



European Medicines Agency

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Product name: **INVANZ**

Procedure No: **EMEA/H/C/389/II/15**

SCIENTIFIC DISCUSSION

1. Introduction

Ertapenem sodium is a sterile, synthetic, long-acting, parental, 1 β -methylcarbapenem that is structurally related to β -lactam antibiotics with activity against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria.

The bactericidal activity of ertapenem results from the inhibition of cell wall synthesis and is mediated through ertapenem binding to penicillin binding proteins.

Ertapenem sodium is a white to off-white hygroscopic, crystalline solid. It is soluble in water and 0.9% sodium chloride solution, practically insoluble in ethanol, and insoluble in isopropyl acetate and tetrahydrofuran.

Invanz is supplied as sterile lyophilized powder for intravenous infusion after reconstitution with appropriate diluent and transfer to 50 ml 0.9% Sodium Chloride Injection; or for intramuscular injection following reconstitution with 3.2 ml of 1% lidocaine hydrochloride. Each vial contains 1.046 grams (g) ertapenem sodium, equivalent to 1 g ertapenem.

The initial Marketing Authorisation was granted on 18 April 2002 by the European Commission.

On the basis of the results of a clinical study named "Protocol 039", *a prospective, multicenter, double-blind, randomised, comparative study to evaluate the safety, tolerability, and efficacy of a single dose of ertapenem sodium (MK-0826) versus cefotetan for the prophylaxis of surgical site infection following elective colorectal surgery*, the MAH submitted in November 2005 the present type II variation to include prophylaxis of surgical site infection elective colorectal surgery in adults to the current approved 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:

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

Postoperative infection is a common complication of surgical procedures. These infections include surgical site infections (SSI), which may be further classified as superficial incisional, deep incisional, or organ space infections as well as remote site infections. It has been established for some time that antimicrobial prophylaxis prior to colon surgery reduces both postoperative infection rate and mortality. However, while it has been established that antimicrobial prophylaxis decreases the rate of post-operative infection, results from numerous clinical trials have shown a wide range of prophylactic success. This range exists not only from regimen to regimen, but across clinical studies using the same regimen. While the reasons for this variability are not definitively known, a variety of causes have been proposed. Among them are differences in patient population and methodology of measurement. Additionally, differences in study design and definition of wound infection may contribute to the differences. Guidelines have been developed to classify operations with respect to risk of postoperative infection, and to guide use of appropriate prophylactic measures intended to reduce the risk of postoperative infection. In addition, guidelines have been published to assist in the design of studies to examine new agents for prophylactic efficacy.

The organisms that cause postoperative infections can vary, but generally include skin flora such as *Staphylococcus aureus*, and in the case of colorectal operations, enteric gram-negative rods and anaerobes, which are abundantly present in the intestinal lumen. Factors associated with increased risk of postoperative infections after colorectal surgery include rectal resection (either low anterior or abdomino-perineal procedures), prolonged surgery (>3.5 to 4 hours), and other general health parameters such as advanced age and underlying illnesses, including diabetes mellitus. Other factors considered important in reducing the risk of postoperative infection are careful attention to skin antisepsis, primary wound closure, and recently, increasing perioperative tissue oxygenation has been suggested.

Mechanical bowel preparation intended to empty the bowel and reduce the luminal bacteria is considered a standard prophylactic measure before elective colorectal surgery. The preferred regimens currently are orally administered osmotic agents such as polyethylene glycol solution, administered alone or in reduced volume after the laxative bisacodyl, and sodium phosphate in appropriate patients after minimal dietary restriction. While sodium phosphate regimens have shown high patient compliance rates, the demonstration of some electrolyte abnormalities and contraindications in the product circular make this an appropriate choice for only some patients.

2. Clinical aspects

2.1 Clinical efficacy

- **Description and methods of the main study: Protocol 039.**

This was a prospective, multicenter, double-blind (with in-house blind), randomised comparative study conducted in 51 centres in the USA to evaluate the safety, efficacy, and tolerability of ertapenem sodium versus cefotetan for prophylaxis of surgical site infection following elective colorectal surgery in adults. This study, which began on 6-May-2002 (FPI), was anticipated to enrol 900 patients (450 on ertapenem) in order to achieve 340 evaluable patients in each treatment group. Each patient was expected to complete the study, including follow-up, within 4 weeks. Last Patient Out (LPO) was on 9-Mar-2005 and all data was received in-house by 11-Mar-2005.

