NOVARTIS

Chief Medical Office & Patient Safety

Piperacillin/Tazobactam

2 g/0.25 g and 4 g/0.5 g

Powder for Solution for Infusion

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Piperacillin/Tazobactam
Product(s) concerned (brand name(s)):	[Nationally completed name] 2 g/0.25 g and 4 g/0.5 g, Powder for Solution for Infusion
Document status:	Final
Version number:	4.2
Data lock point for this RMP	18 Feb 2019
Date of final sign off	09 May 2019

Rationale for submitting an updated Risk Management Plan (RMP):

The RMP has been updated to align the summary of safety concerns as per the concerned member state (CMS) Hungary comment dated 07 May 2019.

Summary of significant changes in this RMP:

Part	Major changes compared to RMP v 4.1
Part I	None
Part II	Deleted 'Resistance (risk on lack of efficacy)' as important potential risk
Part III	None
Part IV	None
Part V	None
Part VI	Deleted 'Resistance (risk on lack of efficacy)' as important potential risk
Part VII	Annex 8 table 'Summary of changes to the risk management plan over time' has been updated

Other RMP versions under evaluation:

No RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 3.0

Approved with procedure: NL/H/0856/001-002 + NL/H/0858/001

Date of approval: 21 Nov 2013

Qualified Person for Pharmacovigilance (QPPV) name:

Dr. David J Lewis B.Sc (Hons) Ph.D

QPPV oversight declaration:

The content of this RMP has been reviewed and approved by the marketing authorization holder´s (MAH´s) QPPV. The electronic signature is available on file.

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List of abbreviations

ADR	Adverse Drug Reaction
AmpC	Class C beta-lactamase
ATC	Anatomical Therapeutic Chemical (Classification System)
B.Sc (Hons)	Bachelor of Science (Honors)
CMS	Concerned Member State
DCP	Decentralized Procedure
Dr.	Doctor
EEA	European Economic Area
EMA	European Medical Association
EU	European Union
HCP	Healthcare Professional
incl.	Including
INN	International Nonproprietary Name
g	Gram
mg	Milligram
MAH	Marketing Authorization Holder
N/A	Not Applicable
Ph.D	Doctor of Philosophy
PhV	Pharmacovigilance
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PSUSA	Periodic Safety Update Single Assessment
PVAR	Preliminary Variation Assessment Report
QPPV	Qualified Person for Pharmacovigilance
RMM	Risk minimization measure
RMP	Risk Management Plan
Rev.2	Revision 2
RMS	Reference member state
SmPC	Summary of Product Characteristics
UK	United Kingdom
WHO	World Health Organization

1 Part I: Product(s) Overview

Table 1-1 Part I.1 - Product Overview

Active substance(s) (INN or common name)	Piperacillin/Tazobactam
Pharmacotherapeutic group(s) (ATC Code)	Antibacterials for systemic use, Combinations of penicillins including (incl.) beta-lactamase inhibitors Anatomical Therapeutic Chemical Classification System (ATC)-code: J01C R05
Marketing Authorization Holder	Novartis
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	[Nationally completed name] 2 g/0.25 g and 4 g/0.5 g, Powder for Solution for Infusion
Marketing authorization procedure	Decentralized Procedure (DCP)
Brief description of the product	Chemical class: Antibacterials for systemic use, Combinations of penicillins incl. beta-lactamase inhibitors
	Summary of mode of action: 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 penicillin's, is an inhibitor of many beta-lactamases, which commonly cause resistance to penicillin's and cephalosporins, but it does not inhibit Class C beta-lactamse (AmpC) enzymes or metallo beta-lactamases. Tazobactum extends the antibiotic spectrum of piperacillin to include many beta-lactamase-producing bacteria that have acquired resistance to piperacillin alone.
	Important information about its composition: *Piperacillin/Tazobactam, 2 g / 0.25 g* This medicinal product contains 109 mg of sodium per vial, equivalent to 6% of the World Health Organization (WHO) recommended maximum daily intake of 2 g sodium for an adult. *Piperacillin/Tazobactam, 4 g / 0.5 g* This medicinal product contains 217 mg of sodium equivalent to 11% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be taken into consideration for patients who are on a controlled sodium diet.
Hyperlink to the Product Information	[Current Summaries of Product Characteristics (SmPCs)]
Indication(s) in the EEA	Current: Piperacillin/Tazobactam is indicated for the treatment of the following infections in adults and children over 2 years of age. **Adults and adolescents**

