SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Invanz. For information on changes after approval please refer to module 8.

1. Introduction

Invanz contains 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*.

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. As imipenem is very susceptible to hydrolysis by human dehydropeptidase-1 (DHP-1), it must be given with cilastatin, an inhibitor of human DHP-1, in order to achieve clinically useful plasma levels for an appropriate period. Meropenem and ertapenem are much more stable to DHP-1 due to the insertion of a 1-β-methyl group on the penem ring and therefore they do not have to be co-administered with a DHP-1 inhibitor.

Invanz has been developed as a once-daily parenteral product. It is presented as a sterile lyophilised powder containing 1.046 g ertapenem sodium, equivalent to 1 g ertapenem.

At the recommended dosage recommendation [1 g daily administered intravenously over a period of 30 minutes for 3 to 14 days depending on the type and severity of infection and causative pathogen(s)] ertapenem is indicated for the 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:

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

2. Chemical, pharmaceutical and biological aspects

Composition

Invanz is a sterile lyophilised powder formulation of ertapenem sodium. Each vial contains 1.046 g ertapenem sodium, equivalent to 1 g ertapenem. The formulation also contains sodium bicarbonate and sodium hydroxide as stabilisers for the active substance.

For intravenous infusion use, the product is reconstituted with 10 ml water for injections or sodium chloride 0.9 % solution for injection (to yield a reconstituted solution of approximately 100 mg/ml), immediately followed by dilution to about 20 mg/ml ertapenem with sodium chloride 0.9% injection (See Summary of Product Characteristics section 6.6).
TSE risk assessments have been conducted in respect of materials used in the production of Invanz and these demonstrate compliance with current guidelines.

The primary container comprises a colourless 20 ml PhEur Type I glass vial with grey butyl rubber stopper (PhEur Type I) and aluminium overseal with integral plastic cap.

Active substance

The development of the active substance synthesis was well described. Ertapenem is a weakly crystalline powder containing 15.5 – 19 % water. Proof of its structure has been provided by means of UV, IR, NMR (^{1}H & ^{13}C) and MS.

Satisfactory control specifications and associated method validations have been demonstrated for the starting materials and key intermediates, and spectroscopic studies support the structures proposed. Satisfactory specifications have also been provided for all reagents and solvents.
Ertapenem is synthesised as a single isomer. Appropriate control of the starting materials, in combination with the nature of the synthesis, ensures the production of a single isomer of ertapenem. Chiral identity is confirmed in the active substance specification by specific optical rotation. Evidence of reproducible manufacture at production scale (16 batches) has been provided and control limits for related substances have been justified in relation to batches used in pre-clinical and clinical studies. The main degradant is also the major hydrolysis metabolite *in vivo*. Satisfactory controls of residual solvents and catalysts are included in the specification and the absence of a test and limits for heavy metals has been justified.

The active substance specification includes tests for appearance and identity (IR, HPLC, presence of sodium, specific rotation) and tests and limits for assay, sodium, impurities (specified, unspecified and total), residual organic solvents, palladium, and water.

All methods in the specification have been satisfactorily described and validated. The reference standards have been adequately characterised. Batch analyses data confirm both compliance with the proposed specification and consistency between batches.

Ertapenem is unstable at ambient temperature and humidity and requires storage in moisture impermeable containers at -20°C over the retest period of 18 months.

In solution, degradation of ertapenem is very rapid outside a very narrow pH range. The instability of the active substance is evident in the reference and sample solutions used for the assay, but the maximum storage periods for the analysis of these samples have been justified.

Other ingredients

Sodium bicarbonate, sodium hydroxide and water for injections are the subject of PhEur monographs.

The glass vial and rubber stopper comply with appropriate pharmacopoeial standards.

Product development and finished product

The finished product is formulated as a lyophilised powder using sodium bicarbonate and control of pH to stabilise the active substance. A reversible carbon dioxide adduct is formed during product manufacture and reduces the degradation rate of the drug substance. Nevertheless a manufacturing overage (total 16 %) of active substance is required to compensate for degradation during manufacture (up to 6 %), for the non-withdrawable component following reconstitution (4 %), and for degradation during the "in-use" storage period (up to 4 %). The level of overage has been justified based on data from pilot and commercial scale manufacture and the data demonstrate that at any time during the shelf-life of the product, a patient will receive a dose within the acceptable range of label claim $\pm$ 10%.

Invanz is manufactured by aseptic filtration and filling into presterilised vials followed by lyophilisation. This method of production is justified by the thermolability of the active substance and full details of all the methods have been provided. In process testing of the solution is performed between the two 0.22µm filters to ensure that the pre-final filtration bioburden limit of 10cfu/100ml is routinely achieved. Process validation studies on three production-scale batches manufactured at the commercial manufacturing site demonstrated the product can be reproducibly manufactured at the proposed site and that the finished product specification is met.

The finished product specification is appropriate for control of this type of product.

The finished product specification includes tests for appearance and identity (NIR, HPLC) and tests and limits for completeness and clarity of solution, particulate matter (visible and sub-visible), assay, degradation products (specified, unspecified and total), content uniformity, pH, water content, endotoxins and sterility.

Acceptance limits for related substances have been justified in relation to process capability and batches used in pre-clinical safety studies. Degradants are a human metabolite, which comprises about 70 % of the total degradants, dimers and oxazinone. The limits for dimers, oxazinone and total impurities have all been justified by reference to pre-clinical safety studies. Analytical methods have been shown to be suitable for the product. Near infra-red (NIRS) methods of analysis have been justified for determination of identity of the active substance and water content in the finished product. 'Conventional' reference methods are also included in the specification for each of these controls.

The shelf-life tests limits differ from those used for release purposes, but all the differences are justified.

All methods have been satisfactorily described and validated.

Batch analyses data have been provided and these demonstrate both compliance with the proposed specification and consistency of manufacture.

Reconstitution of the product with water for injections or 0.9 % sodium chloride injection is rapid, so the omission from the finished product specification of a reconstitution test using these solvents is justified. No significant changes in reconstitution time were observed after storage of the product for up to 78 weeks.

Stability of the Product

Although significant degradation of ertapenem occurs on storage of the lyophilised product, following its reconstitution and "in-use" prior to administration to the patient, the degradation profile is documented and does not give rise to safety concerns. Degradation of ertapenem on storage is temperature dependent and is minimised by storage of the lyophilised product in a refrigerator (2-8°C). Under these conditions, there was very little change in potency of the active substance observed after 78 weeks storage at 5°C and little change in the content of related substances, with the small increase in total impurities being almost entirely accounted for by the ring-opened degradant. Refrigeration of the product minimises degradation. Invanz is not photolabile. The major degradant is also a human metabolite. The proposed shelf-life specification limits for assay and related substances have been justified in relation to product efficacy and safety. Long-term stability data on pilot batches have been reported up to 18 months storage in support of a product shelf-life of the same interval, when stored in a refrigerator.

The proposed in-use shelf-life, following reconstitution and dilution, is 6 hours at room temperature or 24 hours at 2 to 8°C (in a refrigerator), and this has been supported by appropriate data. It has been demonstrated that the product is incompatible with 5 % dextrose solutions and Section 6.2 of the SPC states that dextrose-containing solutions should not be used for preparation or administration of this product.

Compatibility of the reconstituted solutions with commonly used administration sets has been demonstrated.

3. Toxico-pharmacological aspects

Originally, ertapenem was developed using a non-lyophilised powder. In the early studies, ertapenem was either reconstituted with sodium bicarbonate and saline or blended with sodium bicarbonate and then reconstituted with saline. Subsequently it was determined that lyophilising the substance improved its stability. The lyophilised form was therefore used at latter stages of the non-clinical development. It was shown that both forms of ertapenem yielded the same chemical products, including degradates and impurities upon reconstitution.

Pharmacodynamics

Mechanism of action

Like other beta-lactam agents, the mechanism of action of ertapenem involves decreased synthesis of peptidoglycan by inhibition of specific penicillin-binding proteins (PBP). In competitive binding studies in *E. coli*, ertapenem displayed high affinity mainly for PBP2 and PBP3.

Antibacterial activity

The antibacterial activity of ertapenem has been extensively investigated both *in vitro* and *in vivo* with banked clinical isolates from all parts of the EU and many other countries. *In vitro* studies employed the methodologies of the National Committee for Clinical Laboratory Standards (NCCLS; MIC_{90} values defined by broth microdilution). In a study of susceptibility to ertapenem in the EU, 2854 recent clinical isolates of common pathogenic species (range 55-208 per species for those of most relevance) were tested by MIC determination for susceptibility to ertapenem and compared to other antibacterial agents (e.g cefepime, ceftriaxone, imipenem and piperacillin/tazobactam). The main features of the antibacterial activity of ertapenem are summarised below:

- Ertapenem showed activity against methicillin-susceptible *S. aureus* (MSSA), which were generally inhibited at 0.25 mg/l. Most other methicillin-susceptible staphylococci were inhibited at 2 mg/l. As expected, ertapenem was not active against methicillin-resistant staphylococci.
- *Streptococcus pyogenes* and *agalactiae* were inhibited by ≤ 0.06 mg/l whereas the MIC_{90} for *S. pneumoniae* (including penicillin-resistant (Pen-R) strains) was about 1 mg/l.
- Ertapenem was not active against the enterococci, *Corynebacterium jeikeium* or the lactobaccilli.
- *Haemophilus influenzae* and *Moraxella catarrhalis* were both very susceptible to ertapenem (MICs ≤ 0.06 mg/l).
- Ertapenem was very active *in vitro* against most enterobacteriaceae and other common gram-negative rods, but not against the non-fermenting aerobic species. For example, the MIC_{90} of ertapenem was 16 mg/l for *Acinetobacter spp.,* 16 mg/l for imipenem-susceptible *Pseudomonas aeruginosa* and 32 mg/l for imipenem-resistant strains. Ertapenem was not active against *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, or *Aeromonas spp*.
- Activity was generally good against important anaerobic species (*eg*. MIC_{90} of 1 mg/l for *Bacteroides fragilis*, and 0.125 mg/l for *Clostridium perfringens*). However, ertapenem was not active against *Bacteroides distasonis* or *Clostridium difficile*.

