Risk Management Plan for piperacillin/tazobactam

This is a summary of the risk management plan (RMP) for piperacillin/tazobactam. The RMP details important risks of piperacillin/tazobactam how these risks can be minimised, and uncertainties (missing information).

Perasin powder for solution for infusion summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how the drugs should be used.

I. The medicine and what it is used for

Perasin powder for solution for infusion are authorised for the treatment of the following infections in adults and children over 2 years of age:

Adults and adolescents
- 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 bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Perasin 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

Perasin 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.

II. Risks asssociated with the medicine and activities to minimise or further characterise the risks
Important risks of piperacillin/tazobactam, together with measures to minimise such risks, are outlined below.

Measures to minimise the risks identified are:
Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and heathcare professionals;
Important advice on the medicine’s packaging;
The medicine’s legal status- Prescription only product.

Together, these measures constitute routine risk minimisation measures.
No additional risk minimisation measures are proposed.

In addition to these measures, routine pharmacovigilance activities including adverse reactions reporting, PSUR, medical literature monitoring, and other activities as required under EU legislation, are made.

No additional risk minimisation measures are proposed.

If important information that may affect the safe use of piperacillin/tazobactam is not yet available, it is listed under missing information: Safety in pregnancy and lactation and use in infants and neonates (less than 2 years of age).

II. A. List of important risks and missing information

Important risks of piperacillin/tazobactam 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 piperacillin/tazobactam. 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.

Summary of safety concerns	
Important identified risks	1. Severe hypersensitivity reactions (including anaphylactic shock) 2. Pseudomembranous colitis 3. Severe blood disorder e.g., agranulocytosis 4. Bleeding manifestations 5. Incompatibility with aminoglycosides
Important potential risks	1. Convulsion 2. Haemophagocytic lymphohistiocytosis (HLH)
Missing information	1. Safety in pregnancy and lactation 2. Use in infants and neonates (less than 2 years of age)

II. B. Summary of important risks

The safety information in the Product Information for Perasin powder for solution for infusion is aligned to the reference medicinal product – Tazocin powder for solution for infusion.

Important identified risks: **Severe hypersensitivity reactions (including anaphylactic shock)**	
Evidence for linking the risk to the medicine	Simone Fahim and colab. Presented a case report with 28-year-old woman patient who developed DHS after 2 weeks of initiating therapy with PT for osteomyelitis. The reaction caused severe parenchymal nephritis, leading to anuria that necessitated hemodialysis. Interestingly, this patient complained of numbness and paresthesia of the forearm during intravenous PT infusion 2 days prior to developing DHS; a similar symptom was reported by Behbahani and

	Kostman36 with numbness of the patient's upper chest during intravenous infusion. (1)
Risk factors and risk groups	Risk factors and risk groups are represented by patients with history of acute severe allergic reactions to any other beta-lactam active substance, patients with human immunodeficiency virus. DHS occurs more often in women than in men.
Risk minimisation measures	Prescription only medicine.
Additional pharmacovigilance activities	NA

Important identified risks: **Pseudomembranous colitis**	
Evidence for linking the risk to the medicine	C. difficile has emerged as one of the most problematic and challenging bacterial pathogens of the past decade. C. difficile has taken on epidemic proportions in North America and Europe since the early 2000s, leading to devastating outbreaks of C. difficile infection (CDI) in hospitals. Unfortunately it has also been a steep rise in mortality. It shows that the attributable mortality of CDI during the period 2005-2011has increased from 5.7 to 6.9%. Veronica Ahlund study has found a significant difference in Piperacillin/Tazobactam mean MIC values for C. difficile between 2005 and 2015. The mean MIC value is more than 20% higher 2015 compared to ten years earlier, which indicates that C. difficile resistance to Piperacillin/Tazobactam has increased. This result could be considered clinically relevant, and emphasizes the fact that inappropriate uses of Piperacillin/Tazobactam must be prevented to avoid further resistance development. (9)
Risk factors and risk groups	Risk factors and risk groups are represented by duration of TZP therapy, advanced age, weakened immune system, colon disease.
Risk minimisation measures	Prescription only medicine.
Additional pharmacovigilance activities	NA

