ertapenem Villerton, 1 g powder for concentrate for solution for infusion from Villerton Invest S.A.

Ertapenem Villerton is indicated in paediatric patients (3 months to 17 years of age) and in adults for the treatment of the following infections when caused by bacteria known or very likely to be susceptible to ertapenem and when parenteral therapy is required:

- Intra-abdominal infections
- Community acquired pneumonia
- Acute gynaecological infections
- Diabetic foot infections of the skin and soft tissue

In addition, Ertapenem Villerton is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Invanz 1 g, powder for concentrate for solution for infusion which has been registered in the EEA by Merck Sharp & Dohme Ltd. since 18 April 2002 through a centralised procedure (EMEA/H/C/389).

The concerned member states (CMS) involved in this procedure were France, Italy, Romania and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Ertapenem Villerton is a white to yellowish powder for concentrate for solution for infusion. Each vial contains 1 g ertapenem (as ertapenem sodium).

The powder for concentrate for solution for infusion is packed in colourless, clear, Type I glass vials with a chlorobutyl stopper and aluminium flip-off overseal.

The excipients are sodium hydrogen carbonate (E500) and sodium hydroxide (E524) to adjust pH to 7.5.

II.2 Drug Substance

The active substance is ertapenem sodium, an established active substance, however not described in any Pharmacopoeia. The active substance is a white to off-white hygroscopic powder. It is soluble in water and 0.9% sodium chloride solution, practically insoluble in ethanol and insoluble in isopropyl acetate and tetrahydrofuran. Ertapenem sodium is produced as amorphous powder and the stability of the amorphous state is demonstrated by the ASMF holder. The drug substance contains six stereo genic centers and their control is adequately ensured.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The active substance is manufactured in a convergent 11 step process. This process is adequately characterised. The proposed starting materials are acceptable and acceptable specifications have been proposed for the starting materials, solvents and reagents.

Quality control of drug substance

The drug substance specification is considered adequate to control the quality and is acceptable in view of the route of synthesis and the various European guidelines. The specification has been established in-house by the MAH. Batch analytical data demonstrating compliance with this specification have been provided for 6 full-scale batches, 3 by each of the two manufacturers.

Stability of drug substance

Stability data on the active substance have been provided for 6 full-scale batches from one manufacturer and 3 full-scale batches from the other manufacturer stored at -20°C (up to 24 months) and 3 full-scale batches from each supplier stored 5°C (72 hours) in accordance with applicable European guidelines. The proposed retest period of 12 months is justified, as well as the storage condition: "Store in a freezer (-20°C ± 5°C)".

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies consist of determination of the overage, a similarity analysis with the reference product and development of the ranges for temperature, pH and concentration of the lyophilisation

solution. Since Ertapenem Villerton is a powder for concentrate for solution for infusion and administered by intravenous route, a bioequivalence study was not required.

Manufacturing process

The drug product is manufactured in 5 stages; preparation of a bulk solution by mixing and dissolution of all ingredients, followed by aseptic filtration and filling of trays, lyophilisation, milling and packaging of the intermediate, which is unpacked at another site and filled in vials to be closed and labelled. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for 4 full-scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the corresponding Ph.Eur. monographs. These specifications are acceptable.

Microbiological attributes

Appropriate in-process controls serve to maintain the aseptic working conditions required to produce a sterile drug product The sterility and bacterial endotoxins of the product are tested at release and selected stability time points in compliance with the Ph. Eur. In addition, a microbial ingress test including a positive control was performed on the drug product container closure system; however, no ingress was detected on the test samples. The container closure system integrity for both the drug product intermediate and the drug product is adequately demonstrated. The microbiological attributes are adequately discussed.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, sodium content, constituted solution (completeness, clarity, color and visible particles), reconstitution time, water, pH, uniformity of dosage units, assay, related substances, particulate matter, visible particles, integrity, bacterial endotoxins and sterility. The proposed release and shelf-life acceptance limits are almost identical, except for assay, one related substance and total impurities. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 4 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for 4 validation batches stored at 25°C/60%RH (24 months) and 30°C/75% RH (12 months). The batches were stored in the proposed packaging.

The photostability study showed that the product is not sensitive to light. The proposed shelf-life of 24 months and storage condition of ‘stored below 25°C in the original package to protect from moisture’ can be granted.

Stability data has been provided claiming that the final diluted product remains stable for 6 hours in-use following reconstitution and dilution when stored at room temperature (25°C) or for 24 hours at 2-8°C and used within 4 hours of their removal from the refrigerator.

These in-use stability claims can be granted. Adequate compatibility studies with intravenous solutions containing heparin sodium and potassium chloride have been performed with the proposed product.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ertapenem Villerton has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ertapenem Villerton is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Invanz which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ertapenem is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Ertapenem Villerton, 1 g powder for concentrate for solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of the product is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

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 Ertapenem Villerton.

- Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	- Drug resistance
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Invanz. No new clinical studies were conducted. The MAH demonstrated that the quantitative composition of the product is similar to the quantitative composition of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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 test consisted of: a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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

Ertapenem Villerton, 1 g powder for concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Invanz 1 g, powder for concentrate for solution for infusion. Invanz is a well-known medicinal product with an established favourable efficacy and safety profile

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ertapenem Villerton with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 May 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse