Part VI: Summary of the risk management plan

Summary of risk management plan for <Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/infusion

This is a summary of the risk management plan (RMP) for <Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/infusion. The RMP details important risks of <Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/infusion, how these risks can be minimised, and how more information will be obtained about <Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/infusion's risks and uncertainties (missing information).

<Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/infusion's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how <Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/infusion should be used.

I. The medicine and what it is used for

<Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/infusion are authorised for treatment of infections of skin and soft tissue and infections of bones and joints. They are also indicated before, during and after surgery to prevent possible infections (perioperative prophylaxis). <Cefazolin> contains cefazolin as the active substance and it is given by the intravenous (injection or infusion into a vein) or intramuscular (injection to a muscle) route of administration.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of <Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/infusion, together with measures to minimise such risks and the proposed studies for learning more about <Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/infusion'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 patient (e.g. with or without prescription) can help to minimise its risks.

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

If important information that may affect the safe use of <Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/infusion is not yet available, it is listed under 'missing information' below>.

II.A List of important risks and missing information

Important risks of <Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/infusion 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 <Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/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);

List of important risks and missing information	
Important identified risks	Hypersensitivity including anaphylactic reactions Pseudomembranous colitis Nephrotoxicity Overgrowth of resistant microorganisms Toxic epidermal necrolysis and Stevens-Johnson syndrome
Important potential risks	Seizures in patients with renal impairment or receiving an overdose Bleeding risk
Missing information	Use in pregnancy Use in lactating infants Safety in prematures and infants < 1 month of age

II.B Summary of important risks

Important identified risk: Hypersensitivity including anaphylactic reactions	
Evidence for linking the risk to the medicine	Allergic reactions may occur. The most common reactions are skin reactions such as skin rash (maculopapular exanthema) and itchy skin rash (urticarial), which appear

	in 1-3% of the patients administered with cephalosporins. The incidence of severe allergic reactions (anaphylactic reactions) seems to be very low (0.0001-0.1%) but constitute a potential life-threatening condition with serious consequences.
Risk factors and risk groups	Patients with a history of non-severe hypersensitivity to other beta-lactam agents. Cefazolin should be administered only with special caution to patients with allergic reactivity (e. g. allergic rhinitis or bronchial asthma) as the risk for a serious hypersensitivity reaction is increased.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections: 4.3, 4.4 and 4.8.* *SmPC section 4.4 where advice is given on possible cross-sensitivity, discontinuation of treatment in case of severe hypersensitivity reaction, and establishment of patient's history of severe hypersensitivity reactions to cefazolin, or other cephalosporins or any other type of beta-lactam agent or of non-severe hypersensitivity to other beta-lactam agents and caution about the administered medicine to patients with allergic reactivity (e. g. allergic rhinitis or bronchial asthma) are included in SmPC section 4.4.* *PL section:2 and 4* *Informing the healthcare professional about the history of allergic reactions to other beta-lactam antibiotics and if the patient is prone to allergic reactions in PL section 2 and how to detect signs and symptoms of hypersensitivity in PL section 4.* For hospital use only. Legal status: Subject to medical prescription.
Important identified risk: Pseudomembranous colitis	
Evidence for linking the risk to the medicine	Antibacterial agent-associated persistent diarrhoea during or after treatment with <Cefazolin> (pseudomembranous colitis) has been reported with use of cefazolin and may range in severity from mild to life threatening. *Clostridium difficile* infection may occur after a single prophylactic dose of a first-generation cephalosporin. *Clostridium difficile* infection is an unintended consequence of antimicrobial use associated with increased morbidity and mortality for patients.
Risk factors and risk groups	In general, the two biggest risk factors for *Clostridium difficile* infection (CDI) are exposure to antibiotics and exposure to the organism requiring both infection prevention and antimicrobial stewardship interventions. The combination of multiple antibiotics and longer duration

