COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pitaz 2 g/0.25 g powder for solution for infusion (piperacillin/tazobactam)

NL/H/5451/001/DC

Date: 22 January 2026

This module reflects the scientific discussion for the approval of Pitaz 2 g/0.25 g powder for solution for infusion. The procedure was finalised on 21 February 2024. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Pitaz 2 g/0.25 g powder for solution for infusion, from Medochemie Ltd.

The product is indicated for the treatment of the following infections in adults and children over 2 years of age:

Adults and adolescents

- Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Complicated skin and soft tissue infections (including diabetic foot infections)

Children 2 to 12 years of age

- Complicated intra-abdominal infections

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and a European Reference Product (ERP), Tazocin EF, 2/0.25 g/g powder for solution for infusion, which has been registered by Pfizer via a decentralised procedure (UK/H/4984/001; current procedure number IT/H/0675/001).

The concerned member states (CMS) involved in this procedure were Bulgaria, Croatia, Cyprus, Czechia, Estonia, Greece, Latvia, Lithuania, Malta, Portugal, Romania, Slovakia and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Pitaz is a powder for solution for infusion. The product is a white or almost white loose lump or powder.

For the solution reconstituted with 10 ml of water for injection, the pH is 5.0-7.0 and the osmolality is 600-700 mOsm/kg.

Each vial contains as active substance piperacillin (as sodium salt) equivalent to 2 g and tazobactam (as sodium salt) equivalent to 0.25 g.

The excipients are: sodium bicarbonate and water for injection.

The powder for solution for infusion is packed in 30 ml clear glass vials type I, sealed with a 20 mm bromobutyl rubber stopper and an aluminium cap or grey flip off cap suitable for parenteral preparation. The vials are packed in cartons.

II.2 Drug Substance

Piperacillin monohydrate

The active substance is piperacillin monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Piperacillin monohydrate is white or almost white powder. The active substance is slightly soluble in water and ethyl acetate and freely soluble in methanol. No polymorphism is observed.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

The active substance is manufactured at two different sites. A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches per active substance manufacturer.

Stability of drug substance

Stability data on the active substance have been provided for three batches per active substance manufacturer in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months (site I) and 12 months (site II). Based on the data submitted, a retest period could be granted of 12 months when stored under the stated conditions.

Tazobactam

The active substance is tazobactam, an established active substance described in the United States Pharmacopoeia (USP). Tazobactam is a drug substance with a white or off-white powder or crystalline appearance. The active substance is soluble in N,N-dimethylformamide and slightly soluble in water. No polymorphism is observed.

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 at two different sites. The manufacturing process consists of ten steps, starting from two starting materials. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the USP. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches per active substance manufacturer in accordance with applicable European guidelines. Based on the data submitted, a retest period of 24 months could be granted when stored under the stated conditions (site I). For the other site, a shelf life of 24 months could be granted when stored under the stated conditions.

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 development focused mainly on obtaining a stable drug product equivalent to the reference product. The following aspects have been taken into consideration: quality of the active substances, microbiological properties and sterility of the drug product. The choice of excipients has been justified and their functions explained. The choices of the manufacturing process, sterilisation by filtration and packaging are sufficiently justified. The stability of the drug product reconstituted in water, and its compatibility with several diluents has been adequately investigated.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process is a non-standard process, involving the preparation of the lyophilised sterile mixture of piperacillin sodium and tazobactam sodium (sterilised by filtration). Subsequently, the bulk sterile powder is filled into sterilised vials under aseptic conditions. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

Sodium bicarbonate and water for injection are used as excipients. Specifications, description of the analytical procedures and validation data have been submitted for both excipients. Identification is performed. The specification tests are performed according to the either Ph. Eur., USP or Chinese pharmacopoeia. Where needed, equivalency with the Ph. Eur. methods has been demonstrated. These specifications are acceptable.

Microbiological attributes

The integrity of the container closure system of the product as it relates to preventing microbial contamination has been adequately discussed. Results for sterility, microbial endotoxins and microbial challenge tests have been performed, which are satisfactory.

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, identification, water content, pH, uniformity of dosage units, colour and clarity of solution, reconstitution time, particulate matter, assay, related substances, sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from five batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from two batches with the lowest claimed batch size stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Additional data have been provided for three batches with a larger batch size stored at 25°C/60% RH (18 months) and accelerated conditions (6 months). Photostability studies have been conducted on one batch stored either in the primary packaging material, or in both primary and packaging materials. The drug product was not directly exposed to light, which is considered acceptable since this is a sterile formulation. No significant changes are observed for the investigated conditions and the product is considered photostable in solid form. Photostability of the solution has been adequately discussed and it is granted. On basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions needed to be included in the SmPC or on the label.

In-use stability data have been provided demonstrating that the product remains stable for 24 hours following reconstitution/dilution, when stored at 2-8 °C.

Specific measures concerning 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 Pitaz 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 Pitaz is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Tazocin EF which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Piperacillin and tazobactam are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Pitaz 2 g/0.25 g powder 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 Pitaz 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 Pitaz. At the time of approval, the most recent version of the RMP was version 0.1 dated 9 June 2022.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
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 Tazocin EF. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Tazocin EF, IT/H/0675/001 (for product information). For design and layout, reference was made to Suknam (Meropenem) 500 mg and 1000 mg, powder for solution for injection/infusion, PT/H/1854/001-002/DC. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pitaz 2 g/0.25 g powder for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Tazocin EF, 2/0.25 g/g powder for solution for infusion. Tazocin EF 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 Pitaz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 February 2024.

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
NL/H/5451/001/IB/001	Change in the (invented) name of the medicinal product - for Nationally Authorised products	Yes	17-9-2024	Approved	N.A.
NL/H/5451/IB/002/G	Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier. - Re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data.	No	3-10-2024	Approved	N.A.
	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the	No	3-10-2024	Approved	N.A.

	manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer.				
NL/H/5451/001/IA/003	Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)) - Change that affects the product information.	Yes	17-10-2024	Approved	N.A.
NL/H/5451/IB/004/G	Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	No	24-1-2025	Approved	N.A.
	Change in the manufacturing process of the finished product , including an	No	24-1-2025	Approved	N.A.

	intermediate used in the manufacture of the finished product - Minor change in the manufacturing process.				
	Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size.	No	24-1-2025	Approved	N.A.
	Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place.	No	24-1-2025	Approved	N.A.
	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product - Secondary packaging site.	No	24-1-2025	Approved	N.A.
	Replacement or addition of a manufacturing site for part or all of the manufacturing	No	24-1-2025	Approved	N.A.

	process of the finished product - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) manufactured using an aseptic method excluding biological/ immunological medicinal products.				
NL/H/5451/001/IA/005	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from	No	6-3-2025	Approved	N.A.

	an already approved manufacturer				