ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

INVANZ 1 g powder for concentrate for solution for infusion.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each vial contains 1.0 g ertapenem equivalent to 1.046 g ertapenem sodium.

For excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Powder for concentrate for solution for infusion. White to off-white powder.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Treatment of the following infections in adults when caused by bacteria known or very likely to be susceptible to ertapenem and when parenteral therapy is required (see section 4.4 Special warnings and special precautions for use and section 5.1 Pharmacodynamic properties):

- Intra-abdominal infections
- Community acquired pneumonia
- Acute gynaecological infections

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

4.2 **Posology and method of administration**

The dose of INVANZ is 1 gram (g) given once a day by the intravenous route.

*Intravenous administration:* INVANZ should be infused over a period of 30 minutes.

The usual duration of therapy with INVANZ is 3 to 14 days but may vary depending on the type and severity of infection and causative pathogen(s). When clinically indicated, a switch to an appropriate oral antibacterial agent may be implemented if clinical improvement has been observed.

*Renal insufficiency:*

INVANZ may be used for the treatment of infections in patients with renal insufficiency. In patients whose creatinine clearance is > 30 ml/min/1.73 m², no dosage adjustment is necessary. There are inadequate data on the safety and efficacy of ertapenem in patients with advanced renal insufficiency to support a dose recommendation. Therefore, ertapenem should not be used in these patients. (See section 5.2 Pharmacokinetic properties.)

*Patients on haemodialysis:*

There are inadequate data on the safety and efficacy of ertapenem in patients on haemodialysis to support a dose recommendation. Therefore, ertapenem should not be used in these patients.

*Hepatic insufficiency:*

No dosage adjustment is recommended in patients with impaired hepatic function (see section 5.2 Pharmacokinetic properties, Special populations).
Elderly:
The recommended dose of INVANZ should be administered, except in cases of advanced renal insufficiency (see Renal insufficiency).

Children and adolescents:
Safety and effectiveness have not been established. Therefore, use in patients under 18 years of age is not recommended.

4.3 Contraindications

- Hypersensitivity to ertapenem or to any of the excipients
- Hypersensitivity to any other carbapenem antibacterial agent
- Severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g., penicillins or cephalosporins).

4.4 Special warnings and special precautions for use

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before initiating therapy with ertapenem, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens (see section 4.3 Contraindications). If an allergic reaction to ertapenem occurs, discontinue the therapy immediately. **Serious anaphylactic reactions require immediate emergency treatment.**

As with other antibiotics, 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.

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all antibacterial agents, including 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 INVANZ and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

The efficacy of INVANZ in the treatment of community acquired pneumonia due to penicillin-resistant *Streptococcus pneumoniae* has not been established.

Experience in the use of ertapenem in the treatment of severe infections is limited. In clinical studies for the treatment of community-acquired pneumonia, 25 % of evaluable patients treated with ertapenem had severe disease (defined as pneumonia severity index > III). In a clinical study for the treatment of acute gynaecologic infections, 26 % of evaluable patients treated with ertapenem had severe disease (defined as temperature ≥ 39°C and/or bacteraemia); ten patients had bacteraemia. Of evaluable patients treated with ertapenem in a clinical study for the treatment of intra-abdominal infections, 30 % had generalized peritonitis and 39 % had infections involving sites other than the appendix including the stomach, duodenum, small bowel, colon, and gallbladder; there were limited numbers of evaluable patients who were enrolled with APACHE II scores ≥ 15 and efficacy in these patients has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions caused by inhibition of P-glycoprotein-mediated clearance or CYP-mediated clearance of medicinal products are unlikely (see section 5.2 Pharmacokinetic properties).
Penem and carbapenem antibacterial agents may decrease the serum levels of valproic acid. Monitoring of serum levels of valproic acid should be considered if ertapenem is to be co-administered with valproic acid.

4.6 Pregnancy and lactation

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 effects on the infant, mothers should not breast-feed their infants while receiving ertapenem.

4.7 Effects on ability to drive and use machines

Dizziness and somnolence can occur (see section 4.8 Undesirable effects), which may affect some patients’ ability to drive and/or operate machinery.