Ertapenem was efficacious in experimental infection models conducted in immuno-competent and immuno-deficient animals, including experimental septicemia with gram-positive and gram-negative pathogens and deep tissue infection models.

Pharmacokinetic/pharmacodynamic relationship

The antibacterial activity of ertapenem is time dependent, *i.e* the proportion of the dosing interval during which plasma concentrations exceed the MIC of the infecting organism (T> MIC) correlates with efficacy. Maximum activity against gram-negative bacilli, *S. aureus*, and *S. pneumoniae* respectively occurred when the total ertapenem concentration exceeded the MIC of the infecting organism for 34.5 %, 43 % and 24.2 % of the dosing interval.

Breakpoints

The MIC susceptibility testing breakpoints that were applied during clinical trials and that have been included in the Summary of Product Characteristics are: Susceptible ≤ 4 mg/l (except for streptococci where susceptibility was defined as ≤ 2 mg/l) and Resistant > 8 mg/l.

Resistance

As for all other beta-lactams, the possible mechanisms of resistance with ertapenem are:

- Bacterial production of beta-lactamase

The most common types of beta-lactamases, extended-spectrum beta-lactamases or the inducible AmpC-type enzymes that may be produced by bacterial pathogens, do not efficiently hydrolyse the carbapenems. For example, ertapenem was very active against wild-type organisms of species that have inducible chromosomally encoded *AmpC* enzymes (MICs ≤ 0.5 mg/l). Activity against stably-derepressed mutants was less, showing an upward shift in MIC range, MIC_{50} and MIC_{90} values but, for the most part, MICs were still ≤ 1 mg/l. There was no detectable increase in chromosomally-encoded AmpC beta-lactamase production by inducible strains on exposure to ertapenem and ertapenem did not exhibit significant inhibition of AmpC beta-lactamase *in vitro*.

However, ertapenem, like other carbapenems, may be hydrolysed by zinc-containing carbapenemases. For example, IMP-1, which may be chromosomal or plasmid-encoded, is a zinc-containing carbapenemase that has been found in some enterobacteria and in *P. aeruginosa*. Carbapenem resistance has also become a problem in *Acinetobacter baumannii*, in which a non-metallic enzyme (ARI-1) is sometimes the cause, with or without impermeability of the outer membrane to beta-lactam agents and/or changes in the PBPs. Other acquired carbapenemases (*eg*. IMI-1, NMC-A and Sme-1), which also appear to be non-metallic and to have a serine-based mechanism, have a greater effect on imipenem than meropenem, are located on the chromosome, and may be inhibited by clavulanic acid.

- Alteration in the penicillin-binding proteins

The carbapenems are less active against organisms that show reduced susceptibility or frank resistance to penicillins as a result of PBP changes (e.g penicillin-resistant *pneumococci*). However clinical resistance does not always result.

- Impermeability that prevents access of the compound to target sites.

This usually results from changes in porins in the outer membranes of gram-negative organisms that limit the penetration of the compound into the periplasmic space. Cross-resistance between ertapenem and non-beta lactam antibacterial agents may occur if the mechanism involves outer membrane impermeability to several types of molecules,

- efflux pumps that limit accumulation of the compound at the target sites.

Cross-resistance between ertapenem and non-beta lactam antibacterial agents may occur if the mechanism involves an efflux pump with affinity for a wide variety of antibacterial agents.

General and safety pharmacology programme

In a comprehensive programme of general pharmacodynamic studies, no relevant effects of ertapenem were reported. In particular there was no effect on the respiratory, gastro-intestinal and central nervous systems. In addition there was no effect on the ECG of cats receiving an intravenous dose 5-6 times the proposed clinical dose.

Pharmacokinetics

The pharmacokinetic profile of ertapenem was evaluated in species used in the toxicity studies (rats and monkeys). Ertapenem concentrations were measured using validated methods.

Oral absorption of ertapenem was very poor. Indeed, following an oral dose of 10 mg/kg, bioavailability of ertapenem was only about 3.5 %, confirming that the compound was not suitable for oral administration.

Absorption and distribution

The pharmacokinetic profile of ertapenem appeared to be species-dependent and was not linear. Following single intravenous administration of ertapenem (10 mg/kg), elimination of the parent compound was slow and the elimination dose-dependent.
The plasma clearance of ertapenem in rats was about 5.5 ml/min/kg based on the total plasma concentration, which is about 15 times higher than that in primates and humans. The blood clearance in all animal species studied was less than 15 % of hepatic blood flow.

Over a range of 10 to 180 mg/kg the AUC values increased less than dose proportional. A less than proportional increase in AUC was also observed in rats and monkeys after multiple IV administration. No dose accumulation was recorded.

Following intravenous administration of 15 mg/kg [^{14}C] ertapenem to rats, radioactivity was widely distributed, the highest concentrations being detected in the kidney, plasma, small intestine and liver. Radioactivity declined with time in all tissues. With the exception of the kidneys, radioactivity in tissues was less than 0.7 µg/g at 72 hour post-dose. Distribution volumes varied across species, ranging from 84 ml/kg in monkeys to 145 ml/kg in rats.

Ertapenem was extensively bound to rat, monkey and human plasma proteins. Only a small proportion of ertapenem remained unbound to plasma proteins in all species at very high concentrations of 2000 µg/ml (less than 7 %). The saturation of binding that occurred at very high doses was responsible for non-linear kinetics. In fact, as the dose increased, the fraction of unbound ertapenem in plasma available for elimination increased, resulting in a higher clearance value. Results from *in vitro* studies also revealed that the saturation of the plasma protein binding was not extensive at clinically-relevant concentrations (155 to 283 µg/ml) following administration of the recommended 1- to 3-g IV dose in humans. Thus, the degree of non linearity in human pharmacokinetics was expected to be much less significant. As predicted, the observed plasma clearance in humans increased only 23 % over the dose range of 1 to 3.

Following intravenous administration of 700 mg/kg/day of ertapenem to rats, ertapenem was also detected in foetal plasma and milk at 3 % and 7 % of maternal plasma concentration respectively.

Ertapenem was neither a substrate nor inhibitor of P-gP glycoprotein.

Metabolism and elimination

Following intravenous administration of [^{14}C] ertapenem, formation of the beta-lactam ring-open metabolite was the major metabolic pathway in rats, monkeys, and humans. The beta-lactam ring-open metabolite was detected in plasma and urine of all species and the total recovery of this metabolite in the urine of rats, monkeys, and humans was 32 %, 75 % and 37 % of the dose, respectively. In bile duct-cannulated rats, the beta-lactam ring-open metabolite was detected as the major radioactive component (about 8.2 % of the dose) in the bile. In addition, a polar metabolite, M1, tentatively identified as the amide hydrolysis product of the beta-lactam ring-open metabolite, was detected in the urine of rats (20 % of the dose), monkeys (8 % of the dose), and humans (<1 % of the dose).

The excretion was primarily via urine with very little as unchanged parent compound except for the rats in which faecal excretion accounted for 22 % of a radioactive dose. The highest proportion of parent compound (given as radioactive dose) detected in urine occurred in humans (37.5 %).

The conversion of ertapenem to the beta-lactam ring-open metabolite in rats was catalyzed by DHP-I in the lung and kidney, two organs that in rodents are known to contain high levels of DHP-1. Ertapenem did not interact in any manner with the cytochrome P450 system.
Co-administration of cilastatin with ertapenem to rats reduced the plasma clearance of ertapenem by 6-fold. Urinary excretion of the unchanged drug increased from 9 to 36 % of the dose, and was accompanied by a decrease in the urinary recovery of the beta-lactam ring-open metabolitefrom 31 to 9 % of the dose.

The $t_{1/2}$ was much longer in primates (326 min in monkeys) than in rodents (37 min in rats). Since rodents are known to have higher non-renal DHP-1 activities, it is expected that the clearance in humans would be most likely closer to that in primates. The observed human clearance is very similar to that in the monkey and chimpanzee.

Toxicology

The toxicological profile of ertapenem was evaluated in rats, mice, monkeys and rabbits. Based on the pharmacokinetic data, species were considered relevant, with primate being the preclinical species closest to humans. Studies were conducted according to Good Laboratory Practices. Ertapenem was administered via intravenous bolus. This was considered acceptable and since greater exposure would not be achieved by intramuscular dosing, further studies using that route were not warranted.

Single dose toxicity
There was little potential for acute toxicity with LD_{50} values in rodents > 700 mg/kg following intravenous administration and ≥ 500 mg/kg in mice after oral administration.
In an exploratory study in rabbits, single intravenous doses of ertapenem as high as 500 mg/kg did not lead to any functional renal impairment or any histomorphologic changes in the kidney and therefore ertapenem was considered less nephrotoxic than 150 mg/kg imipenem, the positive control. In an additional study in rabbits, ertapenem was not considered nephrotoxic based on the lack of treatment-related changes after administration of a single intravenous dose of 225 mg/kg of ertapenem.