Study objectives

The objective of this study is to evaluate the safety and efficacy of intravenous ertapenem sodium compared to cefotetan in the prophylaxis of surgical site infections following elective colorectal surgery.

Primary: (1) To compare the efficacy of ertapenem sodium with that of cefotetan in the prophylaxis of surgical site infection following elective colorectal surgery.

Secondary: (1) To document the microbiology of surgical site infections in patients who fail prophylaxis and/or who have distant site infections.

(2) To evaluate and compare the safety profile of ertapenem sodium versus cefotetan with respect to the proportion of patients with any drug related adverse experiences (AEs).

Enrolment - Inclusion and exclusion criteria

Inclusion and exclusion criteria were applied in order to enroll patients undergoing appropriate surgery of the colon or rectum and were not complicated by preexisting conditions which could confound the evaluation of the efficacy or safety profiles of the study drugs. The following inclusion and exclusion criteria are from Protocol Amendment 039-01. The inclusion and exclusion criteria did not change over the course of the study.

Particularly, the following **inclusion and exclusion criteria** were considered:

- Patients scheduled to undergo elective colon or colorectal surgery by laparotomy meeting the following criteria:
- Surgery must have been scheduled in advance. Patients with emergency colon or colorectal surgery (unscheduled surgery with insufficient time to complete preoperative bowel preparation) were expressly excluded.
- There must have been adequate time to complete preoperative bowel preparation.
- Patients with active inflammatory bowel disease involving the colon were excluded.
- Patients with a bacterial infection at the time of surgery or with a need for administration of systemic antimicrobial therapy within 1 week prior to surgery were excluded. Coexisting condition at baseline that required antimicrobial therapy during the course of the study.

Patients had an initial eligibility screening assessment within 30 days prior to study therapy that included a complete physical exam and medical history, assessment of baseline risk factors for postoperative infection, and laboratory studies. Any patient whose screening procedures occurred >48 hours prior to study drug administration was to have the medical history and physical examination updated prior to administration of study drug to assess any significant changes that may have occurred.

Patients who met all inclusion criteria and no exclusion criteria were eligible for randomisation into the study at that time.

All patients were to complete an osmotic oral bowel preparation containing polyethylene glycol or oral sodium phosphate prior to surgery. On the day of surgery, patients received a single dose of study medication infused over thirty minutes within one hour prior to incision.

Patients were followed post-operatively for efficacy with the investigator making an assessment of clinical response to therapy at the time of discharge from the hospital and at the follow-up visit 4 weeks posttreatment. Although clinical response was assessed at 2 timepoints for each patient, the primary assessment of clinical response was made at the follow-up or test of success visit, 4 weeks posttreatment. Patients were followed for safety daily up to and including 14 days posttreatment. Patients were to be contacted by telephone on day 14 posttreatment to assess for any adverse experiences. After having been entered into the study, patients were allowed to withdraw from the study at any time or the patient could be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, patients were allowed to be withdrawn if he/she violated the study plan or for administrative and/or other safety reasons. All patients with an unfavorable clinical response at any time before the 4 week posttreatment follow-up assessment was to be considered a failure for analysis and no further assessment or clinical response was required. However these patients were to be followed for at least 14 days after receiving study therapy for safety purposes.

Randomisation

Adult patients scheduled to undergo elective surgery of the colon or rectum with sufficient time for bowel preparation were randomised to 1 of the 2 study regimens in a 1:1 ratio, according to the allocation/randomisation schedule. Allocations were stratified by planned surgical procedure with patients scheduled to undergo an intraperitoneal procedure being stratified to Stratum I and patients scheduled to undergo an abdominoperineal resection being stratified to Stratum II. For the purposes of this study, an abdominoperineal resection was considered to be a procedure in which any portion of the rectum was removed.

Changes in the Conduct of the Study or Planned Analyses

The study protocol (039-00) was amended only once during the course of the study (039-01). This protocol was written and all changes implemented prior to the randomisation of the first patient. Protocol 039-00 was not sent to sites and no patients were entered under this protocol.

The DAP stated that all pre-specified risk factors would be included in the multivariate analysis. However, when performing the multivariate analysis, only significant risk factors from the univariate analysis were included. A p-value cutoff of < 0.3 was utilised to identify factors to be included in the multivariate analysis.