4.8 Undesirable effects

The total number of patients treated with ertapenem in clinical studies was over 1,900 of which over 1,850 received a 1 g dose of ertapenem. Adverse reactions (i.e., considered by the investigator to be possibly, probably, or definitely related to the medicinal product) were reported in approximately 20 % of patients treated with ertapenem. Treatment was discontinued due to adverse reactions in 1.3 % of patients.

For patients who received only INVANZ, the most common adverse reactions reported during therapy plus follow-up for 14 days after treatment was stopped were: diarrhoea (4.8 %), infused vein complication (4.5 %) and nausea (2.8 %).

For patients who received only INVANZ, the following adverse reactions were reported during therapy plus follow-up for 14 days after treatment was stopped:

Common = ≥ 1/100, < 1/10; Uncommon = > 1/1,000, < 1/100; Rare = > 1/10,000, < 1/1,000

**Blood and the lymphatic disorders:**
- Rare: Neutropenia, thrombocytopenia

**Metabolism and nutrition disorders:**
- Rare: Hypoglycaemia

**Nervous system disorders:**
- Common: Headache
- Uncommon: Dizziness, somnolence, insomnia, confusion, seizure
- Rare: Agitation, anxiety, depression, tremor

**Cardiac and vascular disorders:**
- Common: Phlebitis/thrombophlebitis
- Uncommon: Hypotension
- Rare: Arrhythmia, increased blood pressure, haemorrhage, tachycardia

**Respiratory, thoracic and mediastinal disorders:**
- Uncommon: Dyspnoea, pharyngeal discomfort
- Rare: Nasal congestion, cough, epistaxis, pneumonia, rales/rhonchi, wheezing
Gastrointestinal and hepato-biliary disorders:
Common: Diarrhoea, nausea, vomiting
Uncommon: Constipation, oral candidiasis, pseudomembranous enterocolitis, acid regurgitation, dry mouth, dyspepsia, anorexia
Rare: Cholecystitis, dysphagia, faecal incontinence, jaundice, liver disorder

Skin and subcutaneous tissue disorders:
Common: Rash, pruritus
Uncommon: Erythema
Rare: Dermatitis, dermatomycosis, desquamation, postoperative wound infection

Musculoskeletal, connective tissue and bone disorders:
Rare: Muscle cramp, shoulder pain

Renal and urinary disorders:
Rare: Urinary tract infection, renal insufficiency, acute renal insufficiency

Reproductive system and breast disorders:
Uncommon: Vaginitis
Rare: Abortion, genital bleeding

General disorders and administration site conditions:
Common: Infused vein complication
Uncommon: Extravasation, abdominal pain, candidiasis, asthenia/fatigue, fungal infection, fever, oedema/swelling, chest pain, taste perversion
Rare: Allergy, injection-site induration, malaise, pelvic peritonitis, scleral disorder, syncope

Laboratory test findings: for patients who received only INVANZ, the most frequently reported laboratory abnormalities and their respective incidence rates during therapy plus follow-up for 14 days after treatment was stopped were: elevations in ALT (4.6 %), AST (4.6 %), alkaline phosphatase (3.8 %) and platelet count (3.0 %).

For patients who received only INVANZ, the following laboratory abnormalities were reported during therapy plus follow-up 14 days after treatment was stopped:

Common = ≥ 1/100, < 1/10; Uncommon = > 1/1,000, < 1/100; Rare = > 1/10,000, < 1/1,000

Chemistry:
Common: Elevations in ALT, AST, alkaline phosphatase
Uncommon: Increases in total serum bilirubin, direct serum bilirubin, indirect serum bilirubin, serum creatinine, serum urea, serum glucose
Rare: Decreases in serum bicarbonate, serum creatinine, and serum potassium; increases in serum LDH, serum phosphorus, serum potassium

Haematology:
Common: Elevation in platelet count
Uncommon: Decreases in white blood cells, platelet count, segmented neutrophils, haemoglobin and haematocrit; increases in eosinophils, activated partial thromboplastin time, segmented neutrophils, and white blood cells
Rare: Decrease in lymphocytes; increases in band neutrophils, lymphocytes, metamyelocytes, monocytes, myelocytes; atypical lymphocytes
Urinalysis:
Uncommon: Increases in urine bacteria, urine white blood cells, urine epithelial cells, and urine red blood cells; urine yeast present
Rare: Increase in urobilinogen

