# Part VI: Summary of the risk management plan by product

## VI.1 Elements for summary tables in the EPAR

### *VI.1.1 Summary table of Safety concerns*

| **Summary of safety concerns** | |
|---|---|
| **Important identified risks** | • Hypersensitivity/anaphylactic reactions<br>• Seizures<br>• Drug interaction with probenecid<br>• Drug interactions with valproic acid or divalproex sodium<br>• *Pseudomembranous colitis* |
| **Important potential risks** | • Drug resistance |
| **Missing information** | • Use in patients < 3 months of age<br>• Use in pregnancy |

### *VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan*

Not applicable.

### *VI.1.3 Summary of Post authorisation efficacy development plan*

Not applicable.

### *VI.1.4 Summary table of Risk Minimisation Measures*

| **Safety concern** | **Routine risk minimisation activities** | **Additional risk minimisation measures** |
|---|---|---|
| **Important identified risks** | | |
| Hypersensitivity/anaphylactic reactions | Information included in summary of product characteristics and package leaflet<br><br><u>Section 4.3 of the proposed SmPC</u><br>Administration of ertapenem is contraindicated in patients with:<br>- Hypersensitivity to the active substance or to any of the excipients<br>- Hypersensitivity to any other carbapenem | None proposed. |

| Safety concern | Routine risk minimisation activities | Additional risk minimisation measures |
|---|---|---|
| | antibacterial agent.<br>- Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g. penicillins or cephalosporins).<br><br><u>Section 4.4 of the proposed SmPC</u><br>Before initiating therapy with ertapenem, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens .<br><br>If an allergic reaction occurs, the medicinal product should be discontinued and appropriate measures taken. Serious anaphylactic reactions require immediate emergency treatment. | |
| Seizures | Information included in summary of product characteristics<br>and package leaflet<br><br><u>Section 4.4 of the proposed SmPC</u><br>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 | None proposed. |

| Safety concern | Routine risk minimisation activities | Additional risk minimisation measures |
|---|---|---|
| | environment.<br><br>Anti-convulsant therapies should be considered. | |
| Drug interaction with probenecid | Information included in summary of product characteristics and package leaflet<br><br><u>Section 5.2 of the proposed SmPC</u><br>*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.<br><br>Co-administration of probenecid with ertapenem is not recommended. | None proposed. |
| Drug interactions with valproic acid or divalproex sodium | Information included in summary of product characteristics and package leaflet<br><br><u>Section 4.4 of the proposed SmPC</u><br>Concomitant use with valproic acid:<br>The concomitant use of ertapenem and valproic acid/sodium valproate is not recommended.<br><br><u>Section 4.5 of the proposed SmPC</u><br>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 | None proposed. |

| Safety concern | Routine risk minimisation activities | Additional risk minimisation measures |
|---|---|---|
| | 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. | |
| *Pseudomembranous colitis* | Information included in summary of product characteristics and package leaflet<br><br>Section 4.4 of the proposed SmPC<br>Antibiotic-associated colitis and pseudomembranous colitis have been reported with ertapenem and may range in severity from mild to life-threatening. Therefore, 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 AptaPharma and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.<br><br>Section 4.8 of the proposed SmPC<br>For patients who received only Ertapenem AptaPharma, the following adverse reactions were reported during therapy plus follow-up for 14 days after treatment was stopped<br><br>**Infections and infestations:**<br>***Adults 18 years of age and older:***<br>pseudomembranous | None proposed. |

| Safety concern | Routine risk minimisation activities | Additional risk minimisation measures |
|---|---|---|
| | enterocolitis - uncommon | |
| **Important potential risks** | | |
| Drug resistance | Information included in summary of product characteristics and package leaflet<br><br><u>Section 4.4 of the proposed SmPC</u><br>Prolonged use of ertapenem may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. | None proposed. |
| **Missing information** | | |
| Use in patients < 3 months of age | Information included in summary of product characteristics and package leaflet<br><br><u>Section 4.4 of the proposed SmPC</u><br>No data are available in children under 3 months of age. | None proposed. |
| Use in pregnancy | Information included in summary of product characteristics and package leaflet<br><br><u>Section 4.6 of the proposed SmPC</u><br><u>Pregnancy</u><br>Ertapenem should not be used during pregnancy unless the potential benefit outweighs the possible risk to the foetus.<br><br><u>Breast-feeding</u><br>Because of the potential for adverse reactions on the infant, mothers should not breast-feed their infants while receiving ertapenem. | None proposed. |

