PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

FOR

ZAVICEFTA® (CEFTAZIDIME-AVIBACTAM)

Marketing Authorization Number: 66890

Powder for concentrate for solution for infusion, 2g/0.5g

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
EU	European Union
Mg	Milligram

OVERVIEW

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Zavicefta is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Zavicefta in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Pfizer AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Zavicefta.

SUMMARY OF RISK MANAGEMENT PLAN FOR ZAVICEFTA (CEFTAZIDIME-AVIBACTAM

This summary of the RMP for Zavicefta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Zavicefta's RMP.

1. THE MEDICINE AND WHAT IT IS USED FOR

Zavicefta is authorised for the treatment of Complicated Intra-Abdominal Infection, Complicated Urinary Tract Infection, including pyelonephritis, Hospital-Acquired Pneumonia including Ventilator-Associated Pneumonia, and for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options (See SmPC for the full indication). It contains ceftazidime and avibactam as the active substances, and it is given intravenously. Zavicefta is authorised for the treatment of Complicated Intra-Abdominal Infection, Complicated Urinary Tract Infection, including pyelonephritis, Hospital-acquired Pneumonia, including ventilator associated pneumonia and Infections due to aerobic Gram-negative organisms in patients with limited treatment options in children ≥ 3 months to <18 years old.

Safety and efficacy in children <3 months old have not yet been established. No data are available.

Further information about the evaluation of Zavicefta's benefits can be found in Zavicefta's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004027/human_med_001993.jsp&mid=WC0b01ac058001d124

I. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Zavicefta, together with measures to minimise such risks and the proposed studies for learning more about Zavicefta 's risks, are outlined below.

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

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised 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 public (e.g. with or without prescription) can help to minimise its risks.

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

In addition to these measures, information about AEs is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Zavicefta is not yet available, it is listed under 'missing information' below.

I.A. List of Important Risks and Missing Information

Important risks of Zavicefta are risks that need special risk management activities to further investigate or minimise 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 Zavicefta.

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 (eg, on the long-term use of the medicine).

Table 1. List of Important Risks and Missing Information

Important identified risks	None[a]
Important potential risks	Hepatotoxicity Bacterial resistance development
Missing information	Pregnancy exposure Lactation exposure Immunocompromised population exposure

a. The MAH reclassified the Hypersensitivity/anaphylaxis and *Clostridium difficile* associated diarrhoea (CDAD), from important identified risks, to risks not considered important, and therefore removed them from the list of safety concerns and this is approved by European Medicines Agency (April 2018).

I.B. Summary of Important Risks

There are no safety concerns considered important identified risks.

Table 2. Important Potential Risk - Hepatotoxicity

Evidence for linking the risk to the medicine	Clinical studies, recognised class effects, and medical/scientific literature. The incidence of AEs representing possible events of hepatotoxicity was generally balanced across treatment groups in the clinical studies. No cases fulfilled Hy's Law criteria and no cases of actual hepatotoxicity were identified.
Risk factors and risk groups	History of alcohol use, hepatitis, and other pre-existing liver disease; concomitant use of hepatotoxic drugs; infections; age; gender; and daily drug dose. [12]
Risk minimisation measures	Routine risk minimisation measures Statements within SmPC Sections 4.2 (Posology and method of administration), 4.8 (Undesirable effects), and 5.2 (Pharmacokinetic properties). No additional risk minimisation measures.