<table>
<tr><td></td><td>

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 bacteremia 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.
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.
</td></tr>
<tr><td></td><td>Proposed:
Not Applicable (N/A)</td></tr>
<tr><td>Dosage in the EEA</td><td>
Current:
<u>Posology</u>
The dose and frequency of piperacillin/tazobactam depends on the severity and localization of the infection and expected pathogens.
Adult and adolescent patients
<u>Infections</u>
The usual dose is 4 g piperacillin/ 0.5 g tazobactam given every 8 hours. For nosocomial pneumonia and bacterial infections in neutropenic patients, the recommended dose is 4 g piperacillin / 0.5 g tazobactam administered every 6 hours. This regimen may also be applicable to treat patients with other indicated infections when particularly severe.
The following table summarizes the treatment frequency and the recommended dose for adult and adolescent patients by indication or condition:
<table>
<tr><th>Treatment frequency</th><th>Piperacillin/Tazobactam 4 g/0.5 g</th></tr>
<tr><td rowspan="2">Every 6 hours</td><td>Severe pneumonia</td></tr>
<tr><td>Neutropenic adults with fever suspected to be due to a bacterial infection</td></tr>
<tr><td rowspan="3">Every 8 hours</td><td>Complicated urinary tract infections (including pyelonephritis)</td></tr>
<tr><td>Complicated intra-abdominal infections</td></tr>
<tr><td>Skin and soft tissue infections (including diabetic foot infections)</td></tr>
</table>
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	For more detailed information regarding dosage in special populations (Patients with renal and hepatic impairment, elderly patients, pediatric population (2-12 years of age), and use in children aged below 2 years) and instructions on reconstitution of the medicinal product before administration, please refer to the current SmPCs. Treatment duration The usual duration of treatment for most indications is in the range of 5-14 days. However, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress. Method of administration Piperacillin/Tazobactam 2 g/0.25 g is administered by intravenous infusion (over 30 minutes). Piperacillin/Tazobactam 4 g/0.5 g is administered by intravenous infusion (over 30 minutes).
	Proposed: N/A
Pharmaceutical form(s) and strengths	Current: Powder for Solution for Infusion, 2 g/0.25 g and 4 g/0.5 g
	Proposed: N/A
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

2 Part II Safety Specification Module SVII: Identified and potential risks

2.1 Part II SVII.1. Identification of safety concerns in the initial RMP submission

This section is N/A, the RMP was already approved.

2.2 Part II SVII.2: New safety concerns and reclassification with a submission of an updated RMP

Justification of new safety concerns and deleted safety concerns with submission of this RMP in comparison with the reference medicinal product. According to the Pfizer safety concerns reflected in Periodic Safety Update Single Assessment (PSUSA; [PSUSA/00002425/201709]), dated 17 May 2018, the previous important potential risks "Labelled drug-drug interaction medication errors due to drug chemical incompatibility with aminoglycosides (amikacin, gentamicin)" and "Circumstance or information capable of leading to medication errors due to drug chemical incompatibility with Lactated Ringer's (Hartmann's) solution" have been deleted in the update of RMP v.3.0 to v.4.0. In addition, the PSUSA risk profile included "Mix-up with branded product" as important potential risk. However, this was never a quantitative or qualitative signal for Piperacillin/Tazobactam 2 g/0.25 g and 4 g/0.5 g Powder for Solution for Infusion. Hence, this risk was not included in RMP v.4.0. The following summary of safety concerns was included in RMP v.4.0:Important identified risks:
- Anaphylaxis/severe hypersensitivity reactions including serious skin reactions with fatal outcome"
- Pseudomembranous colitis
- Severe blood disorder e.g., agranulocytosis
- Bleeding manifestations

Important potential risks:
- Convulsions

Missing information:
- Safety in pregnancy and lactation
- Use in infants and neonates (less than 2 years of age)

In v.4.1 of the RMP, all the above summary of safety concerns presented in RMP v.4.0 were removed on the basis of RMS PVAR comments dated 21 Jan 2019 in the course of the procedures NL/H/0856/001-002/II/038 and NL/H/0858/001/II/031. The rationale for removal of these safety concerns were considerations on the maturity of the product: only routine pharmacovigilance (PhV) activities and routine risk minimization measures (RMM) were planned for all safety concerns. Additionally, the identified and potential risks were not likely to have an impact on the risk-benefit balance of the product, nor further evaluation of these risks as part of the PhV plan was warranted. Routine PhV appears to be sufficient to identify and characterize the risks of the product. In addition, routine RMM are sufficient to minimize the risks of the product in the proposed indication.

