

SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ZINFORO

This is a summary of the risk management plan (RMP) for ZINFORO. The RMP details important risks of ZINFORO, how these risks can be minimised, and how more information will be obtained about ZINFORO's risks and uncertainties (missing information).

ZINFORO's SmPC and its package leaflet give essential information to healthcare professionals and patients on how ZINFORO should be used.

This summary of the RMP for ZINFORO 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 ZINFORO's RMP.

I. The Medicine and What It Is Used For

ZINFORO is authorised for complicated skin and soft tissue infections (cSSTI) and community-acquired pneumonia (CAP) in neonates, infants, children, adolescents and adults. It contains ceftaroline fosamil as the active substance and it is given by infusion.

Further information about the evaluation of ZINFORO's benefits can be found in ZINFORO'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/002252/human_med_001584.jsp&mid=WC0b01ac058001d124

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

Important risks of ZINFORO, together with measures to minimise such risks and the proposed studies for learning more about ZINFORO'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 adverse events 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 ZINFORO is not yet available, it is listed under ‘missing information’ below.

II.A. List of Important Risks and Missing Information

Important risks of ZINFORO 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 ZINFORO. 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). The MAH proposes to remove missing information (Immunocompromised population, Lactation, Paediatric population exposure, Pre-existing seizure disorder, Pre-existing significant hepatic disease, Pregnancy exposure, Efficacy in MRSA CAP) from the list of safety concerns.

Table 1. List of Important Risks and Missing Information

Important identified risks	None
Important potential risks	Bacterial resistance development Convulsions/seizures Drug induced liver injury Haemolytic anaemia Renal impairment (including potential drug interactions with nephrotoxic agents) Potential for off-label use
Missing information	Immunocompromised population Lactation Paediatric population exposure Pre-existing seizure disorder Pre-existing significant hepatic disease Pregnancy exposure Efficacy in MRSA CAP None

CAP = Community-acquired pneumonia; MRSA = Methicillin-resistant *Staphylococcus aureus*.

Strikethrough text: missing information removed from the list of safety concerns.

II.B. Summary of Important Risks

There are no important identified risks for ceftaroline. Important potential risks are presented below. Missing information listed below is proposed for removal in this RMP:

- Immunocompromised population

- Lactation
- Paediatric population exposure
- Pre-existing seizure disorder
- Pre-existing significant hepatic disease
- Pregnancy exposure
- Efficacy in MRSA CAP

There is no missing information for ceftaroline fosamil.

Table 2. Important Potential Risk – Bacterial Resistance Development

Evidence for linking the risk to the medicine	Bacterial resistance development has been observed in nonclinical studies, and reports indicative of bacterial resistance development have been received in the post-marketing setting.
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 hospitalised 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 (e.g., 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). ¹
Risk minimisation measures	<u>Routine RMMs</u> : the risk is communicated through the label in SmPC Section (4.1 Therapeutic indications) and Section 5.1 (Pharmacodynamic properties) <u>No additional RMMs.</u>

RMM = Risk minimisation measure; SmPC = Summary of product characteristics.

Table 3. Important Potential Risk – Convulsions/Seizures

Evidence for linking the risk to the medicine	Convulsions/seizures is a recognised class effect and it has been observed in nonclinical studies; reports indicative of convulsions/seizures have been received in clinical trials and in the post-marketing setting.
Risk factors and risk groups	Risk factors include advanced age, history of head trauma or neurologic disease, stroke, brain tumours, renal failure or genetic predisposition. Abnormal neurological status, defined as abnormal neurological examination, abnormal CT brain scan, remote symptomatic aetiology or neurological deficits from birth, is considered one of the most important risk factors for recurrence of seizure. Seizures have also been reported with use of a number of antimicrobial agents, including penicillins, cephalosporins, carbapenems and fluoroquinolones. A review study on antibiotic-induced convulsions suggested that risk factors for antibiotic-induced seizures include renal insufficiency, pre-existing CNS disease (including seizure disorder), cardiopulmonary bypass, sepsis and endocarditis. ²

Table 3. Important Potential Risk – Convulsions/Seizures

Risk minimisation measures	<u>RMMs</u> : the risk is communicated through the label in SmPC Section 4.4 (Special warnings and precautions for use) <u>No additional RMMs.</u>
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CNS = Central nervous system; CT = Computed tomography; RMM = Risk minimisation measure; SmPC = Summary of product characteristics.