Miscellaneous:
Uncommon: Positive Clostridium difficile toxin

4.9 Overdose

No specific information is available on the treatment of overdose with ertapenem. Overdosing of ertapenem is unlikely. Intravenous administration of ertapenem at a 3 g daily dose for 8 days to healthy volunteers did not result in significant toxicity. In clinical studies, inadvertent administration of up to 3 g in a day did not result in clinically important adverse reactions.

However, in the event of an overdose, treatment with INVANZ should be discontinued and general supportive treatment given until renal elimination takes place.

Ertapenem can be removed to some extent by haemodialysis (see section 5.2 Pharmacokinetic properties); however, no information is available on the use of haemodialysis to treat overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: carbapenems, ATC code: J01D HXX

Mechanism of action
Ertapenem inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). In Escherichia coli, affinity is strongest to PBPs 2 and 3.

Microbiological Susceptibility
The general MIC susceptibility test breakpoints to separate susceptible (S) pathogens from resistant (R) pathogens are:
S ≤ 4 mg/l and R > 8 mg/l.

The MIC susceptibility test breakpoint for streptococci, including S. pneumoniae, is:
S ≤ 2 mg/l.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. Localized clusters of infections due to carbapenem-resistant organisms have been reported in the European Union. The information below gives only approximate guidance on the probability as to whether the micro-organism will be susceptible to ertapenem or not.
### Pathogens

<table>
<thead>
<tr>
<th>Susceptible:</th>
<th>European range of observed resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive aerobes:</td>
<td></td>
</tr>
<tr>
<td>Methicillin-susceptible staphylococci (including <em>Staphylococcus aureus</em>)*</td>
<td>0-5 %</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em>†</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td></td>
</tr>
<tr>
<td>Gram-negative aerobes:</td>
<td>0-20 %</td>
</tr>
<tr>
<td><em>Citrobacter freundii</em></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter aerogenes</em></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td></td>
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<tr>
<td><em>Escherichia coli</em></td>
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<tr>
<td><em>Haemophilus influenzae</em></td>
<td></td>
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<tr>
<td><em>Haemophilus parainfluenzae</em></td>
<td></td>
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<tr>
<td><em>Klebsiella oxytoca</em></td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
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<tr>
<td><em>Moraxella catarrhalis</em></td>
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<tr>
<td><em>Morganella morganii</em></td>
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<tr>
<td><em>Proteus mirabilis</em></td>
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<tr>
<td><em>Proteus vulgaris</em></td>
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<tr>
<td><em>Serratia marcescens</em></td>
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<tr>
<td>Anaerobes:</td>
<td></td>
</tr>
<tr>
<td><em>Bacteroides fragilis</em> and species in the <em>B. fragilis</em> Group*</td>
<td></td>
</tr>
<tr>
<td><em>Clostridium</em> species (excluding <em>C. difficile</em>)*</td>
<td></td>
</tr>
<tr>
<td><em>Eubacterium</em> species*</td>
<td></td>
</tr>
<tr>
<td><em>Fusobacterium</em> species*</td>
<td></td>
</tr>
<tr>
<td><em>Peptostreptococcus</em> species*</td>
<td></td>
</tr>
<tr>
<td><em>Porphyromonas asaccharolytica</em></td>
<td></td>
</tr>
<tr>
<td><em>Prevotella</em> species*</td>
<td></td>
</tr>
<tr>
<td>Resistant:</td>
<td></td>
</tr>
<tr>
<td>Gram-positive aerobes:</td>
<td></td>
</tr>
<tr>
<td><em>Corynebacterium jeikeium</em></td>
<td></td>
</tr>
<tr>
<td>Methicillin-resistant staphylococci (including <em>Staphylococcus aureus</em>)</td>
<td></td>
</tr>
<tr>
<td>Enterococci including <em>Enterococcus faecalis</em> and <em>Enterococcus faecium</em></td>
<td></td>
</tr>
<tr>
<td>Gram-negative aerobes:</td>
<td></td>
</tr>
<tr>
<td><em>Aeromonas</em> species</td>
<td></td>
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<tr>
<td><em>Acinetobacter</em> species</td>
<td></td>
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<tr>
<td><em>Burkholderia cepacia</em></td>
<td></td>
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<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td></td>
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<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td></td>
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<tr>
<td>Anaerobes:</td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus</em> species</td>
<td></td>
</tr>
<tr>
<td>Others:</td>
<td></td>
</tr>
<tr>
<td><em>Chlamydia</em> species</td>
<td></td>
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<tr>
<td><em>Mycoplasma</em> species</td>
<td></td>
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<tr>
<td><em>Rickettsia</em> species</td>
<td></td>
</tr>
<tr>
<td><em>Legionella</em> species</td>
<td></td>
</tr>
</tbody>
</table>

* Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.
† The efficacy of INVANZ in the treatment of community acquired pneumonia due to penicillin-resistant *Streptococcus pneumoniae* has not been established.

### 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 penicillinas, cephalosporinas and extended spectrum beta-lactamases, but not metallo-beta-lactamases.

The mechanism of action of ertapenem differs from that of other classes of antibiotics, such as quinolones, aminoglycosides, macrolides and tetracyclines. There is no target-based cross-resistance between ertapenem and these substances. However, micro-organisms may exhibit resistance to more than one class of antibacterial agents when the mechanism is, or includes, impermeability to some compounds and/or an efflux pump.

5.2 Pharmacokinetic properties

Plasma concentrations
Average plasma concentrations of ertapenem following a single 30-minute intravenous infusion of a 1 g dose in healthy young adults (25 to 45 years of age) were 155 micrograms/ml ($C_{max}$) at 0.5 hour postdose (end of infusion), 9 micrograms/ml at 12 hour postdose, and 1 microgram/ml at 24 hour postdose.

Area under the plasma concentration curve (AUC) of ertapenem increases nearly dose-proportionally over the 0.5 to 2 g dose range.

There is no accumulation of ertapenem following multiple intravenous doses ranging from 0.5 to 2 g daily.

Distribution
Ertapenem is highly bound to human plasma proteins. In healthy young adults (25 to 45 years of age), the protein binding of ertapenem decreases, as plasma concentrations increase, from approximately 95 % bound at an approximate plasma concentration of < 50 micrograms/ml to approximately 92 % bound at an approximate plasma concentration of 155 micrograms/ml (average concentration achieved at the end of infusion following 1 g intravenously).

The volume of distribution ($V_{dss}$) of ertapenem is approximately 8 litres.

Concentrations of ertapenem achieved in skin blister fluid at each sampling point on the third day of 1 g once daily intravenous doses showed a ratio of AUC in skin blister fluid: AUC in plasma of 0.61.

In-vitro studies indicate that the effect of ertapenem on the plasma protein binding of highly protein bound medicinal products (warfarin, ethinyl estradiol, and norethindrone) was small. The change in binding was < 12 % at peak plasma ertapenem concentration following a 1 g dose. 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. A clinically significant interaction due to ertapenem displacing another medicinal product or another medicinal product displacing ertapenem is unlikely.

In-vitro studies indicate that ertapenem does not inhibit P-glycoprotein-mediated transport of digoxin or vinblastine and that ertapenem is not a substrate for P-glycoprotein-mediated transport.

Metabolism
In healthy young adults (23 to 49 years of age), after intravenous infusion of radiolabelled 1 g ertapenem, the plasma radioactivity consists predominantly (94 %) of ertapenem. The major metabolite of ertapenem is the ring-opened derivative formed by dehydropeptidase-I-mediated hydrolysis of the beta-lactam ring.

In-vitro studies in human liver microsomes indicate that ertapenem does not inhibit metabolism mediated by any of the six major CYP isoforms: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4.

Elimination
Following administration of a 1 g radiolabelled intravenous dose of ertapenem to healthy young adults (23 to 49 years of age), approximately 80% is recovered in urine and 10% in faeces. Of the 80% recovered in urine, approximately 38% is excreted as unchanged ertapenem and approximately 37% as the ring-opened metabolite.