Table 3. Important Potential Risk - Bacterial resistance development

Evidence for linking the risk to the medicine	Nonclinical studies, clinical studies, and medical/scientific literature. No AE of bacterial resistance development was reported from the studies in the CAZ-AVI development programme. One patient from the REPROVE study was infected with *K. pneumoniae* that was confirmed to be susceptible at baseline and, despite a clinical cure, samples collected after 14 days of therapy were found to have a resistant strain.
Risk factors and risk groups	Factors that may contribute to the development of resistance include inadequate infection control measures, high antibiotic use in a specific geographic area per unit time, increased use for prophylaxis, increased use for empiric polymicrobial therapy, greater severity of illness of hospitalized patients, more severely immunocompromised patients, devices and procedures, agricultural use of antimicrobials, social factors, international travel, and evolution of pathogens. Evidence suggests that a causal relationship exists between antimicrobial usage and antimicrobial resistance (eg., hospitals with high antibiotic use have high rates of resistance, changes in antimicrobial usage in such settings are often accompanied by changes in resistance patterns, and an increased duration of antimicrobial exposure is accompanied by an increased risk of colonisation with resistant organisms.[3]
Risk minimisation measures	Routine risk minimisation measures Statement within SmPC Section 5.1 (Pharmacodynamic properties). No additional risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Resistance surveillance programme. See Section PART I.I.C.2 of the RMP v 3.2 for an overview of the post-authorisation development plan.

Table 4. Missing Information - Pregnancy exposure

Evidence for linking the risk to the medicine	CAZ-AVI use was not studied in pregnant women. There is limited clinical data from the use of ceftazidime-avibactam in pregnant women. Animal embryofoetal development studies conducted with ceftazidime or avibactam do not indicate harmful effects at exposures equivalent to therapeutic concentrations. Following administration of avibactam throughout pregnancy and lactation in the rat at maternal exposures greater than or equal to approximately 1.5 times human therapeutic exposures, there were minor changes in the morphology of the kidney and ureters in some (< 10%) rat pups. CAZ-AVI should not be used during pregnancy unless clearly necessary and only if the potential benefit outweighs the possible risk.
Risk minimisation measures	Routine risk minimisation measures: Statements within SmPC Sections 4.6 (Fertility, pregnancy, and lactation) and 5.3 (Nonclinical safety data) No additional risk minimisation measures.

Table 5. Missing Information - Lactation exposure

Evidence for linking the risk to the medicine	CAZ-AVI use was not studied in nursing women. Women who were pregnant or nursing were excluded from clinical study participation.
Risk minimisation measures	Routine risk minimisation measures: Statements within SmPC Sections 4.6 (Fertility, pregnancy, and lactation) and 5.3 (Nonclinical safety data). No additional risk minimisation measures.

Table 6. Missing Information - Immunocompromised population exposure

Evidence for linking the risk to the medicine	These patients were excluded from the clinical development program in contrast to patients who have a normal immune response to their infection, patients who are immunocompromised when they develop an infection are likely to experience a more severe infection, with more associated complications. In addition, they are likely to be treated in secondary or tertiary centres with higher risk of exposure to multi-drug resistant organisms. Population in need of further characterization: Patients with evidence of significant immunologic disease determined by the following: Human immunodeficiency virus infection, with either a current Acquired Immune Deficiency Syndrome defining condition (eg., Kaposi's sarcoma, *Pneumocystis carinii* pneumonia) or a CD4+ T lymphocyte count <200/mm^3 at the time of study entry, metastatic or haematological malignancy requiring chemotherapeutic interventions and immunosuppressive therapy, including maintenance corticosteroid therapy (>40 mg/day of equivalent prednisolone).
Risk minimisation measures	Routine risk minimisation measures: None proposed. No additional risk minimisation measures.

I.C. Post-Authorisation Development Plan

I.C.1. Studies which are Conditions of the Marketing Authorization

Currently there are no studies which are conditions of the EU marketing authorisation or specific obligation of Zavicefta.

I.C.2. Other Studies in Post-Authorization Development Plan

Resistance surveillance programme

Monitor and follow-up on any clinical and/or microbiological failures in the clinical studies where there is potential for development of resistance whilst on therapy. Post approval commitment for monitoring resistance and increasing levels through the Resistance Surveillance Programme.

REFERENCES

[1] Chalasani N, Bjornsson E. Risk factors for idiosyncratic drug-induced liver injury. Gastroenterology 2010;138(7):2246-59

[2] Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. Mayo Clin Proc 2014;89(1):95-106.

[3] Stein GE. Antimicrobial resistance in the hospital setting: Impact, trends, and infection control measures. Pharmacotherapy 2005;25(10 Pt 2):44S-54S.