One additional safety test, not pre-specified in the DAP, was performed. The proportion of patients with any serious drug-related clinical AEs was compared between treatment groups using risk difference. The 95% CI on the risk difference was calculated and Fisher's exact test was performed.

Study medication and Dosage

Ertapenem was given as a single dose of 1.0 g intravenously and cefotetan was given as a single dose of 2.0 g. Both drugs were to be given 30 to 60 minutes prior to the planned initial surgical incision as a single IV dose. There was to be no dose adjustment for renal insufficiency since this was a single dose study.

The rationale for this study is the appropriate aerobic and anaerobic spectrum of ertapenem, and its long half life. Ertapenem has been studied in 8 Phase IIB and III trials, including in complicated intra-abdominal infection, acute pelvic infection in women, and complicated skin and skin structure infection. These 3 studies demonstrated that ertapenem is efficacious in the treatment of polymicrobial infections, in which the pathogens included *S. aureus*, and gram-negative and anaerobic pathogens. Furthermore, ertapenem sodium has an extended half-life of ~4 hours and is administered once daily in therapeutic regimens. After a single 1-g dose of ertapenem given intravenously, a C_{max} of 155 $\mu\text{g/ml}$ is reached, and the plasma concentration of total drug is 31 $\mu\text{g/ml}$ at 6 hours and 9 $\mu\text{g/ml}$ at 12 hours dose. The plasma concentration of total drug declines to 3 $\mu\text{g/ml}$ at 18 hours. Therefore, repeated dosing should not be required even for prolonged operations. Ertapenem penetration into skin

blister fluid has been studied using the suction skin blister model. These data indicate excellent penetration into blister fluid on Day 3 of 1-g IV once daily dosing. Peak skin blister concentrations of 24 µg/ml are achieved at 4 to 8 hours after dosing and sustained above 4 µg/ml for the entire dosing interval. When extrapolating these data to approximate a first (or only dose), the concentration of ertapenem in skin blister fluid is expected to exceed 4 µg/ml within 1 hour of dosing. This level is well above the MIC₉₀ of the anticipated pathogens in surgical infections following colorectal surgery (e.g., *S. aureus*, enterics and anaerobes), all with MIC₉₀ ≤1.0 µg/ml. Therefore, while the dose would be given an expected 1 hour prior to incision, redose would not be required even if there were substantial delay to the initiation of surgery, or with prolonged procedure.

The comparative antibiotic, cefotetan, is a second generation cephalosporin with anti-anaerobic activity and relatively extended half life of approximately 4 hours. Cefotetan has been studied extensively with success rates in prophylaxis in colorectal surgery ranging from 72 to 92%. It is approved for use in prophylaxis of colorectal surgery in the US, and has been used extensively in clinical trials of surgical prophylaxis and in practice. The standard dose of cefotetan is 1 to 2 g IV administered 30 to 60 minutes prior to incision. In accordance with its product circular and other published information, the dose of cefotetan used in the study was 2 g IV given 30 to 60 minutes prior to surgery. Cefotetan was developed by Yamanouchi and marketed outside Japan by Astra Zeneca as Cefotan & Apacef. In the EU, cefotetan has had national licences in a number of countries including Belgium, Italy, Germany, Austria and France but recently a few have been withdrawn (e.g. France 2004, Belgium April 2005) and its MAH has variously ceased production for a few EU states. MSD confirms that in France, there was specific registration for 'prophylaxis in surgical site infection following colo-rectal surgery'. Also, the dosage used in protocol 039 is consistent with that in the Belgian guideline on recommendations for prophylactic use of antibiotic in surgery "HGR Aanbevelingen voor het prophylactisch gebruik van antibiotica in de heelkunde" and the Italian guidelines on the use of antibiotics "Linee guida per la profilassi antibiotica in chirurgia".

Efficacy evaluation

Assessment of clinical response was made for all patients at the time of hospital discharge and at the follow-up visit 4 weeks posttreatment. Although clinical response was assessed at two time points for each patient, the primary assessment of clinical response was made at the follow-up, or test-of-success visit, 4 weeks posttreatment. If a patient had an unfavorable clinical response at any time before the follow-up visit, that was considered the clinical endpoint and no further assessment or clinical response was required. If a patient was not declared a failure and did not return for an appropriate follow-up visit with the investigator, the patient was considered unevaluable with an indeterminate outcome.