In healthy young adults (18 to 49 years of age) given a 1 g intravenous dose, the mean plasma half-life is approximately 4 hours. Average concentrations of ertapenem in urine exceed 984 micrograms/ml during the period 0 to 2 hours postdose and exceed 52 micrograms/ml during the period 12 to 24 hours post-administration.

Special Populations

Gender
The plasma concentrations of ertapenem are comparable in men and women.

Elderly
Plasma concentrations following a 1 g and 2 g intravenous dose of ertapenem are slightly higher (approximately 39% and 22%, respectively) in healthy elderly adults (≥ 65 years) relative to young adults (< 65 years). In the absence of advanced renal insufficiency, no dosage adjustment is necessary in elderly patients.

Paediatric Patients
The pharmacokinetics of ertapenem in patients under the age of 18 have not been established.

Hepatic Insufficiency
The pharmacokinetics of ertapenem in patients with hepatic insufficiency have not been established. Due to the limited extent of hepatic metabolism of ertapenem, its pharmacokinetics are not expected to be affected by hepatic impairment. Therefore, no dosage adjustment is recommended in patients with hepatic impairment.

Renal Insufficiency
Following a single 1 g intravenous dose of ertapenem, AUCs of total ertapenem (bound and unbound) and of unbound ertapenem are similar in patients with mild renal insufficiency (CLcr 60 to 90 ml/min/1.73 m²) compared with healthy subjects (ages 25 to 82 years). AUCs of total ertapenem and of unbound ertapenem are increased in patients with moderate renal insufficiency (CLcr 31 to 59 ml/min/1.73 m²) approximately 1.5-fold and 1.8-fold, respectively, compared with healthy subjects. AUCs of total ertapenem and of unbound ertapenem are increased in patients with advanced renal insufficiency (CLcr 5 to 30 ml/min/1.73 m²) approximately 2.6-fold and 3.4-fold, respectively, compared with healthy subjects. AUCs of total ertapenem and of unbound ertapenem are increased in patients who require haemodialysis approximately 2.9-fold and 6.0-fold, respectively, between dialysis sessions, compared with healthy subjects. Following a single 1 g intravenous dose given immediately prior to a haemodialysis session, approximately 30% of the dose is recovered in the dialysate.

There are inadequate data on the safety and efficacy of ertapenem in patients with advanced renal insufficiency and patients who require haemodialysis to support a dose recommendation. Therefore, ertapenem should not be used in these patients.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated-dose toxicity, genotoxicity and toxicity in reproduction. 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.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bicarbonate (E500).
Sodium hydroxide (E524) to adjust pH to 7.5
The sodium content is approximately 137 mg (approximately 6.0 mEq).

6.2 Incompatibilities

Do not use solvents or infusion fluids containing dextrose for reconstitution or administration of ertapenem sodium.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store at 2 to 8°C.

After reconstitution:

Reconstituted solutions and solutions for infusion: reconstituted solutions should be diluted in sodium chloride 9 mg/ml (0.9 %) solution immediately after preparation (see section 6.6 Instructions for use and handling). Diluted solutions should be used immediately. If not used immediately, in use storage times are the responsibility of the user. Diluted solutions (approximately 20 mg/ml ertapenem) are physically and chemically stable for 6 hours at room temperature (25°C) or for 24 hours at 2 to 8°C (in a refrigerator). Solutions should be used within 4 hours of their removal from the refrigerator.

Do not freeze solutions of INVANZ.

6.5 Nature and contents of container

One vial (20 ml Type I glass vials with a grey butyl stopper and a white plastic cap on a coloured aluminium band seal).

6.6 Instructions for use and handling

For single use only.

Preparation for intravenous administration:

INVANZ must be reconstituted and then diluted prior to administration.

1. Reconstitute the contents of a 1 g vial of INVANZ with 10 ml of water for injection or sodium chloride 9 mg/ml (0.9 %) solution to yield a reconstituted solution of approximately 100 mg/ml. Shake well to dissolve. (See section 6.4 Special precautions for storage, After reconstitution.)