Repeat dose toxicity
Repeated dose toxicity studies were carried out in rats (up to 27 weeks), rabbits (up to 2 weeks) and monkeys (up to 27 weeks). No-treatment related mortality was reported in any of the studies.
The major findings were:
- decreased neutrophil count (up to 50 % reduction in percentage or number) in rats
- irritation at the injection site in rats
- increases in serum ALT concentration in rabbits and monkeys.

Decrease in neutrophil count was not associated with any changes in the bone marrow and was reversible after interruption of ertapenem treatment. The mechanism of this species-specific reversible effect is unknown but was considered unlikely to be of clinical relevance.
There was an increase in the incidence of overall damage at the injection sites of female rats who received 675 mg/kg/day for around 14 weeks (characterised by slight to marked fibrosis, haemorrhage and inflammation at those sites) and the slight increase in serum ALT concentration unaccompanied by histopathological changes were reported in rabbits (60 mg/kg/day for 5 weeks and monkeys (≥ 30 mg/kg/day for 5 weeks). These effects were not considered to be of clinical relevance. This was supported by the clinical studies where the incidence of increased ALT was similar to that of the comparator (5.5 %).
Kidney histopathological changes were also reported in monkeys in the 5-week study at the high doses ≥ 500 mg/kg/day (tubular cytoplasmic rarefaction and vacuolation of cortical tubular epithelial cells) and in the 27 week-study at all doses (40, 120 and 360 mg/kg/day characterised by tubular cytoplasmic rarefaction and luminal eosinophilic granularity). The changes were considered adaptive not degenerative and occurred at high doses and/or after long treatment period. No microscopic alterations of kidneys were observed in rabbits in the exploratory study above referred. In addition since no clinical findings indicative of nephrotoxicity were reported, these were considered of no clinical relevance.

The safety margins of about 10-fold for rat and about 15-fold for monkeys were reached based on Cmax comparison, and about 1-fold for rat and about 6-fold for monkeys based on AUC comparison. It was not feasible to administer higher doses in rats because of irritation of the injection sites and instability of the compound at higher concentrations. Although these did not attain many multiples over expected clinical levels, they were considered acceptable to support the safety of ertapenem administration to patients at the therapeutic doses.

Infant monkeys receiving intravenous doses of ertapenem for up to 5 weeks (60 or 180 mg/kg/day) did not show any major treatment related effects.

Genotoxicity

In a battery of *in vitro* and *in vivo* genetoxicity studies, ertapenem was neither genotoxic nor mutagenic. These studies also gave reassurance on the lack of genotoxicity of the beta-lactam ring-open metabolite.

Carcinogenicity

No carcinogenicity studies have been conducted with ertapenem in view of the expected short duration of treatment. This is consistent with the current international guidelines on carcinogenicity testing.

Reproduction toxicity

Reproduction toxicity studies were conducted in rats and mice. Mice were used as an alternative species to rabbits to evaluate the developmental toxicity of ertapenem. The reason for using this alternative species is based on the excessive toxicity of ertapenem at relatively low doses in rabbits due to sensitivity to antibiotics.

There was no effect on fertility of either female or male rats at doses up to 700 mg/kg/day. The no-effect level for maternal and developmental toxicity was > 700 mg/kg/day in rats. In mice, slight decrease in average foetal weight and an associated decrease in the number of ossified sacrocaudal vertebrae were reported in the 700 mg/kg/day group but no effect on embryo survival or foetal morphology was reported. The no-effect level for maternal toxicity was therefore > 700 mg/kg/day and for developmental toxicity equivalent to 350 mg/kg/day in mice.

Intravenous irritation at the injection site and the instability of ertapenem at high concentrations limited the ability to administer higher doses and therefore systemic exposure were below or similar to those expected to be reached in humans. However studies on structurally related compounds did not give any indication of potential developmental toxicity.

Ertapenem crossed the placenta and was excreted into milk of lactating rats.

Local tolerance

In local tolerance studies, ertapenem exhibited little potential for irritancy. In particular, in intramuscular irritancy in rabbits, the only adverse finding was a moderate degree of muscle necrosis and a slight to moderate degree of cellular infiltration one week after injection. This reaction had almost resolved after a further week.

Other toxicity

In a special toxicity study involving intracisternal administration of ertapenem to rats, it was shown that ertapenem had 5-10 times less convulsant potential than the comparator imipenem. The ED50 for induction of convulsion was 133 µg/ml (93-193 µg/ml). Ertapenem did not show any haemolytic potential.

Ecotoxicity/Environmental risk assessment

An assessment of the environmental risk was did not reveal any potential risk to the environment related to the use of ertapenem.

4. Clinical aspects

Clinical pharmacology

Pharmacodynamics

The main features of the antibacterial activity of ertapenem have been described in section 3.3 above.

Microbiological data were obtained from organisms isolated from patients treated during the phase II and phase III trials and were compared with clinical and microbiological outcomes in the microbiologically evaluable populations.

- Aerobic pathogens

The only species for which MICs of ertapenem exceeded 4 mg/l for some isolates were *E. faecalis* and *E. faecium*, *P. aeruginosa*, *S. aureus* and *S. epidermidis*. The analysis of outcomes by MIC suggested that the infections due to the 17 organisms inhibited at 16 mg/l or more were much less likely to respond clinically or microbiologically to therapy. As already indicated MRSA, MRSE, enterococci and *Pseudomonas spp*. are designated as resistant to ertapenem.
From studies 018 and 020 in CAP, there were 23 pneumococci inhibited at 0.1 mg/l penicillin or more that were treated with ertapenem and 21 that were treated with ceftriaxone. However, 20 and 18 of these were inhibited at < 2 mg/l penicillin, and all were inhibited at 4 mg/l ertapenem (all but one inhibited at 1 mg/l or less). These few data suggest that ertapenem might be efficacious against such pneumococci (most of which were treated at 1 g daily), but there are too few penicillin-resistant strains treated to draw a firm conclusion.

- Anaerobic pathogens

The only species for which MICs of ertapenem exceeded 4 mg/l for some isolates were anaerobic cocci (unspecified), *B. fragilis* and *B. fragilis* group, and *Bilophila wardsworthia*. With so few organisms inhibited at 2 mg/l or more, no assessment of efficacy against less susceptible anaerobes (MIC 4 mg/l or more) could be made. *B. fragilis* and *B. fragilis* group were considered susceptible based on the MIC_{90} of 1 mg/l of these organisms.

Pharmacokinetics

The pharmacokinetic profile of ertapenem was evaluated in healthy volunteers from both sexes, in the elderly and patients with renal impairment, following single and multiple intravenous doses of ertapenem. Ertapenem was measured using validated methods. There was also a limited evaluation of the pharmacokinetics of ertapenem following intramuscular route.

Absorption and distribution

Mean Cmax ertapenem following a single 30-minute intravenous infusion of a 1 g dose in healthy young adults was 155 mg/l at 0.5 hour post-dose (end of infusion), 9 mg/l at 12 hour post-dose, and 1 mg/ml at 24 hours post-dose.
Single and multiple dose studies indicated that total ertapenem AUCs were slightly lower than would be predicted as the dose is increased (0.5 to 2 g), but unbound ertapenem concentrations were higher than expected. Following multiple doses, there was no evidence of any drug accumulation between days 1 and 8 on dosing at up to 3 g/day.

After single intravenous doses of 1 g over 30 minutes in males and females, mean AUCs for total and unbound drug were not significantly different between gender, with or without weight as a covariate in females. The 12 h mean plasma concentration of total ertapenem after 1 g was 8.3 mg/l in females and 12.1 mg/l in males.

In the elderly, exposure to both total (about 1.3:1) and unbound ertapenem (about 1.7:1) was higher than in younger subjects. In the elderly, 12 hour mean plasma concentrations after 1 g dose were

1 mg/l for unbound and 18 mg/l for total ertapenem. The time during which plasma levels exceeded 1 mg/l in the elderly was about 50 % of the dosing interval. After multiple dosing at 1 g/day for 7 days in young or elderly subjects, plasma concentrations of total and unbound ertapenem were slightly lower on day 7 than on day 1.

After intramuscular doses, Cmax was slightly lower but exposure to total drug was similar and the bioavailability of drug following IM injection was 92 %. A comparison of time during which plasma levels of total drug exceeded 4 mg/l showed that this was 18 h after IM dosing and 17 h after IV dosing as a 30-minute infusion. Multiple IM dosing at 1 g/day showed no significant changes in pharmacokinetic parameters between days 1 and 7, although AUC was slightly lower on day 7.

The volume of distribution was estimated between 7-9 l in males and females. Distribution into skin suction blister fluid showed that AUC on the third dosing day was about 60 % of that in plasma, but the 24 h concentration was higher in blister fluid, with a ratio of about 4:1. The lack of data on the distribution of ertapenem in the lung and respiratory secretions was considered acceptable in view of the results from the two large clinical studies in community-acquired pneumonia. Ertapenem was neither a substrate nor an inhibitor of human MDR1 P-glycoprotein.

In vitro, ertapenem was highly bound to plasma proteins (94-95 %). The binding was found to be saturable but increases in free fraction became apparent only when total ertapenem concentrations exceeded 150 mg/l, which is approximately the Cmax obtained at the end of a 30 minute intravenous infusion of 1 g ertapenem. Ertapenem appears to bind to albumin, with more than one binding site identified.