Important identified risks: **Severe blood disorder e.g., agranulocytosis**	
Evidence for linking the risk to the medicine	Although PT-induced HA, thrombocytopenia or neutropenia is rare, they can be life-threatening sometimes. Based on the characteristics of the ADRs, it is necessary to conduct a routine blood test regularly for patients accompanying risk

	factors or having prolonged PT treatment. If the decrease of leukocyte count, platelet or hemoglobin is aggravated accompanying some typical symptoms or not, ADR ought to be considered. (7) The US FDA Adverse Event Reporting System (AERS) database was also screened and the authors identified 366 unique cases of piperacillin- or piperacillin-tazobactam-induced hematological abnormalities, including neutropenia (n = 183, 50%), leukopenia, (n = 99, 27%), agranulocytosis (n = 58, 15.8%), and others. In 62 cases, patients received between 1 and 14 days of therapy (mean 7.7 + 4.1 days). Overall, there were 82 (22.4%) deaths. The authors concluded that while piperacillin-associated neutropenia is rare; cases may arise after treatment duration shorter than 14 days. (2)
Risk factors and risk groups	Risk factors and risk groups are represented by patients with comorbidities, repeated piperacillin treatment and advancing age, duration of TZP therapy. Benli et al. recently reported that people tended to develop leucopenia, neutropenia, or eosinophilia by extended PT therapy, especially in cases with combined antibiotic therapy, younger patient with fewer comorbidities or initial higher eosinophil count. (7)
Risk minimisation measures	Prescription only medicine.
Additional pharmacovigilance activities	NA

Important identified risks: **Bleeding manifestation**	
Evidence for linking the risk to the medicine	A case report with 55-years old Vietnamese male report adds to the growing evidence that TZP can cause clinically significant bleeding by affecting platelet aggregation. Furthermore, this is the case of a clinically significant intracerebral and intraventricular hemorrhage potentially related to TZP. The particularly dire consequences of ICH make this report especially relevant to the fields of neurology and neurosurgery, and warrants further investigation. (4)
Risk factors and risk groups	Risk factors and risk groups are represented by elderly patients, concomitant administration of heparin, oral anticoagulants or other substances that may influence the blood coagulation system.
Risk minimisation measures	Prescription only medicine.

Additional pharmacovigilance activities	NA

Important identified risks: **Incompatibility with aminoglycosides**	
Evidence for linking the risk to the medicine	During investigations of the extent of drug interaction, piperacillin/tazobactam has been coadministered with tobramycin, a compound with very low protein binding that is eliminated entirely by glomerular filtration, and vancomycin, which also has low protein binding and is eliminated primarily by glomerular filtration. There were only minor changes in the pharmacokinetic behaviors of tazobactam and piperacillin in these interaction studies. The elimination half-lives of tazobactam and piperacillin were slightly less when piperacillin/tazobactam was coadministered with tobramycin than when administered alone, but the maximum concentrations achieved in plasma and the AUC were essentially the same. The pharmacokinetic characteristics of tobramycin were significantly ($p < 0.05$) altered when tobramycin was coadministered with piperacillin/tazobactam: the renal clearance of tobramycin decreased from 60.7 to 41.4 ml/min and the AUC increased by 12%. These changes, however, are unlikely to significantly affect the clinical antimicrobial activity of tobramycin. The diminished renal elimination of tobramycin may have been caused by a chemical reaction between piperacillin and tobramycin in vitro; the fact that the renal excretion of piperacillin was not affected has yet to be explained. The peak of MIC concentration, which has been found to predict the outcome of aminoglycoside treatment of patients with severe infections, was unaltered. Further, the frequency and severity of adverse events associated with tobramycin treatment did not appear to change when tobramycin was coadministered with piperacillin/ tazobactam. (16)
Risk factors and risk groups	Risk factor is represented by severe renal impairment.
Risk minimisation measures	Prescription only medicine.
Additional pharmacovigilance activities	NA