	of antibiotic use is associated with increased risk of developing CDI.
Risk minimisation measures	*SmPC sections 4.4 and 4.8.* *Recommendation for discontinuation of therapy with cefazolin and the administration of specific treatment for Clostridium difficile and against the use of anti-diarrhoea medicines are included in SmPC section 4.4* *PL section 2 and 4* *Informing the healthcare professional in case of severe persistent diarrhoea during or after treatment and how to detect signs and symptoms of severe and frequent diarrhoea in PL sections 2 and 4.* For hospital use only. Legal status: Subject to medical prescription.
Important identified risk: Nephrotoxicity	
Evidence for linking the risk to the medicine	Kidney problems (nephrotoxicity) have been reported during treatment with cefazolin although it appears to be rare, mild, and reversible.
Risk factors and risk groups	Potent diuretics, especially furosemide, may potentiate cephalosporin nephrotoxicity. Concomitant administration of aminoglycoside (a type of antibiotics) and cephalosporin antibiotics is associated with synergistic nephrotoxicity.
Risk minimisation measures	*SmPC sections 4.5 and 4.8.* *PL sections 2 and 4* *Monitoring of the kidney function when co-administered with aminoglycosides and diuretics is included in SmPC section 4.5 and PL section 2* For hospital use only. Legal status: Subject to medical prescription.
Important identified risk: Overgrowth of resistant microorganisms	
Evidence for linking the risk to the medicine	Long-term and repeated administration can lead to overgrowth of resistant organisms. There is an association between cephalosporin usage and the emergence of multiply-resistant organisms.
Risk factors and risk groups	Long-term and repeated administration can lead to overgrowth of resistant organisms.
Risk minimisation measures	*SmPC section 4.4*

	Recommendation for appropriate measures to be taken in SmPC section 4.4 *PL section 4* For hospital use only. Legal status: Subject to medical prescription.
Important identified risk: Toxic epidermal necrolysis and Stevens-Johnson syndrome	
Evidence for linking the risk to the medicine	Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe adverse reactions to drugs that cause a life-threatening eruption of mucocutaneous blistering and epithelial sloughing. While the acute complications of SJS/TEN are well described, it is increasingly recognized that survivors may develop delayed sequelae, some of which can be associated with significant morbidity.
Risk factors and risk groups	Genetic factors associated with drug hypersensitivity are implicated in the development of TEN/SHS. The presence of particular genetic variations has been found to be associated with SJS/TEN among particular groups of patients.
Risk minimisation measures	*SmPC section 4.8* *PL section 4* *Discontinuation of treatment with cefazolin and immediate notification of the doctor in PL section 4* For hospital use only. Legal status: Subject to medical prescription.
Important potential risk: Seizures in patients with renal impairment or receiving an overdose	
Evidence for linking the risk to the medicine	Fits/convulsions have been reported with cephalosporins and may be associated with significant morbidity or mortality. Neurotoxicity has been reported with first-generation cephalosporins such as cefazolin. This is particularly true in the setting of kidney problems.
Risk factors and risk groups	Renal function problems and excessive amount of the medicine are risk factors for the development of seizures. Advanced age is an additional risk factor, at least in part by diminished renal function.
Risk minimisation measures	*SmPC sections 4.4, 4.8 and 4.9.* *PL section 4* *Recommendations for dose adjustment and prolongation of*

	dosage interval with renal impairment are included in SmPC sections 4.2 and 4.4. For hospital use only. Legal status: Subject to medical prescription.
Important potential risk: Bleeding risk	
Evidence for linking the risk to the medicine	Although an unusual complication, bleeding while on treatment with cefazolin can be serious.
Risk factors and risk groups	Risk factors that increase the risk for cefazolin-associated bleeding include poor nutrition, renal failure, inadequate vitamin K stores, cancer, recent surgery, ileus, and lack of oral intake of food. Long-term use of cefazolin in patients with renal failure could lead to an accumulation of toxins. This could result in an increased bleeding risk in these patients.
Risk minimisation measures	*SmPC sections 4.4 and 4.8.* *Recommendation for monitoring of prothrombin time and INR is included in SmPC section 4.4* *PL sections 2 and 4* *Informing the healthcare professional in case the patient suffers from disorders of blood clotting or his/her present condition can lead to such defects or the patient takes medicines that prevent blood clotting in PL section 2* For hospital use only. Legal status: Subject to medical prescription.
Missing information: Use in pregnancy	
Risk minimisation measures	*SmPC section 4.6* *PL section 2* *Recommendation for assessment if cefazolin is clearly necessary and after careful consideration of benefits and risks is included in SmPC section 4.6 and PL section 2* For hospital use only. Legal status: Subject to medical prescription.
Missing information: Use in lactating infants	
Risk minimisation measures	*SmPC section 4.6.* *PL section 2* *Recommendation for careful consideration of benefits and*

	risks before administering to lactating women with possible discontinuation of breastfeeding is included in SmPC section 4.6. *Recommendation for possible discontinuation of breastfeeding during treatment with <Cefazolin> is included in PL section 2*. For hospital use only. Legal status: Subject to medical prescription.
Missing information: Safety in prematures and infants < 1 month of age	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2* *PL section 3* *Recommendation against the use of the medicine in this patient population is included in SmPC section 4.2 and PL section 2* For hospital use only. Legal status: Subject to medical prescription.

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 <Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/infusion.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for <Cefazolin> 1 g powder for solution for injection/infusion and <Cefazolin> 2 g powder for solution for injection/infusion.