## VI.2 Elements for a Public Summary

As this application is made under Article 10(1) of European Directive 2001/83/EC, as amended, the public summary should be based on the public summary of the reference product. The reference product is Invanz.
The summary below was prepared based on the public summary of Invanz and on literature.

### *VI.2.1 Overview of disease epidemiology*

**Intra-abdominal infections**

Intra-abdominal infections are caused by organisms, usually bacterial or fungal, situated within the cavity of the abdomen. Intra-abdominal infection continues to be one of the major challenges in general surgery and encompass all forms of bacterial peritonitis, of intra-abdominal abscesses and of infections of intra-abdominal organs. Complicated intra-abdominal infections remain an important source of patient morbidity and are frequently associated with poor clinical prognoses, particularly for patients in high-risk categories. The overall mortality rate is 7.6% (Sartelli, 2013).

**Community acquired pneumonia (CAP)**

A retrospective study using a nationwide claims database to determine the incidence of CAP in the Netherlands identified 195,372 cases of CAP between 2008 and 2011 (Rozenbaum MH, 2015). This represented an average incidence of 295 cases per 100,000 population per year.
Advanced age is associated not only with a higher incidence of CAP but also with more severe disease, greater need for hospitalization, and higher mortality (Mandell, 2007; Teramoto, 2008).
CAP encountered in the ambulatory setting is more common among young adults and is usually due to atypical CAP pathogens (eg, *Mycoplasma pneumoniae*) (Marrie TJ, 2005).

**Acute gynaecological infections**

Acute Pelvic Infections includes Postpartum Endomyometritis, Septic Abortion and Post Surgical Gynecologic Infections.
It is estimated that more than 1 million women experience an episode of Pelvic Inflammatory Disease PID every year in the US (Ness RB, 2006).

The incidence of postpartum endometritis in the United States varies depending on the route of delivery and the patient population. After a vaginal delivery, incidence is 1-3%. It is up to ten times more common after caesarean section. Due to the nature of the complaint, it is most common in females of reproductive age (French LM, 2004).

Septic abortion remains a primary cause of maternal mortality in the developing world, mostly as a result of illegal abortions. Unsafe abortions account for nearly one half of abortions, and morbidity/mortality occurs particularly often women who live in developing nations (Lim LM, 2014).

**Diabetic foot infections of the skin and soft tissue**

Globally, diabetic foot infections are the most common skeletal and soft-tissue infections in patients with diabetes. The incidence of diabetic foot infections is similar to that of diabetes in various ethnic groups and most frequently affect elderly patients. There are no significant differences between the sexes.

Mortality is not common, except in unusual circumstances. The mortality risk is highest in patients with chronic osteomyelitis and in those with acute necrotizing soft-tissue infections (Stuart Bronze, 2016).

### *VI.2.2 Summary of treatment benefits*

**Treatment of infections**

Ertapenem was compared with ceftriaxone (another antibiotic) for the treatment of adults with community acquired pneumonia (866 patients) and urinary tract infections (592 patients), and with a combination of piperacillin and tazobactam for the treatment of abdominal infections (655 patients), gynaecological infections (412 patients), skin and soft tissue infections (infections of the skin and the tissues just beneath the skin, 540 patients); and foot infections in diabetes patients (576 patients). In studies in children, ertapenem was compared with ceftriaxone (for community-acquired pneumonia, 389 children) and with ticarcillin/clavulanate (for intra-abdominal infections, 105 children). The studies examined if the infection was cured after 7 to 28 days of treatment, depending on the type of infection. Ertapenem was as effective as ceftriaxone or piperacillin/tazobactam for the treatment of abdominal infections, community-acquired pneumonia, gynaecological infections and foot infections in diabetes patients: Ertapenem was effective for 87 to 94% of patients compared with 83 to 92% for the comparator antibiotics. However, the data were not sufficient to support the use of ertapenem in the treatment of urinary tract infections and skin and soft tissue infections, except foot ulcers in diabetes patients. In children, ertapenem was as effective as the comparator antibiotics and had similar effectiveness to that in adults.