Table 4. Important Potential Risk – Drug-Induced Liver Injury

Evidence for linking the risk to the medicine	DILI is a recognised class effect and it has been observed nonclinical studies; reports indicative of DILI have been received in clinical studies and in the post-marketing setting.
Risk factors and risk groups	History of alcohol use, pre-existing liver disease, concomitant use of other hepatotoxic drugs and infections.
Risk minimisation measures	<u>Routine RMMs</u> : the risk is communicated through the label in SmPC Section 4.8 (Undesirable effects) <u>No additional RMMs.</u>

DILI = Drug induced liver injury; RMM = Risk minimisation measure; SmPC = Summary of product characteristics.

Table 5. Important Potential Risk – Haemolytic Anaemia

Evidence for linking the risk to the medicine	Haemolytic anaemia is a recognised class effect and it has been observed nonclinical studies; reports indicative of haemolytic anaemia have been received in clinical studies and in the post-marketing setting.
Risk factors and risk groups	Risk factors include autoimmune disease, haematologic neoplasm, immunodeficiency disease, family history of haemolytic disease, and recent viral infections.
Risk minimisation measures	<u>RMMs</u> : SmPC Section 4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects) <u>No additional RMMs.</u>

RMM = Risk minimisation measure; SmPC = Summary of product characteristics.

Table 6. Important Potential Risk – Renal Impairment (Including Potential Drug Interactions with Nephrotoxic Agents)

Evidence for linking the risk to the medicine	Renal impairment is a recognised class effect and it has been observed nonclinical studies; reports indicative of renal impairment have been received in clinical studies and in the post-marketing setting.
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Table 6. Important Potential Risk – Renal Impairment (Including Potential Drug Interactions with Nephrotoxic Agents)

Risk factors and risk groups	<p>Risk factors include: advanced age, severe life-threatening systemic infections, circulatory, respiratory and renal compromise, trauma, history of diabetes mellitus, hypertension, heart failure, hepatic disease and concomitant nephrotoxic drugs.</p> <p>Clinical use of second- and third-generation cephalosporins has not produced clear evidence of significant nephrotoxicity. Decreases in glomerular filtration rate of about 10 mL/minute were seen after ceftazidime treatment courses ranging from 4-31 days. For many other cephalosporins comparable data are lacking.³</p> <p>Drug interactions that may potentially increase the risk of nephrotoxicity cited in the literature mainly relate to the use of older 1st generation cephalosporins (ie, cephaloridine and cefalotin) with either loop diuretics such as furosemide or aminoglycosides.³</p> <p>Conflicting data exist concerning the effect of furosemide on the PK of cephalosporins.³</p> <p>An increase in aminoglycoside nephrotoxicity has only been documented with cefalotin and cephaloridine.³</p>
Risk minimisation measures	<p><u>Routine RMMs</u>: the risk is communicated through the label in SmPC Section 4.2 (Posology and method of administration), Section 4.8 (Undesirable effects), and Section 5.2 (Pharmacokinetic properties)</p> <p><u>No additional RMMs</u>.</p>

PK = Pharmacokinetics; RMM = Risk minimisation measure; SmPC = Summary of product characteristics.

Table 7. Important Potential Risk – Potential for off-label use

Evidence for linking the risk to the medicine	<p>AMR data was used to identify off-label activities in tigecycline. There is no literature evaluating any off-label use that would be relevant here. Reports indicative of off-label use have been received in the post-marketing setting.</p>
Risk factors and risk groups	<p>Patients with infections who are unresponsive and/or resistant to conventional antibiotic therapy or patients with life-threatening infections where no alternative therapy exists.</p>
Risk minimisation measures	<p><u>RMMs</u>: the risk is communicated through the label in SmPC Section 4.1 (Therapeutic indications) and Section 4.2 (Posology and method of administration)</p> <p><u>No additional RMMs</u>.</p>

AMR = Arlington Medical Resources; PK = Pharmacokinetics; RMM = Risk minimisation measure; SmPC = Summary of product characteristics.

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ZINFORO.

II.C.2. Other Studies in Post-Authorisation Development Plan

There are no on-going or planned category 1-2-3 studies for ceftaroline.

¹ Stein GE. Antimicrobial resistance in the hospital setting: Impact, trends, and infection control measures. *Pharmacotherapy* 2005;25(10 Pt 2):44S-54S.

² Wallace KL. Antibiotic-induced convulsions. *Crit Care Clin* 1997;13(4):741-62.

³ Aronson JK. Meyler's side effects of drugs: The international encyclopedia of adverse drug reactions and interactions. 15th ed. Oxford (UK): Elsevier; 2006. Cephalosporins. p. 688-701. Furosemide. p. 1454-60.