The **primary efficacy endpoint** was the proportion of clinically evaluable patients who had a favorable clinical response assessment at the 4 week posttreatment follow-up visit. Clinical response assessments were made by the investigator at hospital discharge and at the 4-week posttreatment follow-up visit. For the efficacy analysis, the clinical response at the 4-week posttreatment visit was considered to be the primary endpoint. Clinical response definitions were success of prophylaxis, failure of prophylaxis, or distant site infection as defined below. Patients experiencing both a failure of prophylaxis and a distant site infection had both clinical responses entered into the database and were considered to be a failure of prophylaxis for the primary endpoint.

Patients assessed as being a **success** of prophylaxis were required to meet all three of the following criteria:

- No signs or symptoms of infection at the surgical site.
- No further antimicrobial therapy was necessary.
- No surgical intervention for infection was necessary

Patients assessed as being a **failure** of prophylaxis were classified as having development of a surgical site infection, receiving unexplained antibiotics, or experiencing an anastomotic leak, as defined below. Patients with development of a surgical site infection were further classified as having a superficial incisional infection, a deep incisional infection, or an organ/space infection as defined below.

(a) **Surgical Site Infection**

1. **Superficial incisional** – Infection occurred within 30 days after the operation and infection involved only skin or subcutaneous tissue of the incision and at least one of the following:

- Purulent drainage, with or without laboratory confirmation, from the superficial incision.
- Organisms isolated from an aseptically obtained culture or fluid or tissue from the superficial incision.
- At least one of the following signs or symptoms of infection: Pain or tenderness, localised swelling, redness, or heat **and** superficial incision is deliberately opened by the surgeon or attending physician.

Stitch abscesses (minimal inflammation and discharge confined to the points of suture penetration) and incisional SSI that extends into the fascial and muscle layers.

2. **Deep incisional** – Infection occurred within 30 days after the operation and infection involved deep soft tissue (eg., fascial and muscular layers) of the incision and at least one of the following:

- Purulent drainage from the deep incision but not from the organ space component of the surgical site.
- A deep incision spontaneously dehisced or was deliberately opened by a surgeon when the patient had at least one of the following signs or symptoms: fever ($>38^{\circ}\text{C}$), localised pain or tenderness.
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.

An organ/space infection that drained through the incision was to be reported as a deep incisional surgical site infection.

3. **Organ/space** – Infection occurred within 30 days after the operation and infection appears related to the operation and infection involves any part of the anatomy (e-g., organ or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:

- Purulent drainage from a drain that is placed through a stab wound into the organ/space.
- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.

An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation or by histopathologic or radiologic examination.

(b) **Unexplained antibiotic use** – Any patient receiving antibiotic therapy within the 4 weeks following colorectal surgery for any reason other than development of a surgical site infection or a distant site infection was considered to be a failure due to unexplained antibiotic use.

(c) **Anastomotic leak** – Patients with an anastomotic leak of the involved bowel requiring additional intervention by surgery or use of antimicrobials was considered a failure due to anastomotic leak. Patients developing an organ/space infection due to an anastomotic leak were assessed as an anastomotic leak for the primary efficacy analysis.

Patients with a final clinical response assessment of “**distant site infection**” were not evaluable for the primary analysis of efficacy. Distant site infections were documented according to the following criteria:

1. **Urinary Tract Infection** - Diagnosed by signs and symptoms of a urinary tract infection and a urine culture with 100,000 colonies/ml (or $\geq 10,000$ colonies/ml if the same bacterial species was isolated from 2 urine samples at different times).
2. **Pneumonia** - Diagnosed by a new infiltrate on the chest x-ray and presence of at least one of the following signs and symptoms: fever (defined as body temperature of $\geq 38^{\circ}\text{C}$), leukocytosis $>12,500$ cells/ mm^3 , increased sputum production with numerous leukocytes, and a predominant bacterial species.
3. **Vascular Site** - Defined by erythema, swelling, tenderness, and/or the presence of purulent material at the catheter site that required systemic antimicrobial therapy.
4. **Other** - Other distant site infections which were clearly unrelated to the surgical site.

