CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Piperacilline/Tazobactam Mylan 2 g/250 mg, powder for solution for injection or infusion
Piperacilline/Tazobactam Mylan 4 g/500 mg, powder for solution for injection or infusion
Mylan B.V., the Netherlands

piperacilline (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/1480/001-002/MR
Registration number in the Netherlands: RVG 35003-35004

1 July 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 first authorisation in NL:	28 February 2008
Concerned Member States:	Mutual recognition procedure with AT, BE, BG, CY, CZ, EL, ES, HU, IE, MT, PL, PT, RO, SI, SK, UK
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 Piperacilline/Tazobactam Mylan 2 g/250 mg and Piperacilline/Tazobactam Mylan 4 g/500 mg, powder for solution for injection or infusion from Mylan B.V. The date of authorisation was on 28 February 2008 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 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 mutual recognition 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 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 Piperacilline/Tazobactam Mylan are identical to the reference product.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. In member states where one of the strengths is not registered, the application is made according to article 10(3) of Directive 2001/83/EC: hybrid application.

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 Mylan 2 g/250 mg and Piperacilline/Tazobactam Mylan 4 g/500 mg, 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.

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 substance. 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 or almost white crystalline powder which is moderately soluble in water.

The Active Substance Master File (ASMF) procedure is used for the 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/EMEA 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. Both substances are used without delay in the manufacturing process of the sterile mixture. The solution is sterilised by filtration and transferred and lyophilised. 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.

Quality control of drug substances
The mixture specification is acceptable in view of the route of synthesis and the various ICH guidelines, additional requirements for residual solvents, bacterial endotoxins and microbiological quality. There are two specified impurities, which are not listed in the transparent list of the Ph.Eur. monograph for piperacillin sodium. The two specified impurities are considered sufficiently qualified for the purpose.
Batch analytical data demonstrating compliance with the specification have been provided for three batches of each strength.

Stability of drug substances
Stability data have been obtained during storage at 25°C/60% RH and 40°C/75% RH. The mixture was adequately stored. Based on the data provided, the recommended retest period of 2 years is justified. The approved storage conditions are *'Do not store above 25 °C*' and the substance must be stored in the original package.

** 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 Mylan 2 g/250 mg contains as active substance 2 g of piperacillin (as sodium salt) and 0.25 g of tazobactam (as sodium salt) per vial, and is a white to off-white, sterile, lyophilised powder for solution for injection or infusion.

Piperacilline/Tazobactam Mylan 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, sterile, lyophilised powder for solution for injection or infusion.

The powder for solution for injection or infusion is packed in colourless glass vials (type II) closed with a chlorobutyl rubber stopper (type I), sealed with an aluminium flip-off cap.

No excipients are used.

Pharmaceutical development
Piperacillin and tazobactam do not present polymorphism. Tazobactam has two chiral carbons, but no diastereoisomers are present due to a stereoselective fermentation process. The mixture of the two active substances is prepared through an aseptic lyophilisation procedure starting from piperacillin acid form and tazobactam acid form. 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 sufficiently described. The mixture is aseptically filled in the pre-sterilised vials. Because sterilisation cannot take place by any other means, so according to Note for guidance CPMP/QWP/054/98, aseptic conditions are used for filling of the pre-sterilised components. Because sterilisation cannot take place by any other means, so according to Note for guidance CPMP/QWP/054/98, aseptic conditions are used for filling of the pre-sterilised components acceptable. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation was performed on 3 batches from each manufacturing site.

Microbiological attributes
The sterility and bacterial endotoxins level are checked according to the Ph.Eur. The limit for bacterial endotoxins is set. The container closure system is suitable to prevent microbial contamination.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The product specifications include requirements for appearance, identification, uniformity of mass, colour, water content, pH, assay, uniformity of dosage units, related substances, sterility, endotoxins and particulate contamination. Moreover, requirements for clarity (of solution), reconstitution time and osmolarity are included. Satisfactory validation data for the analytical methods have been provided. Batch analysis has been performed on three pilot-scale batches of each strength. The batch analysis results show that the finished product meets the proposed specifications. The MAH committed to perform a study in 10 ml sodium chloride 0.9% and to submit data for the reconstitution/dilution before the product is marketed.
Also, the commitment was made to submit the certificate of analysis of a third production batch of the 2 g/250 mg strength as soon as available.

Overages/overfill
It was checked whether the primary container was suitable for the reconstitution/dilution and recovery of the product with appropriate syringes. A mean recovery of more than 98% was obtained after reconstitution in 4 ml or 20 ml of water for injections. It was therefore decided not to apply an overfilling. This is deemed acceptable.

Stability tests on the finished product
Stability data on the product is provided from two pilot scale batches of each strength, tested in compliance with applicable EU guidelines. The batches were stored at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH. Based on the submitted data, a shelf life was granted of 24 months when stored below

25°C. Compatibility of the drug product with the different diluents is demonstrated (sterile water for injection, 0.9% sodium chloride solution, 5% dextrose solution). Although the reconstituted solutions are usually immediately used because of chemical instability, the stability data demonstrate an in-use shelf-life of 18 hours 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.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 Mylan 2 g/250 mg and Piperacilline/Tazobactam Mylan 4 g/500 mg, 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 Piperacilline/Tazobactam Mylan 2 g/250 mg and Piperacilline/Tazobactam Mylan 4 g/500 mg 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 postauthorisation 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 procedures UK/H/0908/001-002/DC and NL/H/963/001-002/DC, for other generic piperacillin/tazobactam products.

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. Two stages of testing were performed. The report details the demographic data of the volunteers, age, gender, social grade and education. Recruiting was performed on the street and by telephone.

At stage 1, 14 specific questions about the content of the leaflet were asked. There were 3 questions in the first round which did not achieve the 90% success rate. Corrective actions were taken to the PIL for round 2. In round 2, one question did not meet the 90% success rate. It concerns a question on the sodium content of the product, which also caused difficulties in the first round. Due to the nature of the product and the clinical setting where the product will be administered, the MEB agrees with the company not to change the leaflet on this point, but stick to the QRD template.

The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Piperacilline/Tazobactam Mylan 2 g/250 mg and Piperacilline/Tazobactam Mylan 4 g/500 mg, 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. Piperacilline/Tazobactam Mylan 2 g/250 mg and Piperacilline/Tazobactam Mylan 4 g/500 mg were authorised in the Netherlands on 28 February 2008.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Piperacilline/Tazobactam Mylan 2 g/250 mg and Piperacilline/Tazobactam Mylan 4 g/500 mg, powder for solution for injection or infusion with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 21 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 July 2009 to September 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 28 February 2013.

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

<u>Quality – medicinal product</u>

- The MAH committed to perform a study in 10 ml sodium chloride 0.9% and to submit data for the reconstitution/dilution before the product is marketed.
- The MAH committed to submit the certificate of analysis of a third production batch of the 2g/250 mg strength as soon as available.

<u>Pharmacovigilance</u>

- The MAH committed to submit 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. This Risk Management Plan has been submitted.
- The MAH committed to adopt the EUCAST Breakpoints when available and perform a PK/PD Monte Carlo Simulation on data for children <12 yrs 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. To maintain the harmonization and consistency achieved so far, the updated product information from UK/H/908/001-002/DC will be considered.

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