ERTAPENEM FRESENIUS KABI 2.5 MG/ML

POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION

Date 30 Jun 2016, Version 2.0

PUBLIC SUMMARY OF RISK MANAGEMENT PLAN

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Ertapenem is an antibacterial for systemic use. It is used in the following indications:

Treatment

It is indicated in paediatric patients (3 months to 17 years of age) and in adults for the treatment of the following infections when caused by bacteria known or very likely to be susceptible to ertapenem and when parenteral therapy is required:

- Intra-abdominal infections
- Community acquired pneumonia
- Acute gynaecological infections
- Diabetic foot infections of the skin and soft tissue

Prevention

Ertapenem Fresenius Kabi is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

VI.2.2 Summary of Treatment Benefits

Ertapenem, a new beta-lactam agent of the carbapenem class (1-β-methyl carbapenem). Carbapenem agents are normally active against common aerobic and anaerobic gram-positive pathogens, but not against methicillin-resistant staphylococci. In vitro, ertapenem is slightly more active against gram-negative than gram-positive organisms. However, ertapenem does not show useful activity against the non-fermenting gram-negative aerobes, such as Pseudomonas aeruginosa.

Ertapenem was as effective as ceftriaxone or piperacillin/tazobactam for the treatment of abdominal infections, community-acquired pneumonia, gynaecological infections and diabetic foot infections: the same cure rates were reached for both Ertapenem and the comparator medicine (between 87 and 94% for Ertapenem, against 83 to 92% for the comparators). However, the data presented were not sufficient to support the use of Ertapenem in the treatment of urinary tract infections and skin and soft tissue infections, except diabetic foot ulcers.

In children, its effectiveness was comparable to that of the comparators, and to the effectiveness seen in adults.

The carbapenems that are already available in the European Union – meropenem and imipenem – are administered by injection only and are usually indicated for the treatment of serious infections in hospitalised patients, often with significant co-morbidities.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Safety Concern	What is known	Preventability
Important Identified Risks		
Hypersensitivity/anaphylactic reactions	Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 of the SmPC may occur	Yes, ertapenem is contraindicated in patients with hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 of the SmPC. It must not be used in patients who are hypersensitive (allergic) to ertapenem or any of the other ingredients, or to other antibiotics of the same group (carbapenems). Its use must also be avoided in patients who are severely allergic to other types of antibiotics, such as penicillins or cephalosporins.
Drug interactions with valproic acid or divalproex sodium	Decreases in valproic acid levels that may fall below the therapeutic range have been reported when valproic acid was co-administered with carbapenem agents. The lowered valproic acid levels can lead to inadequate seizure control; therefore, concomitant use of ertapenem and valproic acid/sodium valproate is not recommended and alternative antibacterial or anti-convulsant therapies should be considered.	Yes, the concomitant use of ertapenem and valproic acid/sodium valproate is not recommended and alternative antibacterial or anti-convulsant therapies should be considered. It is recommended to observe the blood plasma level of the drug (s) or symptoms due to

Safety Concern	What is known	Preventability
		any possible interactions.
Drug interaction with probenecid	In vivo, probenecid (500 mg every 6 hours) decreased the bound fraction of ertapenem in plasma at the end of infusion in subjects administered a single 1 g intravenous dose from approximately 91 % to approximately 87 %. The effects of this change are anticipated to be transient.	Consideration should be given if patient is already taking probenecid. It is recommended to observe the blood plasma level of drug (s) or symptoms due to any possible interactions.
Pseudomonas colitis	Pseudomembranous colitis and antibiotic-associated colitis have been reported with ertapenem and may range in severity from mild to life-threatening.	Yes, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents. Discontinuation of therapy with Ertapenem and the administration of specific treatment for Clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.
Seizures*	Seizures have been reported during clinical investigation in adult patients treated with ertapenem (1 g once a day) during therapy or in the 14-day follow-up period. Seizures occurred most commonly in elderly patients and those with pre-existing central nervous system (CNS) disorders (e.g. brain lesions or history of seizures) and/or compromised renal function. Similar observations have been made in the post-marketing environment.	Yes, precaution must be taken while prescribing ertapenem in in elderly patients and those with pre-existing central nervous system (CNS) disorders (e.g. brain lesions or history of seizures) and/or compromised renal function. The medication should be stopped and corrective measure should be taken keeping the severity of the disease under treatment.

*synonymous with convulsion

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Drug resistance	For species considered susceptible to ertapenem, resistance was uncommon in surveillance studies in Europe. In resistant isolates, resistance to other antibacterial agents of the carbapenem class was seen in some but not all isolates. Ertapenem is effectively stable to hydrolysis by most classes of beta-lactamases, including penicillinases, cephalosporinases and extended spectrum beta-lactamases, but not metallo-beta-lactamases. Methicillin-resistant staphylococci and enterococci are resistant to ertapenem; P. aeruginosa and other non-fermentative bacteria are generally resistant. Resistance is uncommon in Enterobacteriaceae and ertapenem is generally active against those with extendedspectrum beta-lactamases (ESBLs). Resistance can however be observed when ESBLs or other potent betalactamases Resistance can also arise via the acquisition of betalactamases with significant carbapenem-hydrolysing activity (e.g. IMP and VIM metallo-beta-lactamases or KPC types), though these are rare.

Missing information

Risk	What is known
Use in pregnancy	Adequate and well-controlled studies have not been performed in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo-foetal development, parturition or post-natal development. However, ertapenem should not be used during pregnancy unless the potential benefit outweighs the possible risk to the foetus. Ertapenem is excreted in human milk. Because of the potential for adverse reactions on the infant, mothers should not breast-feed their infants while receiving ertapenem. There are no adequate and well-controlled studies regarding the effect of ertapenem use on fertility in men and women. Preclinical studies do not indicate direct or indirect harmful effects with respect to fertility. Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated-dose toxicity, genotoxicity and toxicity to reproduction and development. Decreased neutrophil counts, however, occurred in rats that received high doses of ertapenem, which was not considered a significant safety issue. Long-term studies in animals to evaluate the carcinogenic potential of ertapenem have not been performed.
Use in patient < 3 months of age	The safety and efficacy of Ertapenem in children below 3 months of age have not yet been established.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics for Ertapenem can be found in Annex 2 of this RMP.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.