Important potential risks: **Convulsions**	
Evidence for linking the risk to the medicine	Despite popular use of piperacillin, the dire neurotoxicity associated with piperacillin still goes unrecognized, leading

	to a delay in appropriate management. The researchers report a 57-year-old woman with end-stage renal disease receiving continuous ambulatory peritoneal dialysis (CAPD), who developed slurred speech, tremor, bizarre behavior, progressive mental confusion, and 2 episodes of generalized tonic-clonic seizure (GTCS) after 5 doses of piperacillin/tazobactam (2 g/250 mg) were given for bronchiectasis with secondary infection. The laboratory data revealed normal plasma electrolyte and ammonia levels but leukocytosis. Neurologic examinations showed dysarthria and bilateral Babinski sign. Computed tomography of brain and electroencephalogram were unremarkable. Despite the use of antiepileptic agents, another GTCS episode recurred after the sixth dose of piperacillin/tazobactam. Brain magnetic resonance imaging did not demonstrate acute infarction and organic brain lesions. Initiation of highflux hemodialysis rapidly reversed the neurologic symptoms within 4 hours. Piperacillin-induced encephalopathy should be considered in any uremic patients with unexplained neurological manifestations. CAPD is inefficient in removing piperacillin, whereas hemodialysis can rapidly terminate the piperacillin-induced encephalopathy. (11)
Risk factors and risk groups	Risk factors and risk groups are represented by patients with patients with pre-existing risk factors such as renal or hepatic insufficiency, central nervous system pathology, neurological diseases, history of epilepsy or seizures, critical illness, and increased age are more susceptible to seizure development as a consequence of antibiotic therapy. (10)
Risk minimisation measures	Prescription only medicine.
Additional pharmacovigilance activities	NA

Important potential risks: **Haemophagocytic lymphohistiocytosis (HLH)**	
Evidence for linking the risk to the medicine	In the present study, the authors reported three patients with HLH associated with PIPC-TAZ, which was used for treatment of AFBN. PIPC-TAZ was chosen for the treatment of AFBN, because it not only has indications for complicated urinary tract infections but also covers most of the causative bacteria of urinary tract infections including β-lactamaseproducing E. coli. All of patients showed cytopenia after two-week of antibiotic therapy without any signs of recurrence of AFBN. Although Cases 1 and 2 developed febrile exanthema, only Case 2 was classified as a possible case of DRESS based on the regiSCAR criteria for DRESS.

	However, to the best of authors knowledge, this is the first report on HLH associated with TAZ/PIPC. In addition, Miyabayashi, H et al. could not find any report on HLH associated with AFBN. Cessation of PIPC-TAZ combined with corticosteroid therapy improved clinical symptoms. From the previous experience, the physicians intentionally stopped PIPC-TAZ and started corticosteroid therapy in Case 3 when febrile cytopenia developed, although the patient did not fulfill the criteria of HLH. The patient recovered from cytopenia promptly. DLST using PIPC-TAZ was performed in Cases 1 and 3, and was positive in both cases. Since the physicians used the commercially available premixed antibiotic PIPC-TAZ for DLST, they could not specify which drug (PIPC or TAZ) was the causative agent. Unfortunately, DLST could not be done in Case 2, because the patient's family had to moved far away. Taken together, HLH of these patients was thought to be a result of prolonged antibiotic therapy of PIPC-TAZ as demonstrared by the timing of the onset, and the positivity of DLST. Most cases of drug reaction are induced by a single drug. However, patients with drug reaction are known to be at risk for multiple drug hypersensitivity. Some patients are sensitized to unrelated drugs during the course of drug reactions to the first causative drug. In case 1, fever and the skin rash recurred even though antibiotics were switched from PIPC-TAZ to CTX. The result suggests that initial drug reaction that was triggered by PIPC-TAZ sensitized the patient to another antibiotic CTX. In conclusion, Miyabayashi, H et al propose that prolonged therapy with PIPC-TAZ could be a cause of HLH. It is, therefore, important to consider HLH when patients requiring longterm antibiotic therapy show febrile cytopenia. (13)
Risk factors and risk groups	Risk factor is represented by treatment longer than 10 days.
Risk minimisation measures	Prescription only medicine.
Additional pharmacovigilance activities	NA

Missing information: **Safety in pregnancy and lactation**	
Risk minimisation measures	Prescription only medicine.
Additional pharmacovigilance activities	NA

Missing information: **Use in infants and neonates (less than 2 years of age)**

Risk minimisation measures	Prescription only medicine.
Additional pharmacovigilance activities	NA

II. C. Post- authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation
Not applicable.

II.C.2 Other studies in post-authorisation development plan
Not applicable.

Part VII: Annexes