Ertapenem is excreted into human milk. Ertapenem concentration in the milk was < 0.4 mg/l within 24 h of a dose, but the maximal drug concentration in milk is unknown. As recommended in the Summary of Product Characteristics, ertapenem should not be used in women who breast-feed.

Metabolism and excretion

A study with ^{14}C-labelled ertapenem administered at the single dose of 1 g showed that radioactivity mirrored total ertapenem concentrations as determined by HPLC. In this study, cumulative recovery of dose administrated in urine and faeces was 90 % over 168 h. The majority of the radioactivity was recovered during the initial 24 hour post-dose, predominantly in urine (81 %), 9 % being recovered from the faeces, indicating that a small portion of the dose was eliminated by biliary or intestinal secretion.
In the urine, unchanged ertapenem accounted for 38 % of the dose administered and 37 % appeared as the beta-lactam ring-open metabolite. Each of the other six components detected accounted for less than 1% of the administered dose. The conversion to the open ring form in man has been ascribed to DHP-1, and appears to occur very predominantly in the renal tissues. There was no evidence *in vivo* that microbiologically active metabolites might be present in either plasma or urine. Ertapenem was neither a substrate nor an inhibitor of CYP 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4.

Renal clearance of ertapenem was slightly higher in females, with plasma elimination half-life for total ertapenem equivalent to 4.6 h in males and 3.6 h in females. Renal excretion of intact ertapenem as a percent of dose was about one-third higher in females, while $t_{1/2}$ for total ertapenem was shorter in females (3.5 h *vs* 4.2 h after 1 g doses). Renal clearance of total (ratio 0.7:1) and unbound (ratio 0.55:1) ertapenem was lower in the elderly, as was non-renal clearance (approximately 0.9:1 and 0.7:1, respectively). The $t_{1/2}$ for total ertapenem was about 5 h in the elderly and about 4 h in younger subjects.

Special populations

The pharmacokinetic profile of ertapenem has not yet been evaluated in children.

In a study involving subjects with CrCl 60-90 ml/min/1.73 m^2 (mild impairment), 31-59 ml/min/1.73 m^2 (moderate impairment), 5-30 ml/min/1.73 m^2 (advanced impairment), or <

10 ml/min/1.73 m^2 (end-stage and on haemodialysis), AUCs for total and unbound fractions increased with decreasing renal function. Compared with data from healthy young and elderly subjects, AUCs for total ertapenem were more than 2.5-fold higher, and for the unbound fraction more than 3-fold higher, in patients with advanced or end-stage disease. This finding correlated with decreasing renal clearance and prolonged $t_{1/2}$ as CrCl decreased. In those with moderate impairment of renal function, exposure increased 1.5-fold for total and 1.8-fold for unbound ertapenem, with decrease in renal clearance to 60 %. In the subgroup on haemodialysis, dosing occurred on a non-dialysis day and 4 h before haemodialysis. Haemodialysis increased the apparent plasma clearance of total drug by 1.3-fold.
Based on these data, no dosage recommendation is warranted in patients with mild and moderate renal impairment. In patients with advanced renal insufficiency or on haemodialysis, the SPC recommends that ertapenem should not be used due to the lack of safety and efficacy data to support a dosage recommendation.

The pharmacokinetic profile of ertapenem has not been evaluated in patients with hepatic impairment. Considering that the hepatic metabolism of ertapenem is limited, it is not expected that pharmacokinetic parameters will be affected in these patients.

Interaction studies
Data from *in vitro* studies were provided to describe the potential for ertapenem to displace highly protein bound substances. When ertapenem (12-190 mg/l) was added to radiolabelled warfarin (1.5 mg/l) in human plasma, the unbound fraction of warfarin reached 2.7 % compared with 2.5 % in the absence of ertapenem. Ertapenem (at Cmax) had therefore no effect on the protein binding of warfarin.
With ethinyloestradiol, the mean unbound proportion was 2.9 % in the absence of ertapenem, increasing to a maximum of 3.2 % with ertapenem concentrations of 200 mg/l. Similarly, the mean unbound proportion of norethindrine was 4.7 % in the absence of ertapenem, increasing to 5 mg/ml with ertapenem concentrations of 200 mg/l.
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 91 % to 87 %.
Overall a clinically significant interaction with ertapenem (displacement of an other substance and *vice versa*) is unlikely to occur.
Interactions caused by inhibition of P-gP or CYP mediated clearance of substances are unlikely.
No interaction study between valproic acid and ertapenem has been carried out, however since carbapenems are known to decrease serum levels of valproic acid, monitoring of serum levels should be considered when co-administered with ertapenem as recommended in the SPC.

Clinical efficacy

Dose-response studies and main clinical studies

The clinical programme of ertapenem aimed to demonstrate the efficacy of ertapenem in the treatment of adult patients infected with the following infections:

- Community-acquired pneumonia (CAP) (studies 002 and 008 combined 018 and 020)
- Intra-abdominal infections (IAI) (studies 004 and 017)
- Acute gynaecological infections (study 023)
- Skin and soft tissue infections (SST) (studies 003 and 016)
- Urinary tract infections (UTI) (studies 007, 014 and 021)

All these studies were conducted in accordance with agreed International Ethical principles and Good Clinical practices standards.

Over 3000 patients were included in the main and supportive studies, of whom over 1000 received ertapenem.

The summary of the ertapenem phase II and III trials is displayed in table 1.

Table 1: Summary of Ertapenem Phase II to III Clinical Development Programme

Protocol	Pivotal/ Supportive	Study Regimens				Oral switch?	IM Therapy?	Primary Analysis	
		Ertapenem	N (n)	Comparator	N (n)			Evaluable-Population	Primary Analysis Response
Complicated Intra-Abdominal Infection									
004	IIa	1 g q.d. 1.5 g q.d.	59 (31) 51 (29)	CRO 2 g q.d.[†]	110 (72)	Yes	No	Clinical and Microbiologic	Clinical and microbiologic
017	Pivotal	1 g q.d.[‡] 1.5 g q.d.[‡]	323 (203) 14 (7)	P/T 3.375 g q6h[‡]	328 (207)	No	No	Clinical and Microbiologic	Clinical and microbiologic
Acute Gynaecological Infection									
023	Pivotal	1 g q.d.[‡]	216 (163)	P/T 3.375 g q6h[‡]	196 (153)	No	No	Clinical	Clinical response
Community-Acquired Pneumonia									
002/008[¶]	IIa	1 g q.d. 2 g q.d.	28 (16) 30 (24)	CRO 2 g q.d.	27 (19)	Yes	No	Clinical	Clinical response
018	Pivotal	1 g q.d.[§]	244 (182)	CRO 1 g q.d.[§]	258 (201)	Yes	Yes	Clinical	Clinical response
020	Supportive	1 g q.d.[§]	239 (100)	CRO 1 g q.d.[§]	125 (49)	Yes	Yes	Microbiologic	Clinical response
Skin And Skin Structure Infection									
003[%]	IIa	1 g q.d.	15 (7)	CRO 2 g q.d.	11 (5)	Yes	No	Clinical	Clinical response
016	Pivotal	1 g q.d	274 (185)	P/T 3.375 g q6h	266 (174)	No	No	Clinical	Clinical response
Urinary Tract Infection									
007[%]	IIa	1 g q.d.	19 (12)	CRO 1 g q.d.	14 (9)	Yes	No	Microbiologic	Microbiologic response
014	Pivotal	1 g q.d.	298 (159)	CRO 1 g q.d.	294 (171)	Yes	No	Microbiologic	Microbiologic response
021	Supportive	1 g q.d.	175 (97)	CRO 1 g q.d.	83 (53)	Yes	Yes	Microbiologic	Microbiologic response
	Totals	1 g q.d. 1.5 g q.d. 2 g q.d.	1890 (1155) 65 (36) 30 (24)	CRO 1 g q.d. CRO 2 g q.d. P/T 3.375 g q6h	774 (483) 148 (96) 790 (534)				

[†] Patients on CRO also received blinded metronidazole therapy for anaerobic coverage.

[‡] Patients could have received optional open vancomycin therapy for resistant gram-positive infections.

[§] For patients with documented penicillin-resistant *S. pneumoniae* pneumonia and inadequate clinical response, the dose of ETP or CRO could have been increased to 2 g q.d. in a blinded fashion.

[%] Protocol 007 was a study of uncomplicated upper urinary tract infection; Protocol 003 was a study of uncomplicated skin and skin structure infection.

[¶] Protocols 002 and 008 were studies of lower respiratory tract infection, including acute exacerbation of chronic bronchitis, and are reported in a single study report.

CRO, ceftriaxone; IIa, Phase IIa study; P/T, piperacillin/tazobactam; TOC, test-of-cure

N, number of patients randomized to each regimen; n, number of patients in primary analysis evaluable-population.

Dose rational

The dose of ertapenem was selected according to the PK/PD relationship and the phase II clinical studies.

The rational for an ertapenem 1 g once daily dosage regimen was based on the observation that T>MIC is the critical pharmacodynamic parameter that correlates with efficacy. As already indicated in section 3.3 of this document, it was suggested that the time above MIC for free drug needed to be between 20 % and 40 % of the dosing interval, depending on the bacterial species. It was calculated that this might be achieved with 1 g every 24 h provided that the MICs were no higher than 1-4 mg/l.

