

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Piperacilline/Tazobactam 4 g/500 mg, powder for solution for
injection or infusion
Sandoz B.V., the Netherlands**

piperacillin (as sodium) / tazobactam (as sodium)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/ 0858/01/DC
Registration number in the Netherlands: RVG 34088**

26 May 2010

Pharmacotherapeutic group:	combinations of penicillins, incl. beta-lactamase inhibitors
ATC code:	J01CR05
Route of administration:	intravenous
Therapeutic indication:	moderate to severe systemic and/or local bacterial infections with betalactamase producing bacteria
Prescription status:	prescription only
Date of authorisation in NL:	28 July 2009
Concerned Member States:	Decentralised procedure with AT, DE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Piperacilline/Tazobactam 4 g/500 mg, powder for solution for injection or infusion from Sandoz B.V. The date of authorisation was on 28 July 2009 in the Netherlands.

The product is indicated for the treatment of the moderate to severe systemic and/or local bacterial infections in which betalactamase producing bacteria are suspected or have been detected, such as:

Adults/Adolescents and the Elderly

- Nosocomial pneumonia;
- Complicated urinary tract infections (including pyelonephritis);
- Intra-abdominal infections;
- Skin and soft tissue infections;
- Bacterial infections in neutropenic patients.

Children (2 to 12 years)

Bacterial infections in neutropenic children.

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

Piperacillin, a broad spectrum, semisynthetic penicillin active against many Gram-positive and Gram-negative aerobic and anaerobic bacteria, exerts bactericidal activity by inhibition of both septum and cell wall synthesis. Tazobactam, a triazolymethyl penicillanic acid sulphone, is a potent inhibitor of many beta-lactamases, in particular the plasmid mediated enzymes which commonly cause resistance to penicillins and cephalosporins including third-generation cephalosporins. The presence of tazobactam in the piperacillin/tazobactam formulation enhances and extends the antibiotic spectrum of piperacillin to include many beta-lactamase producing bacteria normally resistant to it and other beta-lactam antibiotics. Thus, piperacillin/tazobactam combines the properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product 4 g/500 mg, powder for solution for infusion (NL license RVG 15328) which has been registered in the Netherlands by Wyeth Pharmaceuticals B.V. since 1993. In addition, reference is made to Tazocin authorisations in the individual member states (reference product). The reference product is marketed in the EU under different names: Tazocin®, Tazocilline®, Tazocel®, Tazonam® and Tazobac®. The composition and the pharmaceutical form of Piperacillin/Tazobactam t 4 g/500 mg is identical to the reference product.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Piperacilline/Tazobactam 4 g/500 mg, powder for solution for injection or infusion is a product for aqueous parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No scientific advice has been given to the MAH with respect to this product. No paediatric development plan has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substances

The active substances are piperacillin and tazobactam, both of which are established active substance. Piperacillin is described in the European Pharmacopoeia (Ph.Eur.*). Tazobactam is not, but a draft USP* monograph has been published. The USP also has a draft monograph on a sterile 8:1 mixture of the two substances and on an injection of the same composition. Piperacillin is a white or almost white powder which is slightly soluble in water. Tazobactam is a white or almost white crystalline powder which is very slightly soluble in water.

The Active Substance Master File (ASMF) procedure is used for both active substances. 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.

Manufacture

The sterile mixture is prepared from the two active ingredients. Both substances have been adequately characterized. In general sufficient information has been provided on the synthesis. Also, for the starting material and solvents acceptable specifications have been adopted.

Specification

The two active substances are adequately characterised. The processes are not expected to change them. The specifications in the draft USP monograph for the mixture have been incorporated into the MAH's specification. Batch analytical data demonstrating compliance with the specifications have been provided for 3 industrial-scale batches.

Stability

Stability data have been obtained for 3 full-scale batches during storage at 25°C/60%RH and 40°C/75%RH. Test conditions were in compliance with ICH Guidelines. Based on the results, a re-test period of 1 year could be granted. The applicable storage conditions are '*Do not store above 25°C*'. The MAH committed to continue the long-term studies until 60 months have been covered or until batches start to fail. Every year another commercial batch will be put on stability studies.

* *Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA, respectively.*

Medicinal Product

Composition

Piperacilline/Tazobactam 4 g/500 mg contains as active substance 4 g of piperacillin (as sodium salt) and 0.5 g of tazobactam (as sodium salt) per vial, and is a white to off-white powder. The powder for solution for injection or infusion is packed in a type II glass vial, with halogenated butyl rubber stopper and aluminium overseal with red flip-off cap.

No excipients are used.

Pharmaceutical development

Piperacillin and tazobactam do not present polymorphism. Deduced from investigations with the originator products an overfill of 2% is applied. The actual overfill (seen from a patients point of view) is the sum of the portion of the drug remaining in the vial, in the needle, in the syringe, in the bag and in the tubes when the drug has been administered. The product contains enough drug substance in the pharmaceutical dosage form to cover all these losses. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

Manufacturing process

The manufacturing process has been adequately described. Aseptic precautions are used at all stages until the vials have been sealed. Since the piperacillin-tazobactam mixture is a thermo-labile substance, terminal sterilization cannot be applied. Process validation data on the product have been presented for 3 batches in accordance with the relevant European guidelines.