2. For a 1 g dose, immediately transfer contents of the reconstituted vial to 50 ml of sodium chloride 9 mg/ml (0.9 %) solution and infuse over a period of 30 minutes.

Compatibility of INVANZ with intravenous solutions containing heparin sodium and potassium chloride has been demonstrated.
The reconstituted solutions should be inspected visually for particulate matter and discolouration prior to administration, whenever the container permits. Solutions of INVANZ range from colourless to pale yellow. Variations of colour within this range do not affect potency.

Any unused solution should be discarded.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Laboratoire Merck Sharp & Dohme – Chibret (Mirabel), Route de Marsat
F-63963 Clermont-Ferrand Cedex 9, France

B CONDITIONS OF THE MARKETING AUTHORISATION

- CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription

- OTHER CONDITIONS

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

**OUTER CARTON**

1. **NAME OF THE MEDICINAL PRODUCT**
   
   INVANZ 1 g Powder for concentrate for solution for infusion
   Ertapenem

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   
   Each vial contains: 1.0 g ertapenem equivalent to 1.046 g ertapenem sodium.

3. **LIST OF EXCIPIENTS**
   
   Sodium bicarbonate (E500); sodium hydroxide (E524) to adjust pH to 7.5.

4. **PHARMACEUTICAL FORM AND CONTENTS**
   
   1 vial

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   
   Read the package leaflet before use.
   Intravenous use after reconstitution and dilution.
   For single use only.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   
   EXP

9. **SPECIAL STORAGE CONDITIONS**
   
   Store at 2°C – 8°C.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

INVANZ 1 g Powder for concentrate for solution for infusion
Ertapenem
Intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
For single use only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
B. PACKAGE LEAFLET
1. **What is INVANZ?**

INVANZ is an injectable antibiotic which will always be prepared and given to you by a doctor or another healthcare professional.

INVANZ is a sterile, white to off-white, freeze-dried powder. The active ingredient of INVANZ is ertapenem. The other ingredients are: sodium bicarbonate (E500) and sodium hydroxide (E524).

INVANZ 1 g powder for concentrate for solution for infusion is supplied in a vial.

2. **What is INVANZ used for?**

INVANZ contains ertapenem which is an antibiotic of the beta-lactam group. It has the ability to kill a wide range of bacteria (germs) that cause infections in various parts of the body.

Your doctor has prescribed INVANZ because you have one (or more) of the following types of infection:

- Infection in the abdomen
- Infection affecting the lungs (pneumonia)
- Gynaecological infections.

3. **Before you are given INVANZ**

**Which patients should not be given INVANZ?**

You should not be given INVANZ if you are allergic to:

- The active substance (ertapenem) or any of the other ingredients of INVANZ
- Antibiotics such as penicillins, cephalosporins or carbapenems.

**What are the appropriate precautions for use?**

Tell your doctor about any medical condition you have or have had including:

- Kidney disease (see Patients with kidney disease)
- Allergies to any medicines, including antibiotics
- Colitis or any other gastrointestinal disease.
Using INVANZ with other medicines

Always tell your doctor about all medicines that you are taking or plan to take, including those obtained without a prescription.

Patients with kidney disease

It is particularly important that your doctor knows if you have kidney disease and whether you undergo dialysis treatment.

Children and adolescents

INVANZ is not recommended in children and adolescents, because there is no experience with the use of INVANZ in patients under 18 years of age.

Elderly

INVANZ works well and is well tolerated by most older and younger adult patients. The recommended dosage of INVANZ can be administered without regard to age.

Pregnancy

It is important that you tell your doctor if you are pregnant or are planning to become pregnant before receiving INVANZ. INVANZ has not been studied in pregnant women. INVANZ should not be used during pregnancy unless your doctor decides the potential benefit justifies the potential risk to the foetus.

Breast-feeding

It is important that you tell your doctor if you are breast-feeding or if you intend to breast-feed before receiving INVANZ. Women who are receiving INVANZ should not breast-feed, because it has been found in human milk and the breast-fed baby may therefore be affected.