Main clinical studies

All main studies were multi-centre, randomised and double blind trials in which ertapenem was administered intravenously at the dose of 1 g daily; a small subset of patients received 1 g ertapenem administered intramuscularly daily as an option in some studies.
The comparative agent was ceftriaxone 1 g IV once daily in the CAP Phase III studies.
The comparative agent was IV piperacillin/tazobactam in IAI and gynaecological infections studies. Although the dose studied was different to the most commonly approved regimen in EU (3 g piperacillin: 375 mg tazobactam given every 6 h versus 4 g piperacillin: 500 mg tazobactam every 8 hours), the applicant provided an acceptable justification based on pharmacokinetic and pharmacodynamic considerations for the comparative dosage regimens.

A switch to oral therapy after a minimum of three days of ertapenem or the comparative agent by the parenteral route was allowed when protocol-defined criteria had been met (temperature and other clinical findings). Follow-on therapy was to complete a maximum total number of days treatment (IV plus oral) as follows: in CAP studies (10-14 days) switch to amoxycillin/clavulanate; in UTI trials (up to 14 days) switch to ciprofloxacin. There was no switch in the study in gynaecological infections or the main studies in SSTIs and IAIs.

Population

All protocols planned to enrol patients of 18 years of age or older (16 years or older in the acute pelvic infection study). In Phase III trials, there was a general exclusion of those patients with < 500 neutrophils mm^3, with > 6 x upper the normal limit (ULN) ALT or AST, > 3 x ULN ALP or bilirubin. Limits were also set on haemoglobin (minimum 8g/dl) and platelets (50,000 mm^3) and on CD4 cell counts in HIV positive patients.
Patients who had received > 24 h of a potentially effective antimicrobial agent before study entry (sometimes specified as within 72 h) were excluded, unless failing.
Patients found to have treatment-resistant pathogens or no pathogens were not necessarily removed from Phase III studies unless failing. Diagnostic criteria are presented in table 2.

Table 2: Diagnostic Criteria

Diagnosis	Entry criteria
CAP	Men and women > 18 years Clinical signs + new infiltrate on chest X-ray within 48 hours of study entry in patients hospitalised or nursed in other health care facilities for < 48 hours Sputum purulence defined as > 25 leucocytes and < 10 epithelial cells per 1pf Patients required to have initial hospitalisation but not assisted ventilation
IAI	Men and women > 18 years evidence of peritoneal infection (*i.e.* infection extending beyond the wall of a hollow organ), including established abscesses. Upper gastrointestinal organ perforation was allowed if there was a delay of at least 24 h before surgery. Appendicitis had to be complicated by peritoneal irritation (004) or perforation (017).
Gynaecological infection	Women > 16 years with diagnosis of acute pelvic infection requiring parenteral therapy

SST	Men and women > 18 years with a diagnosis of complicated SST infections (defined as lower limb infections in diabetics, infected pressure sores, deep tissue infections in which enterobacteria or anaerobes were likely or which required surgical drainage, extensive cellulites, wound infections, and perineal abscesses) considered to be moderate or severe in intensity and requiring 7 to 14 days of parenteral antibiotic therapy.
UTI	Complicated UTI included those UTIs that occur at sites other than the bladder (*e.g* pyelonephritis), UTIs in men as well as UTIs associated with obstruction, the presence of foreign body (e.g catheter) or urologic abnormalities that interfere with normal voiding. Patients with complicated UTIs characterised by the investigator as serious (requiring parenteral therapy) were included.

Endpoints

Phase III trials focused on clinical outcome in clinically evaluable populations, except for IAI (clinical and microbiological outcomes) and CAP trial 020 (microbiological).
The primary endpoint was analysed at a number of timepoints in each trial, but for each indication, a primary timepoint, test-of-cure (TOC) visit, was defined in the protocol. For instance, TOC was at least 7-14 days post-therapy in CAP trials and at 14-28 days post-therapy in study 023 (gynaecological infections).
For Phase III comparative trials, sample sizes were based on the expected success rates i.e δ was chosen to be: 10 % or 20 % in CAP, 15 % in IAI, and 10 % in gynaecological infections.

Statistical analysis

The studies aimed to demonstrate non-inferiority to the active comparator. Ertapenem was deemed to be non-inferior if the lower limit of the 95 % two-sided confidence interval for the difference between proportion of responders in each treatment group excluded –10 % (if the response in the active comparator was > 90 %), - 15 % (if the response in the active comparator was > 80 % but less than 90 %) or – 20 % (if the response in the active comparator was > 70 % but less than 80 %). Confidence intervals accounting for stratification were based on the Cochran-Mantel-Haenszel approach.

Statistical analyses were performed on 2 populations: modified intention to treat population and evaluable population (clinically or microbiologically). The analysis for the primary clinical endpoints was mostly based on the **clinically evaluable population.** The microbiological endpoints, either primary or secondary, where evaluated, were assessed using the **microbiologically evaluable population**. Table 3 presents the definition for the relevant population for efficacy criteria.

Table 3

ITT population	All randomised patients who received at least 1 dose of study therapy
Clinical Modified Intent-to-Treat (MITT) population	All ITT patients that met the minimal disease definition
Microbiologic MITT population	Subset of the clinical MITT population including patients with a baseline pathogen identified, regardless of susceptibility to study agents and a subsequent microbiologic response assessment
Clinically Evaluable Population	Subset of the clinical MITT population comprised of patients in whom sufficient information was available to determine the patient's outcome and no confounding factors were present that interfered with the assessment of that outcome at time of cure visit; furthermore, it was required that if baseline pathogens were identified, one or more of these pathogens were susceptible to both parenteral study therapies.
Microbiologically Evaluable population	Subset of the clinically evaluable population, comprised of those clinically evaluable patients who had a baseline pathogen identified and a microbiologic response assessed.

The criteria for the choice of the **clinically evaluable population** to be included in most of the primary efficacy analyses are stringent, as only patients with a recognized susceptible pathogen to both treatments were analyzed, thus tending to artificially increase the favorable outcome rate.

As all microbiologically evaluable patients were required to be clinically evaluable, the population of clinically and microbiologically evaluable patients is identical to the microbiologically evaluable population; for all data presented hereafter, this group will be referred to as the microbiologically evaluable population. Determinations of evaluability were made prior to unblinding using prespecified criteria as indicated in the protocols.

Subgroup analyses by demographic factors and level of severity at baseline were also performed.
As the phase III studies were similar in design, it was considered appropriate to combine efficacy data in those indications with more than one trial.

Community Acquired Pneumonia (CAP)

Phase II: studies 002/008 combined report.

These early studies aimed to evaluate the efficacy and safety of ertapenem versus ceftriaxone in the treatment of serious uncomplicated lower respiratory tract infections (CAP or acute exarcerbetion of chronic obstructive pulmonary disease) either in the United States (study 002) or outside (study 008). When combining data, 75/85 patients had CAP. Mean exposure to IV treatment was 4 days in all 3 treatment groups (ceftriaxone 2 g/day, ertapenem 1 or 2 g/day). All but two ertapenem treated patients and all ceftriaxone treated patients were switched to oral therapy (amoxicillin/clavulanate potassium) for a mean of 6 days.

Results
At TOC, for the evaluable population, the percentage of patients experiencing a favourable clinical outcome was 83 % in the 1 g ertapenem group, 96 % in the 2 g group and 92 % in the ceftriaxone group. MITT results showed that the favourable response accounted for 82 %, 93 % and 81 % respectively.

Phase III studies

The two main studies in CAP (018 and 020) employed baseline stratification according to pneumonia severity index scores (PSI ≤ 3 or > 3) and age (≤ 65 or > 65 years). Ertapenem 1 g was compared to 1 g ceftriaxone daily, using 1:1 randomisation in study 018, compared to 2:1 randomisation in study 020. The median duration of study therapy was 11 days, including 4 days IV followed by 7 days switched oral therapy. Of the great majority of patients who switched to oral treatment, more than 75% received amoxycillin/clavulanate.
In both studies, there were approximately 25 % of clinically evaluable patients who had a severe infection indicated by a PSI > 3.

Study 018

Of the 502 patients randomised, 54 % per group had received an antimicrobial agent within 14 days of study entry and about one-third had received a beta-lactam agent.

Results

Clinical responses
In the clinically-evaluable population (383 patients of whom 182 for ertapenem) at TOC, a favourable outcome was assigned to 92 % of the patients in ertapenem group versus 91 % in the ceftriaxone group (95 % CI -5, +7). Favourable clinical outcome rates were numerically similar between treatment groups for patients in high and low age and PSI categories. Only one patient per group who failed therapy had a documented atypical pneumonia. In the MITT population (486 patients of whom 236 in the ertapenem group), favourable clinical response rates were 85 % in both treatment groups (95 % CI -7, +7).

In the microbiologically evaluable population (209 patients of whom 96 in the ertapenem group) at TOC, the by-pathogen favourable clinical response rates were 92 % for ertapenem and 93 % for ceftriaxone for the 47 and 57 *S. pneumoniae*, but 81% and 96 % for the 21 and 23 *H. influenzae* in the respective groups. Four patients with Pen-R pneumococci (> 2 mg/l), all treated with 1 g/day ertapenem, were cured. By-pathogen clinical response rates were 80 % and 83 % per treatment group for the 10 and 18 organisms isolated from blood cultures (5/6 and 15/17 for pneumococci) and there was no documented persistence in blood cultures.