**Prevention of infections after colorectal surgery**

Ertapenem was compared with cefotetan for preventing infection after colorectal surgery. Effectiveness was measured as absence of infection 4 weeks after treatment, which involved 952 adults. Infection was absent in about 60% patients given ertapenem compared with 49% of patients given cefotetan.

### *VI.2.3 Unknowns relating to treatment benefits*

The safety and efficacy of ertapenem in children under 3 years have not yet been established. There is relatively little experience with ertapenem in children less than two years of age. In this age group, particular care should be taken to establish the susceptibility of the infecting organism(s) to ertapenem.

Efficacy and safety have also not been studied in patients with advanced renal impairment and patients who require haemodialysis to support a dose recommendation. Therefore, ertapenem should not be used in these patients.

Efficacy and safety of ertapenem have not been established in patients with hepatic impairment.

Also there are no adequate data from the use of ertapenem in pregnant and lactating women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### *VI.2.4 Summary of safety concerns*

**Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Hypersensitivity/allergic reactions to ertapenem (Hypersensitivity/anaphylactic reactions) | This medicine may cause a serious type of allergic reaction called anaphylaxis. Anaphylaxis can be life-threatening allergy reaction and requires immediate medical attention. | Stop taking this medicine and call your doctor right away if you have trouble breathing, trouble swallowing, or any swelling of your hands, face, or mouth while you are using this medicine . |
| Sudden electrical activity in the brain (Seizures) | Some patients may develop tremors or seizures while receiving this medicine. | If you already have a history of seizures and you are taking anticonvulsants, you should continue to take them unless otherwise directed by your doctor. |
| Drug interaction with probenecid | Probenecid interferes with the active tubular secretion of ertapenem, resulting in increased plasma concentrations of ertapenem. Co-administration of probenecid with ertapenem is not recommended. | Using this medicine with probenecid may cause an increased risk of certain side effects, but using both drugs may be the best treatment for the patient. If both medicines are prescribed together, your doctor may change the dose or how often you use one or both of the medicines. |
| Drug interactions with valproic acid or divalproex sodium | Valproic acid concentrations in the blood may drop below the therapeutic range upon co-administration with ertapenem. | Tell your doctor, nurse or pharmacist if you are taking medicines called valproic acid or sodium valproate (used to treat epilepsy, bipolar disorder, migraines, or schizophrenia). This is because ertapenem can affect the way some other medicines work. Your doctor will decide whether you should use ertapenem in combination with these other medicines. |
| *Pseudomembranous colitis* (an inflammation of the bowel) | Antibiotic-associated colitis and pseudomembranous colitis have been reported with ertapenem and may range in severity from mild to life-threatening. | It is important that you tell your doctor if you have diarrhoea before, during or after your treatment with ertapenem. This is because you may have a condition known as colitis (an inflammation of the bowel). Do not take any medicine to treat |

| Risk | What is known | Preventability |
|---|---|---|
| | | diarrhoea without first checking with your doctor. |

**Important potential risks**

| Risk | What is known |
|---|---|
| Resistance to penems of microorganisms (Drug resistance) | As with other antibiotics, prolonged use of ertapenem may result in overgrowth of non-susceptible organisms. |

**Missing information**

| Risk | What is known |
|---|---|
| Use in patients < 3 months of age | Appropriate studies performed to date have not demonstrated pediatrics-specific problems that would limit the usefulness of ertapenem in infants and children 3 months to 17 years of age. Use in infants younger than 3 months of age is not recommended . |
| Use in pregnancy | There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. |

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 and the Package leaflet for Ertapenem AptaPharma will be kept up to date according to the corresponding product information of the innovator. This medicine has no additional risk minimisation measures.