Driving and operating machinery

Don’t drive or operate machinery until you know how you react to the medicine. Certain side effects, such as dizziness and sleepiness, have been reported with INVANZ, which may affect some patients’ ability to drive or operate machinery.

4. How is INVANZ given?

INVANZ will always be prepared and given to you by a doctor or another healthcare professional.

INVANZ is given intravenously (into a vein).

The normal dose of INVANZ is 1 gram (g) given once a day. Your doctor will decide how many days’ treatment you need.

It is very important that you continue to receive INVANZ for as long as your doctor prescribes it.

If you receive more INVANZ than you should:

If you are concerned that you may have been given too much INVANZ, contact your doctor or another healthcare professional immediately.
If you miss a dose of INVANZ:

If you are concerned that you may have missed a dose, contact your doctor or another healthcare professional immediately.

5. What undesirable effects may INVANZ have?

Any medicine may have unintended or undesirable side effects. The most common side effects are:
- Headache
- Diarrhoea, nausea, vomiting
- Rash, itching
- Problems with the vein into which the medicine is given (including inflammation, formation of a lump, swelling at the injection site, or leaking of fluid into the tissue and skin around the injection site).

Less common side effects are:
- Dizziness, sleepiness, sleeplessness, confusion, seizure
- Low blood pressure
- Shortness of breath, sore throat
- Constipation, yeast infection of the mouth, antibiotic-associated diarrhoea, acid regurgitation, dry mouth, indigestion, loss of appetite
- Skin redness
- Vaginal discharge and irritation
- Abdominal pain, fatigue, fungal infection, fever, oedema/swelling, chest pain, abnormal taste.

Side effects reported rarely are:
- Decrease in white blood cells, decrease in blood platelet count
- Low blood sugar
- Agitation, anxiety, depression, tremor
- Irregular heart rate, increased blood pressure, bleeding, fast heart rate
- Nasal congestion, cough, bleeding from the nose, pneumonia, abnormal breathing sounds, wheezing
- Inflammation of the gall bladder, difficulty in swallowing, faecal incontinence, jaundice, liver disorder
- Inflammation of the skin, fungal infection of the skin, skin peeling, infection of the wound after an operation
- Muscle cramp, shoulder pain
- Urinary tract infection, kidney impairment
- Miscarriage, genital bleeding
- Allergy, feeling unwell, pelvic peritonitis, changes to the white part of the eye, fainting.

There have also been reports of changes in some laboratory blood tests.

Tell your doctor, pharmacist or other healthcare professional immediately about these or any other unusual symptoms.

6. How should INVANZ be stored?

Keep out of the reach and sight of children.

Store at 2 to 8°C.

Do not use this medicine after the expiry date stated on the container.
The first 2 numbers indicate the month; the next 4 numbers indicate the year.

**Further information**

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The following information is intended for medical or healthcare professionals only:

Instructions of how to reconstitute and dilute INVANZ:

For single use only.

**Preparation for intravenous administration:**

**INVANZ must be reconstituted and then diluted prior to administration.**

1. Reconstitute the contents of a 1 g vial of INVANZ with 10 ml of water for injection or sodium chloride 9 mg/ml (0.9 %) solution to yield a reconstituted solution of approximately 100 mg/ml. Shake well to dissolve.

2. For a 1 g dose, immediately transfer contents of the reconstituted vial to 50 ml of sodium chloride 9 mg/ml (0.9 %) solution and infuse over a period of 30 minutes.

The reconstituted solution should be diluted in sodium chloride 9 mg/ml (0.9 %) solution immediately after preparation. Diluted solutions should be used immediately. If not used immediately, in use storage times are the responsibility of the user. Diluted solutions (approximately 20 mg/ml ertapenem) are physically and chemically stable for 6 hours at room temperature (25°C) or for 24 hours at 2 to 8°C (in a refrigerator). Solutions should be used within 4 hours of their removal from the refrigerator. Do not freeze the reconstituted solutions.

The reconstituted solutions should be inspected visually for particulate matter and disccolouration prior to administration, whenever the container permits. Solutions of INVANZ range from colourless to pale yellow. Variations of colour within this range do not affect potency.

Any unused solution should be discarded.