CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Piperacillin/Tazobactam 2 g/250 mg PCH, powder for solution for injection or infusion
Piperacillin/Tazobactam 4 g/500 mg PCH, powder for solution for injection or infusion
Pharmachemie 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/0829/001-002/DC
Registration number in the Netherlands: RVG 34034, 34045

15 December 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:	8 December 2010
Concerned Member States:	Decentralise procedure with AT, BE, CZ, DE, DK, EE, FI, FR, HU, IE, LT, LU, LV, NO, PL, SE, Sl, SK, UK (withdrawn on 23 March 2010)
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) and 10(3)

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 Piperacillin/Tazobactam 2 g/250 mg PCH and Piperacillin/Tazobactam 4 g/500 mg PCH, powder for solution for injection or infusion, from Pharmachemie B.V. The date of authorisation was on 8 December 2010 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, children >12 years of age 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 triazolylmethyl 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 products Tazocin 2 g/250 mg and 4 g/500 mg, powder for solution for infusion (NL license RVG 15326, 15328 respectively) which have been registered in the Netherlands by Wyeth Pharmaceuticals B.V. since 30 March 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®. For DE, LT an LV is referred to a European reference product, i.e. the Dutch innovator product Tazocin. The composition and the pharmaceutical form of Piperacillin/Tazobactam PCH are identical to the reference product.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. In several member states, the application for one of the strengths is made according to article 10(3), hybrid application, as only one of the strengths of the innovator product has been authorised.

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 Piperacillin/Tazobactam 2 g/250 mg PCH and Piperacillin/Tazobactam 4 g/500 mg PCH, powder for solution for injection or infusion are products for aqueous parenteral use, these are exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme 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 substance
The active substances are piperacillin and tazobactam, both of which are established active substances. The product contains the sodium salts of these substances. Piperacillin is described in the European Pharmacopoeia (Ph.Eur.*). Tazobactam is not, but a draft USP* monograph has been published. Piperacillin is a white or almost white powder which is slightly soluble in water. Tazobactam is a white to off-white crystalline powder which is moderately 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.

Manufacturing process
The sterile mixture in ratio 8:1 is prepared from the two active ingredients. The active substances have been adequately characterized and acceptable specifications have been adopted for the starting materials, solvents and reagents. The neutral solution is sterile filtered. Aseptic conditions are maintained. It is then lyophilised, granulated, sieved, homogenised, and packaged in the (pre-sterilised) packaging. The process is a standard process, and has been adequately validated. The integrity of the container closure system to prevent microbial contamination has been demonstrated to be adequate.

Quality control of drug substances
The specification for piperacillin is in line with the Ph. Eur. with additional requirements for residual solvents and microbiological purity. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three consecutive production batches.
The drug substance specification for tazobactam is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the specification have been provided for three consecutive production batches.
Adequate tests and limits are included for the blend, in conformity with the specification for the finished drug product.

Stability of drug substance
Stability data of several production batches on the active substances have been provided. Sufficient data of stability indicating parameters have been provided. Batches were stored at ICH conditions.
The stability of the blend, in the proposed container has been demonstrated with several batches, according to the requirements in the EU/ICH guidelines. Based on the data provided, retest period of 24 months could be granted.

** 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
Piperacillin/Tazobactam 2 g/250 mg PCH contains as active substance 2 g of piperacillin (as sodium salt) and 250 mg of tazobactam (as sodium salt) per vial, and is a white or off-white lyophilised powder for solution for injection or infusion.

Piperacillin/Tazobactam 4 g/500 mg PCH contains as active substance 4 g of piperacillin (as sodium salt) and 500 mg of tazobactam (as sodium salt) per vial, and is a white or off-white lyophilised powder for solution for injection or infusion.

The powder for solution for injection or infusion is packed in glass vials (type II) closed with a bromobutyl rubber stopper and an aluminium/polypropylene (red) flip-off cap.

The 2 g/250 mg product is packed in 20 ml vials, and the 4 g/500 mg product in 50 ml vials.

No excipients are used.