Microbiological attributes

Sterility is guaranteed by the aseptic working procedure and the sterile materials used.

Quality control of drug product

The product specifications cover appropriate parameters for this dosage form. The specification includes tests for appearance, identification, water content, clarity, pH, assay, uniformity of dosage units, related substances, sterility, endotoxins and visible particles. The analytical methods are valid.

Batch analysis has been performed on three full-scale batches. The batch analysis results show that the finished product meets the proposed specifications.

Compatibility

The product has been shown to be compatible with the following solutions:

- 0.9 % sodium Chloride for Injection
- Water for Injection
- Dextrose 5%
- Dextrose 5% + 0.9% NaCl solution
- Bacteriostatic Saline/ Parabens
- Bacteriostatic water/ Parabens
- Bacteriostatic Saline/ Benzyl alcohol
- Bacteriostatic Water/ Benzyl alcohol
- Dextran in 6% saline
- Lidocain 0.5% in water for injection.

Stability tests on the finished product

Stability data on the product is provided from three full-scale scale batches, tested in compliance with applicable EU guidelines. Two years are covered. Base on the presented data a shelf-life of three years without specific storage conditions can be granted. However, the MAH has proposed to maintain the claimed shelf-life of two years, in order to comply with the NfG on start of shelf-life. The justified holding time of the (8:1) bulk mixture is one year, giving an overall shelf-life of 3 years.

The MAH committed to include the first 3 production batches in the stability studies. Two more commitments have been made regarding stability testing. These are stated on page 6 of this report.

In-use stability

Sample vials were reconstituted in various ways:

- with 10 ml of normal saline,
- with water for injections,
- with equal parts of 5% dextrose and normal saline,
- with equal parts of 6% dextrose and normal saline.
- with lidocain 0.5% in water for injections

Reconstituted samples were stored in a refrigerator for 2 days, other samples were stored at 20-25°C for one day. The data provided justify an in-use period 24 hours at 20-25°C and of 2 days, stored in a

refrigerator, with the standard caveat that from a microbiological safety point of view only 24 hours are recommended unless the dilution is done under validated aseptic working conditions.

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.2 Non clinical aspects

These products are generic formulations of Tazocin 2 g/250 mg and 4 g/500 mg, powder for solution for infusion, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of these products will not result in an increase in the total quantity of piperacilline or tazobactam released into the environment. These do not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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

Piperacilline/Tazobactam 4 g/500 mg, powder for solution for injection or 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Piperacilline/Tazobactam 4 g/500 mg 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.

Risk management plan

The combination of piperacillin and tazobactam has been authorised since 1992, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of piperacillin/tazobactam can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Compared to the originally approved formulation, the current formulation of the reference product contains a chelating agent with claimed improvement of compatability. For this reason the MAH committed to submit studies on compatability. The product will not be marketed before agreement is reached on the compatibility data and, if deemed necessary by the member states, approval of an RMP.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with the SPC established during procedure UK/H/0908/001-002/DC, for another generic piperacillin/tazobactam product.

Readability test

A readability test was performed for the PIL as submitted for procedure UK/H/0908/001-002/DC, with which the PIL for the current procedure has been harmonised. This package leaflet was approved. Hence, no reassessment of the readability test was performed, as the member states agreed that the current PIL is in line with the above mentioned PIL.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Piperacilline/Tazobactam 4 g/500 mg, powder for solution for injection or infusion has a proven chemical-pharmaceutical quality and is a generic form of Tazocin 4 g/500 mg, powder for solution for infusion. Tazocin 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.

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

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other piperacillin/tazobactam containing products.

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 Piperacilline/Tazobactam 4 g/500 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 August 2008. Piperacilline/Tazobactam 4 g/500 mg were authorised in the Netherlands on 28 July 2009.

A European harmonised birth date has been allocated (2 July 1992) and subsequently the first data lock point for piperacillin/tazobactam is 30 September 2009. The first PSUR will cover the period from August 2008 to September 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 22 June 2013.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to perform respective in-use stability studies also at the end of shelf-life of the finished drug product.
- The MAH committed to include the first 3 production batches in the stability studies.
- The MAH committed to perform a stability study with one batch, manufactured with sterile mixture at the end of the intermediate shelf-life.

Pharmacovigilance

- The MAH committed to submit studies on compatability. The product will not be marketed before agreement is reached on the compatibility data and, if deemed necessary by the member states, approval of an RMP.
- The MAH committed to perform a PK/PD Monte Carlo Simulation on data for children <12yrs of age to support the indication for abdominal infections in children with an adequate posology and to update the product information accordingly by means of a proper variation procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Submission of Risk Management Plan.	NL/H/0858/001 /II/001	II	13-10-2008	18-6-2009	Approval	N
Addition of pack size of 10 vials.	NL/H/0858/001 /IA/002	IA	2-12-2008	16-12-2008	Approval	N
Increase the batch size of piperacillin active ingredient.	NL/H/0858/001 /II/003	II	9-9-2009	26-2-2010	Approval	N
Change in the batch size of active substance or intermediate; up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation.	NL/H/0858/001 /IA/004	IA	4-8-2009	18-8-2009	Approval	N
Change in the name and/or address of the marketing authorisation holder.	NL/H/0858/001 /IA/008	IB	3-4-2010	3-5-2010	Approval	N