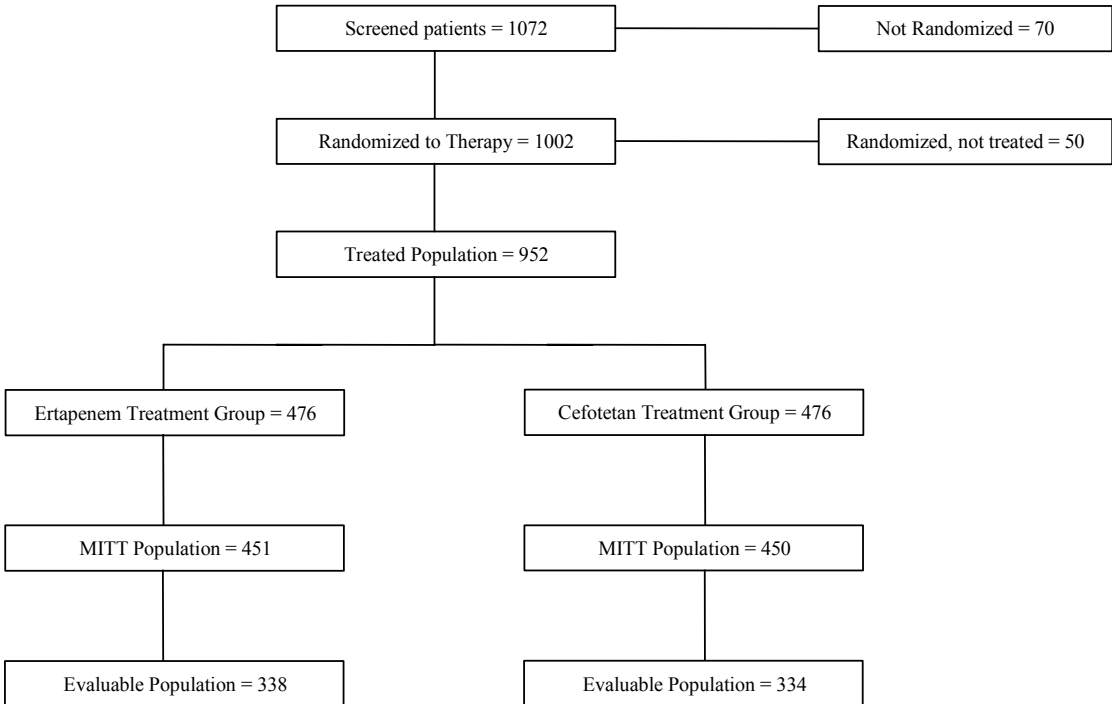
Other endpoints: (1) The proportion of patients with a distant site infection any time up to the 4-weeks posttreatment visit. (2) The proportion of patients who develop the presence of microbiologic pathogens (any pathogen and for each pathogen). (3) The proportion of patients with any drug-related AEs.

Definitions of populations

The following terms are used to describe the study populations analyzed in this study:

- **Screened population:** all patients who signed a consent form for the study. This population includes those patients who were not randomised to therapy and those patients who were randomised to therapy.
- **Randomised population:** a subset of the screened population comprised of patients who were randomised to a study regimen, irrespective of whether the patient actually received study therapy. Patients randomised to one treatment group who, due to dispensing errors, mistakenly received study therapy with the other study treatment were analyzed and displayed throughout the report based on the study therapy actually received.
- **Treated population:** a subset of the randomised population comprised of patients that received at least a partial dose of study therapy. Only treated patients are included in the safety analysis.
- **Modified Intent-to-Treat (MITT) population:** a subset of the treated population that met the minimal disease definition, received a complete dose of study therapy at any time before or during surgery, and underwent elective surgery of the colon or rectum with completion of an appropriate bowel preparation. Determination of the MITT population was made prior to unblinding using prespecified criteria as indicated in the Efficacy Evaluability Document.
- **Evaluable population:** a subset of the MITT population comprised of patients who met the evaluability criteria specified in the Efficacy Evaluability Document up to and including their 4-week follow-up assessment. This population comprises patients who received a complete dose of study therapy no more than two hours prior to initial surgical incision and no more than six hours before surgical closure and in whom sufficient information was available to determine their outcome at the 4-week follow-up assessment and for whom no confounding factors were present that interfered with the assessment of that outcome.

The figure below is the profile of study enrollment and summarizes the number of patients in the MITT and evaluable populations.