Pharmaceutical development
The development of the product was adequately performed. The MAH analysed the innovator product (two batches) and established that it has the same impurity profile as the generic product. The packaging materials are suitable and uncomplicated. No overage is applied, which is acceptable.
The product is an established pharmaceutical form and its development was adequately described in accordance with the relevant European guidelines.

Manufacturing process
The manufacturing process considered standard. The sterile intermediate product is aseptically filled into the vials. The manufacturing process has been adequately validated according to relevant European guidelines. The MAH committed to provide additional data on the validation as a further support, when these are available.

Microbiological attributes
The products are sterile, and adequate limits for bacterial endotoxins are set. The container closure system is suitable to prevent microbial contamination.

Quality control of drug product
The product specification includes tests for appearance, appearance of solution, identity, assay, degradation, particulate matter, sterility, endotoxins, dissolution time, water, average mass, and uniformity of dosage units. The product specifications cover appropriate parameters for this dosage form. The analytical methods are valid. Batch analysis results of several batches show that the finished product meets the proposed specifications.
The MAH made several commitments regarding quality control of the drug product, which can be found on page 7 of this report.

Stability of drug product
Stability data on the product have been provided from pilot-scale batches and commercial batches, stored in the proposed containers, tested in compliance with applicable EU/ICH guidelines. Thirty-six months are covered for most parameters tested, at 24 months all parameters have been tested. Based on the presented data, a shelf-life of 24 months without specific storage conditions was granted.

Compatibility/In-use stability

Compatibility of the product with injection and infusion solutions has been established: after reconstitution with water, sodium chloride (0.9%), Dextrose (5%) and Dextrane 6% in physiologic serum, stable solutions has been obtained.
In-use shelf lives have been established at 8 hours at temperatures below 25°C and 48 hours when refrigerated. The MAH committed to submit results from in-use stability tests with the commercial batches at their end of shelf-life when available.

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.

Piperacillin/Tazobactam 2 g/250 mg PCH and Piperacillin/Tazobactam 4 g/500 mg PCH, 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 2 g/250 mg PCH and Piperacillin/Tazobactam 4 g/500 mg PCH 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. The current products can be used instead of their reference products.

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 post authorisation which are not adequately covered by the current SPC. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.
The MAH has submitted a Risk Management Plan, addressing the implications for safe use of the proposed generic product and discussing the process to detect any potential risks arising as a result of the different product compatibilities between the MAH’s product and the innovator product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with the SPC established during procedure NL/H/0963/001-002/DC, for another generic piperacillin/tazobactam product.

The MAH committed to update the product information with the harmonized text of the innovator product Tazozin, when the article 30 referral is finalised.

Readability test

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 with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Each question separately scored above 81 % and therefore no revisions were made. Overall, the readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Piperacillin/Tazobactam 2 g/250 mg PCH and Piperacillin/Tazobactam 4 g/500 mg PCH, powder for solution for injection or infusion have a proven chemical-pharmaceutical quality and are generic forms of Tazocin 2 g/250 mg and 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 Piperacillin/Tazobactam 2 g/250 mg PCH and Piperacillin/Tazobactam 4 g/500 mg PCH with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 8 March 2010. Piperacillin/Tazobactam 2 g/250 mg PCH and Piperacillin/Tazobactam 4 g/500 mg PCH, powder for solution for injection or infusion were authorised in the Netherlands on 8 December 2010.

A European harmonised birth date has been allocated (2 July 1992) and subsequently the first data lock point for piperacillin/tazobactam is 30 September 2012. The first PSUR will cover the period from March 2010 to September 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 May 2013.

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

<u>Quality - medicinal product</u>

- The MAH committed to submit an updated finished product specification and analytical method within a month after approval of the procedure.
- The MAH committed to submit results of test for uniformity of dosage units when available.
- The MAH committed to tighten the limit for residual dichloromethane in piperacillin and tazobactam (8:1) sterile blend.
- The MAH committed to submit results from in-use stability tests with the commercial batches at their end of shelf-life when available.

<u>Product information</u>

- The MAH committed to update the product information with the harmonized text of the innovator product Tazocin, when the article 30 referral is finalized.

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
$t_{½}$	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
Withdrawal in the UK.	--	Withdrawal	--	23-3-2010	Approval	Y