Additionally, “Resistance (risk on lack of efficacy)” has been included as new important potential risk in RMP v.4.1 based on RMS PVAR comments dated 21 Jan 2019. The rationale behind this addition were considerations on this medicinal product as antibiotic resistance for it among others being a growing issue. Continued monitoring therefore was deemed necessary.

In v.4.1 of the RMP “Resistance (risk on lack of efficacy)” has been deleted as important potential risk on request of the CMS Hungary. Their rationale was that this risk is not specific for this product, it is a general issue relating to the use of antibiotics. There is no need for additional pharmacovigilance activity or additional risk minimization measures in the case of this risk, so it is not important according to the revised RMP guidance document.

2.3 Part II SVII.3: Details of important identified risks, important potential risks, and missing information

N/A

3 Part II Safety Specification Module SVIII: Summary of the safety concerns

Table 3-1 Part II SVIII.1: Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

4 Part III: Pharmacovigilance plan (including post-authorization safety studies)

4.1 Part III.1. Routine pharmacovigilance activities

No special important risks have been identified for piperacillin/tazobactam, 2 g/0.25 g and 4 g/0.5 g, powder for solution for infusion which require additional Pharmacovigilance (PhV) activities other than Routine PhV.

The Global PhV System ensures the services of a Qualified Person responsible for PhV and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

4.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

None

4.2 Part III.2. Additional pharmacovigilance activities

No additional PhV activities are proposed for Piperacillin/Tazobactam powder for solution for infusion.

4.3 Part III.3. Summary Table of additional pharmacovigilance activities

N/A

5 Part IV: Plans for post-authorization efficacy studies

No post-authorization efficacy studies are in place or planned.

6 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

The safety information in the proposed product information is aligned to the originator medicinal product.

6.1 Part V.1. Routine risk minimization measures

Routine risk minimization measures are aligned to the originator medicinal product.

6.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

6.3 Part V.3. Summary of risk minimization measures

N/A

7 Part VI: Summary of the risk management plan (RMP) Piperacillin/Tazobactam, 2 g/0.25 g and 4 g/0.5 g, Powder for Solution for Infusion

This is a summary of the RMP for piperacillin/tazobactam, 2 g/0.25 g and 4 g/0.5 g, powder for solution for infusion. The RMP details important risks of piperacillin/tazobactam powder for solution for infusion, how these risks can be minimized, and how more information will be obtained about piperacillin/tazobactam powder for solution for infusion's risks and uncertainties (missing information).

Piperacillin/Tazobactam powder for solution for infusion's summaries of product characteristics (SmPCs) and its package leaflets (PLs) give essential information to healthcare professionals (HCPs) and patients on how piperacillin/tazobactam powder for solution for infusion should be used.

Important new concerns or changes to the current ones will be included in updates of piperacillin/tazobactam powder for solution for infusion's RMP.

7.1 Part VI: I. The medicine and what it is used for

Piperacillin belongs to the group of medicines known as “broad-spectrum penicillin antibiotics”. It can kill many kinds of bacteria. Tazobactam can prevent some resistant bacteria from surviving the effects of piperacillin. This means that when piperacillin and tazobactam are given together, more types of bacteria are killed.

Piperacillin/Tazobactam is used in adults and adolescents to treat bacterial infections, such as those affecting the lower respiratory tract (lungs), urinary tract (kidneys and bladder), abdomen, skin or blood. Piperacillin/Tazobactam may be used to treat bacterial infections in patients with low white blood cell counts (reduced resistance to infections).

Piperacillin/Tazobactam is used in children aged 2-12 years to treat infections of the abdomen such as appendicitis (condition in which appendix becomes inflamed (red or swollen) and painful), peritonitis (infection of the fluid and lining of the abdominal organs), and gallbladder (biliary) infections. Piperacillin/Tazobactam may be used to treat bacterial infections in patients with low white blood cell counts (reduced resistance to infections).

In certain serious infections, doctor may consider using piperacillin/tazobactam in combination with other antibiotics.

It contains piperacillin/tazobactam as the active substance and is administered via parenteral route as powder for solution for infusion (2 g/0.25 g and 4 g/0.5 g).

7.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of piperacillin/tazobactam powder for solution for infusion, together with measures to minimize such risks are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment (if applicable) so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance (PhV) activities*.

If important information that may affect the safe use of piperacillin/tazobactam powder for solution for infusion is not yet available, it is listed under 'missing information' below.

7.2.1 Part VI – II.A: List of important risks and missing information

Important risks of piperacillin/tazobactam powder for solution for infusion are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of piperacillin/tazobactam powder for solution for infusion. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 7-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

7.2.2 Part VI – II.B: Summary of important risks

The safety information in the proposed Product Information is aligned to the originator medicinal product.