Determinations of evaluability were made prior to unblinding using prespecified criteria as indicated in the Efficacy Evaluability Document. All changes to clinical response and evaluability prior to unblinding are captured in the audit list for patient evaluability and clinical response modules. Any change to data subsequent to unblinding is captured in the critical change memo.

The most common reason patients were excluded for the MITT population was minimal surgical definition not met. This included 41 patients who did not undergo an appropriate colorectal surgery in addition to 49 of the 50 patients randomised but not treated.

The other primary reason patients were not qualified for the MITT population was study therapy violation. To be considered qualified for the MITT population, patients were required to receive a full dose of study medication. However, receiving a dose of study medication within 2 hours of incision and 6 hours of wound closure was not required to be qualified for the MITT population as it was in the evaluable population. Twenty-four (24) patients in the ertapenem group and 26 patients in the cefotetan group were randomised but did not receive study medication and were excluded from the MITT population. One patient in the cefotetan group received only a partial dose of study medication and was thus excluded from the MITT population.

Analysis populations

The “evaluable-patients-only” approach was the primary efficacy approach. A criterion for exclusion from the evaluable-patients-only approach was concomitant antibiotic therapy to treat a distant site infection, with no evidence of subsequent surgical site infection. However, patients who received concomitant antibiotic therapy to treat a distant site infection, and developed a subsequent surgical site infection were considered evaluable failures.

A modified intent-to-treat (MITT) efficacy analysis was also performed for the primary endpoint. This analysis was considered supportive of the primary evaluable-patients-only analysis. All patients randomised and treated, who underwent elective colorectal surgery with completion of bowel preparation procedure were included in the modified intent-to-treat analysis. All patients who were considered non-evaluable for the primary analysis because of concomitant antibiotic use for a distant site infection were considered failures for the MITT analysis, regardless of investigator’s assessment of the surgical site. In addition to the primary efficacy endpoint, all other efficacy endpoints were analysed for the MITT patient population.

• Discussion and results from the main study: Protocol 039.

The study 039 was planned for a total enrollment of approximately 900 patients to achieve 340 evaluable patients in each arm. However, during the enrollment period, an assessment of the evaluability rate on the blinded data showed a lower than expected rate of evaluability. Therefore, enrollment was extended and 1002 patients were randomised into 1 of 2 treatment groups: 500 patients were randomised to receive ertapenem and 502 patients were randomised to receive cefotetan. Four hundred and seventy six (476) patients received ertapenem and 476 patients received cefotetan. Fifty (50) patients were randomised to 1 of the 2 treatment arms (24 to ertapenem and 26 to cefotetan) but received no study therapy.

The primary efficacy analysis included all patients who were considered evaluable up until the 4-week follow-up assessment. Six hundred seventy-two (672) patients were considered evaluable for the primary efficacy analysis: 338 patients received ertapenem and 334 received cefotetan. A modified intent-to-treat (MITT) analysis was done to support the evaluable population analysis; 901 (89.9%) randomised patients were included in this analysis.

In terms of **accounting of patients in the evaluable population**, the 2 treatment groups were generally similar with respect to reasons that patients discontinued from the study. A high proportion of evaluable patients in both treatment groups had an elective colorectal surgical procedure for colon or rectal cancer. Patients could have multiple procedures, additional surgical findings, and procedure requirements but were required to undergo a procedure involving resection of the colon or rectum to be included in the evaluable and MITT population. The 3 commonest procedures were hemicolectomy (31.1%), sigmoidectomy (39.6%) and resection of the rectum (22.9%). Of these procedures, it may be

considered that resection of the rectum, sigmoidectomy and hemicolectomy have descending risk of contamination, with resection of the rectum associated with the highest risk of the 3 procedures. Between the 2 treatment groups, the comparator group has a slightly lower proportion of the resection of the rectum (cefotetan 20.7% vs. ertapenem 25.1%) (arguably highest contamination risk of the 3 procedures) and sigmoidectomy (cefotetan 34.4% vs. ertapenem 44.7%). This maybe related to the lower rate of rectal cancer subjects in the comparator group (cefotetan 14.1% vs. ertapenem 20.4%). With regard to hemicolectomy (arguably the lower contamination risk of the 3 procedures), the comparator group has a slightly higher proportion than the test group (cefotetan 33.5% vs. ertapenem 28.7%).