Microbiological responses
In the MITT population with a pathogen, favourable microbiological outcomes were recorded for 94 % in the ertapenem group and 91 % in the ceftriaxone group.
There were six patients with superinfections and eight patients with new infections recorded but the pathogens in these patients were too varied species to draw firm conclusions.

Study 020

Of the 364 patients randomised, about 50 % per group had received an antimicrobial agent within 14 days of study entry.

Results

Clinical response
In the microbiologically-evaluable population (149 patients including 100 in ertapenem group) at TOC, a favourable outcome was assigned to 92 % for both treatment group (95 % CI -12, +10). As for study 018, results were numerically similar between treatments for the small subgroups of patients in high and low age and PSI categories. By-pathogen favourable response rates were 88 % for the 49 *S. pneumoniae* treated with ertapenem and 96 % for the 22 treated with ceftriaxone. There were 12/13 and 8/8 blood culture isolates per group for which the clinical outcome was favourable (12 and 6 were pneumococci) and all blood cultures became negative. In the MITT population (183 patients of whom 123 in ertapenem group), favourable clinical response rates were 86 % for ertapenem and 87% for ceftriaxone, compared with 89 % and 90 %, respectively, for those patients with a pathogen.

Microbiological response
In the microbiologically-evaluable population at TOC, the by-pathogen eradication rates were 88 % and 100 %, respectively, for the 49 and 22 *S. pneumoniae* per group and all blood cultures became negative.

Other analyses in this study, and the comparisons made in trial 018, all gave very similar favourable outcome rates between treatments. Patients were allowed to switch therapy after 3 days of treatment and therefore a concern was raised that the timing of switching could have masked differences of potential importance. It was considered however that the (predominant) use of sequential oral amoxycillin-clavulanate provided a similar contribution to the final resolution of pneumonia in both treatment groups. Although the use of 1 g/day ceftriaxone rather than 2 g/day might be questioned, all clinical and microbiological success rates in evaluable patients were in excess of 90 % (and ≥ 8 5% in the MITT population). Thus, it would be reasonable to assume that comparison with a higher dose of ceftriaxone would not have changed these findings. A subgroup analysis showed the treatments appeared to be similarly effective between patients with PSI scores ≤ 3 and those with PSI scores > 3 (that accounted for 25 % of patients). Therefore, it was considered that the data supported the use of ertapenem in CAP.

Intra-Abdominal Infection (IAI)

Study 004

In this phase II trial, patients were initially randomised 1:1 to 1.5 g ertapenem daily or 2 g ceftriaxone daily plus metronidazole. Following the results of a planned interim analysis, the dose of ertapenem was changed to 1 g daily. In the microbiologically evaluable population at TOC, 84 % in the 1 g

ertapenem group and 86 % in the comparative group had a favourable clinical and microbiological outcome. Rates were 88 % and 91 % for those with appendicitis. In the MITT population with a pathogen at TOC, 88 % in the 1 g ertapenem group and 85 % in the comparative group had a favourable clinical outcome.

Study 017

This main study compared the efficacy of ertapenem versus piperacillin/tazobactam in patients stratified at baseline according to APACHE II scores (≤ 15 or > 15) and according to diagnosis (complicated appendicitis *versus* all other diagnoses).
Of the 665 patients randomised, 43 % of patients had complicated appendicitis and 57 % had other diagnoses, of whom 88 % had been treated with open abdominal surgery and 80 % had received prior antibacterial therapy. Only 8 % of patients had APACHE II scores > 15, although the study allowed for score up to 30. More than 80 % of evaluable patients had a polymicrobial infection. The median duration of therapy was 6-7 days in both treatment groups and vancomycin was given to 4 % of patients per group.

The results are displayed in the below table:

Proportion of patients with favourable clinical and microbiological response at test of cure (microbiologically evaluable population)

	Ertapenem 1 g (A) N = 203		**Piperacillin/tazobactam 1 g (B) N = 193**		**Observed difference (A-B) (95 % CI)**
Site of infections	n/m	Observed response	n/m	Observed response	
Overall	176/203	86.7 %	157/193	81.3 %	5.4 % (-2; + 13)
Complicated appendicitis*	85/94	90.4 %	82/91	90.1 %	0.3 %
Other diagnoses	91/109	83.5 %	75/102	73.5 %	10.0 %

n/m: number of patients with favorable assessment/number of patients with assessment
* without generalized peritonitis

The favourable clinical and microbiological outcomes in patients with APACHE II score > 15 were 63.6 % (7/11) in the ertapenem group and 83.3 % (10/12) in the piperacillin/tazobactam group. When viewed by range, favourable outcomes were recorded in 10/13 patients of the ertapenem group and 10/12 patients of the piperacillin/tazobactam group with baseline scores ranging from 15 to 19 and for 3/5 and 1/1 patients per group with scores of 20 or more. There were only 12 and 19 patients per group with positive blood cultures, of whom 9/12 and 15/19 had a favourable clinical outcome. There was no documented persistence recorded in these patients.

In the clinically evaluable population at TOC, 87 % and 83 % of patients in the ertapenem and piperacillin/tazobactam groups had a favourable clinical outcome rates (95 % CI –3; + 11). Outcomes viewed by infectious processes showed no numerical inferiority for ertapenem in the four categories (generalised peritonitis, multiple abscess, single abscess or localised disease).

This single phase III trial in IAI demonstrated overall equivalence between treatments. Due to the small numbers of patients with APACHE scores, efficacy in this population cannot be confirmed.

Acute gynaecological infections

Study 023

A total of 412 females were randomised 1:1 to 1 g ertapenem daily or piperacillin/tazobactam. Patients were stratified at baseline according to whether the diagnosis was obstetric/postpartum (85 %) or gynaecological/post-operative (15 %), with a one-month limit set on the timing of the event predisposing to infection. Overall, 75 % of women were considered to have endomyometritis and about 55 % had received a prior antibacterial agent. Most patients had a mild to moderately severe infection, but 26 % of clinically-evaluable patients had a severe infection (defined as either a

temperature > 39 ºC and/or a positive blood culture at baseline). Ten patients had bacteriaemia. The median duration of therapy was four days in both treatment groups. Results are displayed in the table.

Favourable responses at TOC

Study population	**Treatment groups**				**95 % CI**
	Ertapenem		**Piperacillin/tazobactam**		
	n	**Response %**	**n**	**Response %**	
Clinical response					
clinically-evaluable population	163	94 %	153	92 %	-4 ; + 9
Clinical MITT	211	86 %	191	88%	-9, +5
Microbiological response (*i.e.* pathogen eradication)					
Microbiologically-evaluable population	128	94 %	129	94 %	-7, +7
Microbiological MITT	161	88 %	158	89 %	-9, +7

In the clinically-evaluable population, clinical responses rates were 40/42 (95 %) and 30/35 (86 %) in respective treatment groups for those with severe infections compared to 93 % in both groups for all other infections. Similar findings were reported for the subgroups according to diagnosis, and to mono- or polymicrobial infections. The ten and six patients per group with positive blood cultures all had a favourable outcome.

In the microbiologically-evaluable population, by-pathogen eradication rates, including blood culture isolates, reflected the clinical response rates (as above). There were only one and three patients in the respective groups with superinfections and one patient per group with a new infection.

This single trial in gynaecological infections predominantly enrolled women with post-partum infections. This probably reflects a very rapid switch to oral treatment in the majority of other types of gynaecological infections that initially require intravenous therapy, such that few women would have completed an IV-only trial. A concern was raised with respect to the efficacy of ertapenem in patients with severe infection since only 26 % of evaluable patients treated with ertapenem had severe disease. The SPC points out this feature of the patient population.

Skin and skin structure infections (SSTIs) and urinary tract infections (UTIs)

In study 016, the efficacy of ertapenem, 1.0 g IV once daily was compared with piperacillin/tazobactam, 3.375 g every 6 hours, in the treatment of complicated **skin and skin structure infections**, defined as lower limb infections in diabetics, infected pressure sores, deep tissue infections in which enterobacteria or anaerobes were likely or which required surgical drainage, extensive cellulititis, wound infections and perineal abscesses. Patients were stratified at baseline according to the presence or absence of complicating underlying disease. Stratum I consisted of those with decubitus ulcers, diabetes mellitus or other neuropathic conditions whereas Stratum II contained all other patients. Overall 60 % of patients had received an antimicrobial agent within 14 days of study entry, predominantly beta-lactam compound.

Results

Proportion of patients with favourable clinical response at test of cure

Study population	**Ertapenem 1 g**		**Piperacillin/tazobactam 1g**		**95 % confidence interval**
	n/m	**cure rate %**	**n/m**	**cure rate %**	
Clinically evaluable population					
Overall	152/185	82 %	147/174	84 %	-10, +6
Moderate	120/145	83 %	125/143	88 %	
Severe	32/40	82 %	22/31	71 %	

However, there was concern regarding the efficacy of ertapenem in SST infections, particularly since only one-fifth of the patients enrolled had a severe infection. There were also several instances of

numerical inferiority for ertapenem, and microbiological response rates could have been clouded by the fact that the pathogenicity of several of the species that have been counted among the pathogens was dubious. It was considered that these data could not support the use of ertapenem in complicated SSTIs.

In addition, results from two studies evaluating the efficacy of ertapenem versus ceftriaxone **in urinary tract infections** (UTIs) were presented: one main trial (study 014 where 592 patients were randomised) and one supportive trial (study 021 where 258 patients were randomised). Patients were stratified at baseline according to the diagnosis i.e. acute pyelonephritis, with or without structural or functional renal tract abnormalities, or other complicated UTIs. After at least 3 days of treatment, a switch to oral treatment was allowed.