7.2.3 Part VI – II.C: Post-authorization development plan

7.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of piperacillin/tazobactam powder for solution for infusion.

7.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for piperacillin/tazobactam powder for solution for infusion.

8 Part VII: Annexes

Annex 1 – EudraVigilance Interface

Available in electronic format only.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study program

N/A

Annex 3 - Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

N/A

Annex 4 - Specific adverse drug reaction follow-up forms

N/A

Annex 5 - Protocols for proposed and ongoing studies in RMP part IV

N/A

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

N/A

Annex 7 - Other supporting data (including referenced material)

References List

External references

NoneNovartis internal references

[SmPC (2018)] Sandoz Summary of Product Characteristics Piperacillin/Tazobactam-2 g/ 0.25 g and 4 g/ 0.5 g, Powder for solution for infusion Apr 2018.

[SmPC (2018)] Sandoz Summary of Product Characteristics Piperacillin/Tazobactam-4 g/ 0.5 g, Powder for solution for infusion, Apr 2018.

Annex 8 – Summary of changes to the risk management plan over time

Table 8-1 Summary of changes to the RMP over time

Version	Approval date Procedure	Change
1.0	30 Oct 2008 + 19 Dec 2008 NL/H/0856/001-002 + NL/H/0858/001	Initial Submission
2.0	13 Jun 2012 NL/H/0856/001-002 + NL/H/0858/001	The RMP has been updated to include final data of following studies corresponding to important potential risks: • Compatibility study of piperacillin/tazobactam with aminoglycosides • Compatibility study of piperacillin/tazobactam with Lactated Ringer's (Hartmann's) solution Amendment of SmPC, labelling and PL is proposed. An additional risk minimization measure (a training package with educational material for HCPs) has been agreed for United Kingdom (UK).
3.0	21 Nov 2013 NL/H/0856/001-002 + NL/H/0858/001	The RMP has been updated to include post-marketing exposure of piperacillin/tazobactam parenteral application from 01 Sep 2008 to 31 May 2012. Epidemiology of indication(s) and important adverse events, sections of Potential for off label use and Potential for off label pediatric use and the Detailed action plan for specific safety concerns have been updated. Additionally, all the relevant parts of the RMP have been amended according to the updated SmPC and PL.
4.0	N/A NL/H/0856/001-002 + NL/H/0858/001	The RMP has been updated to align the risk profile according to Periodic Safety Update Single Assessment (PSUSA) dated 17 May 2018. Also, related additional risk minimization measures and PhV measures have been deleted per PSUSA recommendation. <u>Deleted safety concerns:</u> *Important potential risks:* • Labelled drug-drug interaction medication errors due to drug chemical incompatibility with aminoglycosides (amikacin, gentamicin) • Circumstance or information capable of leading to medication errors due to drug chemical incompatibility with Lactated Ringer's (Hartmann's) solution <u>Added safety concerns:</u> *Important identified risks:* • Anaphylaxis/severe hypersensitivity reactions including serious skin reactions with fatal outcome

		• Pseudomembranous colitis • Severe blood disorder e.g., agranulocytosis • Bleeding manifestations *Important potential risks*: • Convulsions *Missing information:* • Safety in pregnancy and lactation • Use in infants and neonates (less than 2 years of age) Additionally, the RMP has been transferred to the new EU RMP template (EMA/PRAC/613102/2015 Rev.2)
4.1	N/A NL/H/0856/001-002/II/038 NL/H/0858/001/II/031	The RMP has been updated as per the PVAR comments dated 21 Jan 2019. Following updates were made in the summary of safety concerns and in Part II Module SVII, respectively: <u>Deletion of safety concerns:</u> *Important identified risks:* • Anaphylaxis/severe hypersensitivity reactions including serious skin reactions with fatal outcome • Pseudomembranous colitis • Severe blood disorder e.g., agranulocytosis • Bleeding manifestations *Important potential risks:* • Convulsions *Missing information:* • Safety in pregnancy and lactation • Use in infants and neonates (less than 2 years of age) <u>Addition of safety concern:</u> *Important potential risk:* • Resistance (risk on lack of efficacy)
4.1	N/A NL/H/0856/001-002/II/038 NL/H/0858/001/II/031	The RMP has been updated as per the CMS HU and RMS comments dated 07 May 2019. Following update was made in Part II Module SVII and VIII and Part VI, respectively: <u>Deletion of safety concern:</u> *Important potential risk:* Resistance (risk on lack of efficacy)