The 2 treatment groups appear similar with respect to the **distribution of surgical details in the evaluable population** and are similar to the treated population. Between the 2 treatment groups, the comparator group has a slightly lower proportion of inadvertent perforation or spillage of luminal contents (cefotetan 1.8% vs. ertapenem 3.6%), adjuvant chemotherapy ≤ 30 days prior to surgery (cefotetan 1.5% vs. ertapenem 3.0%) and radiation therapy ≤ 30 days prior to surgery (cefotetan 1.8% vs. ertapenem 2.7%).

The 2 treatment groups appear similar with respect to **risk factors for infection by treatment group for the evaluable population** and the evaluable population appears similar to the treated population. Between the 2 treatment groups, the comparator group has a slightly lower proportion of obesity (cefotetan 27.5% vs. ertapenem 30.5%), but a slightly higher mean BMI (cefotetan 6.4% vs. ertapenem 5.9%).

The 2 treatment groups appear similar with respect to **specific secondary diagnoses with an incidence $\geq 3\%$ in one or more treatment groups by body system in the evaluable population** and the evaluable population appears similar to the treated population.

The 2 treatment groups appeared to be generally similar with respect to the **therapies administered prior to study entry** (systemic antibacterial, steroid, or chemo therapies within 14 days prior to study therapy). All prior therapy was appropriately accounted for in the evaluability determination. It should be noted that patients who received antibacterial therapy within 7 days of study therapy and patients with immunosuppression due to use of high-dose corticosteroids (e.g. 40 or more of prednisone or equivalent per day) were considered to be non-evaluable. A numerically higher number of patients in the cefotetan group took concomitant antibiotics. It should be noted that patients receiving antimicrobials for a distant site infection with no subsequent sign of infection at the operative site were considered non-evaluable.

Efficacy evaluation

The primary efficacy analysis was performed on the evaluable patient population. The primary endpoint of interest was the favorable clinical response rate at the 4-weeks posttreatment follow-up assessment. The difference in response rates between the 2 treatment groups was calculated as ertapenem response rate (%) minus cefotetan response rate (%). Evaluable patients who were clinical failures prior to the 4-week visit were considered failures/unfavorable for all subsequent time points, including the 4-weeks posttreatment follow-up assessment. All missing clinical outcomes (after carry forward rules were applied) were excluded from the analysis. The modified-intent-to-treat (MITT) analyses considered missing outcomes as unfavorable and were supportive of the respective evaluable patient analysis.

To address the primary hypothesis, the estimated proportion, adjusting for surgical procedure, of evaluable patients with a favorable clinical response assessment 4-weeks posttreatment was evaluated in both treatment groups. For the evaluable population, 72.0% of patients in the ertapenem group and 57.2% of patients in the cefotetan group had a favorable clinical response assessment. The difference in the clinical response rates between the 2 treatment groups was 14.8 percentage points favoring ertapenem with a 95% CI of (7.5%, 21.9%). The lower limit of the 95% CI was greater than the prespecified non-inferiority margin of -10 percentage points. In addition, the lower limit of the 95% CI was greater than 0.

The estimated proportion, adjusting for surgical procedure, of MITT qualified patients with a favorable clinical response assessment 4-weeks post-treatment was evaluated in both treatment groups. Fifty-nine point eight percent (59.8%) of patients in the ertapenem group and 49.1% of patients in the cefotetan group had a favorable clinical response assessment. The response rates for both treatment groups are lower in the MITT population compared to the evaluable population. This is mainly due to patients with missing 4-week responses as well as patients who took concomitant antibiotics for a distant site infection as they were considered failures for the MITT analysis. The difference in the clinical response rates between the 2 treatment groups was 10.7 percentage points favoring ertapenem with a 95% CI of (4.2%, 17.1%). The lower limit of the 95% CI is 4.2% which is greater than the prespecified non-inferiority margin of -10 percentage points and greater than 0. The MITT data, although numerically lower, supports the primary analysis results. Thus the data indicate that ertapenem is superior to cefotetan with respect to clinical response rates in MITT qualified patients at the 4-weeks post-treatment follow-up assessment.

Subgroup Analysis

The clinical response assessment at the 4-weeks post treatment follow-up assessment was also analysed within a number of specific predefined subgroups of the evaluable population. These subgroups include: gender, age, race, bowel preparation, and creatinine clearance.

Younger age was associated with lower response than older age in the ertapenem group (age <62 yrs. 67.9% vs. age >62 yrs. 75.6%). In contrast, male gender was associated with lower response than female gender in the comparator group (male 52.3% vs. female 62.7%).