Results showed that the lower 95% CI were ≤ -10% for clinical responses in the microbiologically evaluable population in study 014 (90 % versus 94 % in ertapenem and ceftriaxone groups respectively; 95 % CI -10, +3), and for by-patient microbiological responses in the microbiologically-evaluable population in study 021 (86 % versus 85 % in ertapenem and ceftriaxone groups respectively; 95 % CI -13, +14); the latter study used 2:1 randomisation. Although response rates between treatments were similar at the time of discontinuation of intravenous therapy (3-4 day median duration), the sequential therapy (median of 7-9 days of mainly ciprofloxacin) was likely to have exerted a very considerable influence on outcome, especially in patients with underlying renal tract abnormalities and/or prostheses. Thus, there was concern that any real difference between the two parenteral treatments may have been clouded by the study design. These results were not considered sufficient to support a recommendation of use of ertapenem in this indication.

Summary of efficacy in bacteraemic patients across all trials

Across the reported trials, there were 172 fully evaluable patients with a documented bacteraemia at baseline, of whom 86 received ertapenem. In studies *versus* ceftriaxone, overall favourable response rates were 87 % for ertapenem and 86 % for the comparator. In studies *versus* piperacillin/tazobactam, favourable response rates were 24/34 (71 %) for ertapenem and 28/35 (80 %) for the comparator. Favourable response rates in patients with *E. coli* in blood at baseline were 23/25 for ertapenem and 15/18 for ceftriaxone. Similarly, rates were 16/18 and 21/23, respectively, for those with pneumococcal bacteraemia. Of the 120 isolates analysed, all were inhibited at < 1 mg/l ertapenem. There was no demonstrable correlation between MIC and outcome.

Since outcomes in the bacteraemic patients were not notably different between treatments as far as could be judged by the relatively small numbers, there did not appear to be a need for a cautionary statement in the SPC regarding use in patients suspected of having a concomitant bacteraemia at presentation.

Special populations

Age and gender

The overall rates for favourable primary responses were 91 % for females and 88 % for males treated with ertapenem; rates by indication did not show consistent differences in response rates by gender. In CAP studies, there was no notable difference in response rates to ertapenem in the elderly (either ≥ 65 or 75 years compared with all others). However, the elderly had notably numerically lower response rates to ertapenem in studies in SST and IAI than younger subjects; this latter pattern was less marked or not apparent in the piperacillin/tazobactam-treated groups, but numbers are relatively small.

Intramuscular administration

Although PK/PD considerations supported the use of the same dose of ertapenem IM as IV, the bioavailability from IM administration in patients may not be as high or as reliable as that recorded in healthy volunteers with presumptively normal blood flow distribution patterns. A double-blind study (029) was conducted to assess the safety of ertapenem when given by the IM route in comparison with ceftriaxone (3:1 randomisation) to patients (n = 117) with lower respiratory tract infections, skin and soft tissue infections and urinary tract infections. This study did not raise any concern with respect to safety. There was a limited number of patients enrolled to assess efficacy. It was considered that the

data were inadequate to support the efficacy of intramuscular ertapenem (1 g daily) as an alternative route of administration.

Children
The efficacy of ertapenem has not yet been evaluated in children but the applicant agreed to provide details of the proposed paediatric development plan as part of the follow-up measures to be fulfilled post-authorisation.

Clinical safety

Patient exposure

Approximately 4,000 subjects/patients were enrolled in the clinical development programme, of which more than 2,000 received at least 1 dose of ertapenem administered parentally.

There were 220 subjects in the clinical pharmacology studies who received ertapenem, involving doses up to 3 g for up to 8 days. However, the majority received 1 g/day for a mean duration of 4 days (range 1-15 days).

In phase II/III studies, including studies in other infections (SSTIs and UTIs), the majority of patients (approximately 1800) received 1 g ertapenem daily. Of those approximately 100 patients received ertapenem intramuscularly. The median duration of therapy at 1 g/day ertapenem was 5 days (range 1-28 days). There were 472 patients aged at least 65 years randomised to 1 g ertapenem daily. In addition, there were 64 patients treated with 1.5 g ertapenem daily for one or more days and 155 received 2 g/day for all or part of the total treatment period, although only 30 were actually randomised to this dose. Twelve patients received at least one dose 0.5 g daily in accordance with dose adjustment for renal insufficiency.

Adverse events (AEs) and serious adverse event (SAEs)/deaths

Clinical pharmacology studies

Overall, 62 % of subjects on ertapenem and 34 % on placebo experienced at least one AE, whereas 40 % and 16 %, respectively, experienced an event related to treatment. The commonest events were diarrhoea (24 % in ertapenem group; 41/52 cases deemed related *versus* 9 % in placebo group), headache (22 % in ertapenem group; 28/49 cases deemed related *versus* 9 % in placebo group) and nausea (16 % in ertapenem group; 28/35 cases deemed related *versus* 6 % in placebo group). Rates for these three events among those who received 1 g ertapenem daily were 18 %, 20 % and 12 % respectively. There was an overall trend to increased reporting rates with increase of the dose. Five ertapenem group subjects (2 %) had a rash and two had urticaria (1 %), of which three and one cases, respectively, were considered related to treatment. Among 58 subjects who received single or multiple doses of 1 g ertapenem intramuscularly, four reported pain and there was one report of each of swelling and tenderness.

Eleven subjects discontinued ertapenem due to AE(s) related to treatment. These included three subjects with a rash and one with urticaria. Five subjects had a gastrointestinal event(s). There were no SAEs or deaths recorded in these trials.

Based on ECGs data collected routinely in two phase I studies, and results from an additional study in which single IV doses (2 g) were given to 24 healthy volunteers (ten males) to evaluate ECG parameters at the time of Cmax, it was confirmed that ertapenem had no discernable effect on cardiac conduction.

Phase II/III trials

AEs during parenteral treatment only
Because a switch to oral therapy was allowed in all but three trials, the AEs that occurred during parenteral treatment only were presented separately. Overall, 48 % of patients randomised to 1 g

ertapenem daily reported an AE compared with 56 % on piperacillin/tazobactam and 48 % on ceftriaxone, while 20-22% per treatment group had at least one treatment-related AE.

At least one event at the infusion site, mainly pain and erythema, was reported in 22 % of patients in ertapenem group, 26% in piperacillin/tazobactam group and 23% in ceftriaxone group. However, only 7-8 % per group had a moderately severe or severe infusion site problem.

The other commonest events were diarrhoea (7 % in 1g ertapenem group, 11% in piperacillin/tazobactam groups and 6 % in ceftriaxone groups), nausea (6-7 % per group), and headache (5-6 % per group). Treatment-related events included infusion site problems (5 %, 7 % and 6 % respectively), diarrhoea (4 %, 7 % and 4 % respectively) and nausea (3 % per group).
Testing for *Clostridium difficile* associated diarrhoea was not performed routinely and no comparison with other injectable beta-lactam with comparable antibacterial activity can be made. In the absence of evidence, it should be assumed that cases of diarrhoea are antibiotic associated diarrhoea.

Rash was reported in 1-3 % per group and treatment-related rash in 1-2 % per group. Rashes ranged from macular or maculopapular, with or without erythema, eruptions to hives and urticaria. Rash was mild and lasted mostly 1-7 days, with resolution in most of the patients.
Seizure was reported in four patients treated with 1 g ertapenem and two patients treated with piperacillin/tazobactam. An analysis showed that the causal relationship is unknown considering the possible degree of renal impairment related to the age of these patients (75-89 years) and the concomitant medications.

AEs for patients who did not switch to oral treatment up to 14 days post-therapy
This additional analysis showed that the total rate of diarrhoea was 10 %, but the rate related to treatment was 5 %. Seven cases of seizure were recorded, two being considered treatment-related. The total rash rate was 3 %, and treatment-related rash was reported in 1 %.

AEs during parenteral therapy plus oral treatment and up to 14 days post-therapy
Similar proportions in ertapenem and comparative groups switched to similar ranges of oral therapies. Therefore these analyses give higher numbers but the same picture for between-group comparisons to that described for parenteral use only. The number of reports of seizure increased to ten among patients initially randomised to ertapenem. However, none of the additional cases was considered to be treatment-related; all patients had completed ertapenem therapy before seizure onset.

Discontinuation of therapy
Parenteral therapy was discontinued due to AE(s) in 4 % of patients treated with 1 g ertapenem, 5 % of those treated with piperacillin/tazobactam group and 4 % who received ceftriaxone. AEs considered related to ertapenem that prompted discontinuation from treatment included five cases of rash, three cases of pruritus, two cases of seizure, two of diarrhoea, and single cases of facial and tongue oedema with rash, cholecystitis, thrombocytopenia, and allergy (including burning and itching skin).

Serious adverse events and deaths
During parenteral therapy, 6 % ertapenem, 7 % piperacillin/tazobactam 5 % ceftriaxone patients had at least one SAE; these were of very mixed types. In the ertapenem group, SAEs related to ertapenem included three cases of seizure, two of renal insufficiency, and single cases of spontaneous abortion, thrombocytopenia, colitis and cholecystitis.
Numbers experiencing SAEs were higher but the overall picture was similar for SAEs reported up to day 14 post-therapy.

