IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Piperacillin/Tazobactam 2g/0.25g powder for solution for infusion
Piperacillin sodium
Tazobactam sodium
PA1122/012/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Piperacillin/Tazobactam 2g/0.25g powder for solution for infusion, from Noridem Enterprises Limited.

This medicinal product was initially authorised on 20th March 2011 under procedure number UK/H/1209/001-002/DC with the UK as Reference Member State (RMS) and IE, AT, DE, PL and SE as Concerned Member States (CMS). This application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC, as amended, and concerns a generic version of Piperacillin/Tazobactam powder for solution for infusion. The reference medicinal product for these applications is Tazocin 2/0.25g & 4/0.5g Powder for solution for injection/infusion first authorised in the EU on 28th July 1993.

The responsibility of RMS was transferred to Ireland on 22nd October 2018 under procedure number IE/H/0708/001-002.

In this Repeat Use Procedure (IE/H/0708/001-002/E/001), authorisation is extended to CMSs BE, CZ, DK, ES, FI, FR, HU, IT, NO, PT, RO, SK on 26th May 2025.

Piperacillin/Tazobactam 2g/0.25g powder for solution for infusion & Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion, from Noridem Enterprises Limited, are indicated as follows:

Piperacillin/Tazobactam is indicated for the treatment of the following infections in adults and children over 2 years of age (see sections 4.2 and 5.1):

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)

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Piperacillin/Tazobactam may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.

Note: Use for bacteraemia due to extended-beta-lactamase (ESBL) producing E. coli and K. pneumoniae (ceftriaxone non-susceptible), is not recommended in adult patients, see section 5.1.

Children 2 to 12 years of age

- Complicated intra-abdominal infections

Piperacillin/Tazobactam may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

This product is prescription only.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Piperacillin/Tazobactam 2g/0.25g powder for solution for infusion
Name(s) of the active substance(s) (INN)	piperacillin/tazobactam
Pharmacotherapeutic classification (ATC code)	J01C R05: Antibacterials for systemic use, Combinations of penicillins incl. beta lactamase inhibitors
Pharmaceutical form and strength(s)	Powder for solution for infusion 2g/0.25g
Marketing Authorisation Number(s) in Ireland (PA)	PA1122/012/001
Marketing Authorisation Holder	Noridem Enterprises Limited
MRP/DCP No.	IE/H/0708/001/E/001
Reference Member State	IE
Concerned Member State	BE, CZ, DK, ES, FI, FR, HU, IT, NO, PT, RO, SK

II. QUALITY ASPECTS

II.1. Introduction

This application is for Piperacillin/Tazobactam 2g/0.25g powder for solution for infusion & Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion

II.2 Drug substance

The active substances are Piperacillin and Tazobactam, established active substances described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substances specifications are considered adequate to control the quality and meet current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each vial contains 2.085 g of piperacillin sodium, equivalent to 2 g of piperacillin and 0.268g tazobactam sodium equivalent to 0.25 g of tazobactam.
Each vial contains 4.17 g of piperacillin sodium, equivalent to 4 g of piperacillin and 0.536 g tazobactam sodium equivalent to 0.5 g of tazobactam.

The products do not contain any excipients.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

The products do not contain any excipients.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for parenteral preparations, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with relevant Ph. Eur. requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Piperacillin/Tazobactam 2g/0.25g powder for solution for infusion & Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Tazocin 2/0.25g & 4/0.5g Powder for solution for injection/infusion first authorised in the EU on 28th July 1993 No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology

No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/environmental risk assessment

A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this generic product onto the market is unlikely to result in an increase in the combined sales of all piperacillin and tazobactam-containing products, which, in turn, is unlikely to increase exposure of the environment to these drug substances.

III.6 Discussion on the non-clinical aspects

The grant of marketing authorisations of Piperacillin/Tazobactam 2g/0.25g powder for solution for infusion & Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion is recommended.

IV. CLINICAL ASPECTS

IV.1 Introduction

Piperacillin and Tazobactam are well known active substances with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Tazocin 2/0.25g & 4/0.5g Powder for solution for injection/infusion.

Piperacillin/Tazobactam 2/0.25g and Piperacillin/Tazobactam 4/0.5g, powder for solution for injection or infusion are parenteral formulations and therefore fulfil 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Piperacillin/Tazobactam 2g/0.25g and Piperacillin/Tazobactam 4g/0.5g is entirely the same as the originator. Therefore, these may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product.

IV.2 Pharmacokinetics

Absorption

The peak piperacillin and tazobactam concentrations after 4 g / 0.5 g administered over 30 minutes by intravenous infusion are 298 µg/mL and 34 µg/mL respectively.

Distribution

Both piperacillin and tazobactam are approximately 30% bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible.

Piperacillin / tazobactam is widely distributed in tissues and body fluids including intestinal mucosa, gallbladder, lung, bile and bone.Mean tissue concentrations are generally 50 to 100% of those in plasma. Distribution into cerebrospinal fluid is low in subjects with non-inflamed meninges, as with other penicillins.

Biotrasformation
Piperacillin is metabolised to a minor microbiologically active desethyl metabolite. Tazobactam is metabolised to a single metabolite that has been found to be microbiologically inactive.

Elimination

Piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins incl. beta-lactamase inhibitors; ATC code: J01C R05.

Piperacillin, a broad-spectrum, semisynthetic penicillin exerts bactericidal activity by inhibition of both septum and cell-wall synthesis.

Tazobactam, a beta-lactam structurally related to penicillins, is an inhibitor of many beta-lactamases, which commonly cause resistance to penicillins and cephalosporins, but it does not inhibit AmpC enzymes or metallo beta-lactamases. Tazobactam extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.

IV.4 Clinical Efficacy

The efficacy of Piperacillin/Tazobactam in the proposed indications is established in clinical use. No new clinical efficacy studies are provided, and none are required.

IV.5 Clinical Safety

The overall safety profile of Piperacillin/Tazobactam is established and generally known. No new safety studies are provided, and none are required.

The schedule for Periodic Safety Update Reports (PSUR) submission is every 5 years.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required. No bioequivalence studies were required as the product is for intravenous use.

V. OVERALL CONCLUSIONS

Piperacillin/Tazobactam 2g/0.25g powder for solution for infusion & Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion, from Noridem Enterprises Limited is a generic form of Tazocin 2/0.25g & 4/0.5g Powder for solution for injection/infusion first authorised in the EU on 28th July 1993, a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

No bioequivalence studies were submitted as bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Piperacillin/Tazobactam 2g/0.25g powder for solution for infusion & Piperacillin/Tazobactam 4 g/0.5 g powder for solution for infusion, is similar to the reference product and has a satisfactory risk/benefit profile and therefore granted a marketing authorisation.