Laboratory findings

Clinical pharmacology studies

Laboratory AEs as reported by the investigators (*i.e.* not all findings outside normal ranges) occurred in 9 (4 %) ertapenem and 1 (3 %) placebo subjects. Six subjects in the ertapenem group had an increased ALT and three had an increased AST.

Laboratory abnormalities as determined by the sponsor's criteria indicated that a drop in neutrophils to < 1.8 x 10^3 mm^3 occurred in 12 % ertapenem and 9 % placebo group subjects. Despite the investigators' reports above, only one subject had an AST or ALT > 2.5 x ULN. However, 11 had an increase in creatinine to 1.5 x ULN, and eight to > 3 x ULN compared with no subjects on placebo.

Phase II/III trials

Laboratory AEs that occurred during parenteral therapy, as reported by the investigators (as defined above), occurred in 23 % of patients treated with 1g ertapenem, 28 % treated with piperacillin/tazobactam and 19 % treated with ceftriaxone. In each group, about 50 % were considered to be treatment-related by the reporting investigator, but < 1% discontinued therapy due these AEs and < 2% were considered to be SAEs. The most common reports were of increased ALT or AST (each in 6-8 % per group; values up to 200-300 U/l), about two-thirds of which were considered to be treatment-related, increased ALP (3-6 % per group), and anaemia (3-4 % per group). Less than 1 % per group had a decrease in neutrophils or platelets reported as an AE. Treatment-related abnormalities up to 14 days post-therapy in those who did not switch to oral treatments gave similar results to the above analysis.
Laboratory abnormalities during parenteral therapy, as determined by the *sponsor's* criteria, indicated that a drop in neutrophils to < 1.8 x 10^3 mm^3 occurred in 3 % of patients in ertapenem, 1 % piperacillin/tazobactam and 2 % ceftriaxone groups. There were 1 % patients in each treatment group with platelet counts < 75,000 mm^3. There were 5 % and 6 % ertapenem group patients with an AST or ALT > 2.5 x ULN, compared with 3-6 % in comparative groups, while 2 % per group had an increase in ALP to > 2.5 x ULN. There were 22 (1 %) ertapenem group patients who had an increase in creatinine to 1.5 x ULN, and four to > 3 x ULN; these findings were similar to those in comparative groups.
Over the IV/PO treatment period plus up to 14 days post- therapy, a drop in neutrophils to < 1.8 x 10^3 mm^3 occurred in 4 % of patients in ertapenem, 2 % piperacillin/tazobactam and 4 % ceftriaxone groups. The analysis of these patients showed that the relation between ertapenem and neutropenia is unclear. There were still only 1% patients in each treatment group with platelet counts < 75,000 mm^3. However, there was no evidence that ertapenem was more likely to trigger neutropenia than other beta-lactam agents. There were 6 % ertapenem group patients with an AST or ALT > 2.5 x ULN, compared with 4-7 % in comparative groups, while 2-4 % per group had an ALP to > 2.5 x ULN.

Safety in special populations

Regarding age and gender, AE reporting rates were not notably different between age groups and gender. Incidences of all and specific AEs were generally higher in females, but this pattern also applied to comparative therapies.

Regarding renal insufficiency, there were 54 patients with CrCl estimated at < 60 ml/min/1.73m^2 who were treated with ertapenem 1 g/day, 20 with piperacillin/tazobactam and 30 with ceftriaxone. The overall rates of AE reports were slightly increased in these patients compared with all other patients (*eg.* 54 % *versus* 48 % with any AE in the ertapenem 1 g group). Few patients had a protocol-recommended dose adjustment due to renal insufficiency, but these data are too scarce to draw firm conclusions.

Regarding intramuscular administration, there were similar types and rates of reactions as for intravenous, but data were considered insufficient to support this route of administration.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

In general the quality dossier has been well presented and indicates that the active substance and the finished product are manufactured and controlled in a relevant way, in compliance with current EU

and ICH guidelines. Satisfactory information has been provided to demonstrate that these manufacture and control processes routinely and consistently generate a product of uniform quality when used in accordance with the conditions defined in the Summary of Product Characteristics.

Preclinical pharmacology and toxicology

Like other beta-lactam agents, the mechanism of action of ertapenem involves inhibition of bacterial cell-wall synthesis by binding to specific penicillin-binding proteins. Overall, the primary pharmacodynamic studies adequately described the antibacterial activity of ertapenem in relation to the proposed indications. The possible mechanisms of resistance to ertapenem have been adequately explored.

The pharmacokinetic profile of ertapenem was found to be very straightforward. The saturation of plasma protein binding that occurred at very high doses was responsible for non-linear kinetics in preclinical species. This will not occur in clinical use at the recommended daily dose of 1 g, since Cmax is around 150 mg/l. Metabolism of ertapenem to the ring-opened form is catalysed by dehydropeptidase-1. The cytochrome P_{450} system is not involved in the metabolism of ertapenem and the drug does not induce or inhibit any of the isoenzymes. Excretion was primarily via urine as the ring-opened form.

The toxicology programme did not reveal any major toxic effects of ertapenem. A decrease in neutrophil count was reported in rats but this was considered unlikely to be of clinical relevance. There were no adverse findings of clinical significance in reproduction toxicity studies. However in the absence of data in women, ertapenem should not be used during pregnancy unless the potential benefit outweighs the possible risks to the foetus. This information has been included in the SPC. Ertapenem was neither mutagenic nor clastogenic and the absence of carcinogenicity data was adequately justified in view of the short duration of treatment.

Efficacy

Microbiological data obtained from patients treated during the phase II and phase III trials supported general MIC susceptibility test breakpoints of Susceptible ≤ 4 mg/l and Resistant > 8 mg/l. The MIC susceptibility test breakpoint for streptococci, including *S. pneumoniae*, is: S ≤ 2 mg/l.

For species susceptible to ertapenem, resistance was not frequently reported in surveillance studies in Europe. Outbreaks of carbapenem-resistant organisms have however occurred and the applicant agreed to implement appropriate post-authorisation studies to collect data on the prevalence of resistance, both within and outside the EU to enable periodic updating of the SPC.

The pharmacokinetic profile of ertapenem was adequately defined in healthy volunteers. No dosage adjustment is warranted according to gender or age or in patients with mild to moderate renal impairment.

The once-daily administration of ertapenem is different to the regimens approved for other carbapenems. The rational for the dosage regimen was based on the fact that the efficacy correlates with the proportion of the dosing interval that plasma levels exceed the MIC of ertapenem for the infecting organism (T> MIC).

The clinical benefit of ertapenem was demonstrated for the following infections, in which non-inferiority to approved comparative regimens was demonstrated:

- Community-acquired pneumonia

In two Phase III trials, the favourable outcome rates in patients receiving ertapenem were not inferior to those in the ceftriaxone groups, including patients with severe disease (pneumonia severity index >3) that accounted for 25 % of evaluable patients treated with ertapenem in each trial.

- Intra-abdominal infections

A single phase III trial in IAI included demonstrated overall non-inferiority between ertapanem and piperacillin/tazobactam. Of the evaluable patients, 30 % had generalized peritonitis and 39 % had infections involving sites other than the appendix including the stomach, duodenum, small bowel, colon, and gallbladder. It was considered however that the clinical benefit of ertapenem has not been demonstrated in patients with APACHE scores > 15 due to the limited number of patients included, as reflected in the Summary of Product Characteristics.

- Acute gynaecological infections

The results of a single trial, enrolling predominantly women with post-partum infections showed that ertapenem was non-inferior to piperacillin/tazobactam and therefore could support an indication for use in acute gynaecological infections. The percentage of evaluable patients treated with ertapenem who had severe disease (temperature ≥ 39°C and/or bacteraemia) accounted for 26 %.

The CPMP considered, however, that there were insufficient data to support the use of ertapenem in complicated skin and skin structure infections and in urinary tract infections.

The clinical benefit of ertapenem in children has not yet been investigated, however the applicant undertook to conduct a clinical programme in this population.

Safety

The most common adverse events reported related to infusion site problems, diarrhoea and nausea. With respect to laboratory abnormalities, increased ALT or AST, increased ALP, and anaemia were the most frequently reported. The applicant agreed to evaluate the impact of ertapenem on faecal flora.

Benefit/risk assessment

During an oral explanation before the CPMP, the applicant addressed concerns that had been raised regarding the appropriateness of 1 g daily dosing in CAP, IAI and acute gynecological infections, especially with regard to the more severe infections. It was confirmed that the efficacy of ertapenem in patient subgroups with more severe infections was consistent with the overall results in these studies. However considering the limited number of patients with severe infections (approximately 20-30 % for each indication), it was agreed to reflect in the "Special warnings and precautions for use" section of the Summary of Product Characteristics the limited experience in the use of ertapenem in the treatment of complicated and severe infections.

As already highlighted the applicant agreed to provide further data as part of the follow-up measures to be fulfilled post-authorisation with respect to the prevalence of resistance to ertapenem, the paediatric population and the effects on faecal flora. In addition the applicant will further investigate the efficacy of ertapenem using shorter durations of treatment.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by majority that the benefit/risk profile of Invanz in the treatment of intra-abdominal infections, community acquired pneumonia and acute gynaecological infections was favourable.
There were however divergent opinions mainly based on the fact that experience in the use of ertapenem in the treatment of severe infections is limited.

The CPMP however, recommended the granting of the marketing authorisation for Invanz (1 g powder for concentrate for solution for infusion) for the following indication:

"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:

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

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