Distant Site Infections

Although the overall incidence of distant site infections was similar across treatment groups (10.6% ertapenem and 12.3% cefotetan) the incidence of specific types of infections varied across treatment. Cefotetan had a numerically higher incidence of pneumonia and Urinary Tract Infection while ertapenem had a numerically higher incidence of distant site infections categorised as other.

Nineteen (19) pathogens were isolated from 14 patients in the ertapenem group and 29 pathogens were isolated from 21 patients in the cefotetan group. The most frequently documented pathogens were generally consistent with what was seen in the surgical source with *Enterococcus*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli*, being the predominate organisms identified. Additionally, *Pseudomonas aeruginosa* was seen in a higher percentage of distant site infections, primarily in the cefotetan treatment group. There were no anaerobic pathogens identified from the distant site source.

Risk Factor Analysis

An exploratory evaluation of baseline and surgery factors was performed to assess whether they were risk factors for favorable clinical outcome or postoperative infections. The following factors were pre-specified for evaluation: BMI, diabetes, tobacco use (current user, ex-user, non-user), time from study medication given to surgical incision, baseline albumin, creatinine clearance subgroup (>30 ml/min/1.73 m², ≤30 ml/min/1.73 m²), surgical drains used (yes, no), duration of surgery, occurrence of inadvertent perforation or spillage of luminal contents (yes, no), bowel preparation (sodium phosphate, polyethylene glycol) and surgical site shaved or clipped (no, yes: immediately prior to surgery, within 24 hours of surgery, >24 hours prior to surgery).

The association between the favorable clinical response and each of the risk factors was assessed using a univariate model. The most significant factors (p-value <0.01) were treatment, occurrence of perforation/spillage, baseline albumin, BMI, obesity, and duration of surgery.

Microbiology of Failures

Specimens from the surgical site were to be appropriately obtained and sent for aerobic and anaerobic culture if a patient developed a postoperative infection at the surgical site, or in circumstances of an anastomotic leak.

One hundred and twenty four (124) pathogens were isolated from 30 patients in the ertapenem group and 151 pathogens were isolated from 55 patients in the cefotetan group. The most frequently isolated

pathogens were gram positive aerobic cocci with *Enterococcus*, *Enterococcus faecalis*, and *Staphylococcus aureus* being the predominate species identified. Gram negative anaerobic coccobacilli were also isolated with *Bacteroides fragilis* and *Bacteroides thetaiotaomicron* being the most frequently observed. Gram negative aerobic bacilli were isolated in fewer numbers with *Escherichia coli* and *Pseudomonas aeruginosa* being the most frequently identified. Gram positive anaerobic bacilli were isolated but no organisms were frequently seen with the exception of *Clostridium innocuum* and *Eubacterium lentum* in the cefotetan group. In general, the pathogens identified were similar across the treatment groups and specific pathogen isolated with the exception of the *Clostridium innocuum* and *Eubacterium lentum* isolated in the cefotetan group.

A review of the most frequently isolated pathogens reveals no strong evidence of a relationship between type of surgical infection and pathogens isolated. *Enterococcus* and *Enterococcus faecalis* were seen in a slightly higher number in superficial incisional and organ/space infection in the cefotetan group but were evenly distributed across infection type in the ertapenem group. *Staphylococcus aureus* was isolated most frequently in superficial incisional infection in both groups and *Escherichia coli* was seen most frequently in patients with an anastomotic leak in both groups. *Bacteroides fragilis* was evenly distributed across infection type and *Bacteroides thetaiotaomicron* was seen most frequently in superficial incisional infections in the cefotetan group and evenly distributed across infection type in the ertapenem group. *Clostridium innocuum* and *Eubacterium lentum* isolated in the cefotetan group were isolated from superficial incisional infections.

Consistent with established information from the product circulars and published information for both products, some resistant pathogens were isolated. *Enterococcus* (*avium*, *durans*, *faecalis*, *faecium*, *raffinosis*) isolated from patients treated with ertapenem as well as those treated with cefotetan exhibited a high prevalence of resistance to both study drugs. In addition, methicillin resistant *Staphylococcus aureus* isolated from patients in each group was also resistant to both study products. *Escherichia coli* identified was susceptible to both study products. All species of *Bacteroides* identified were susceptible to ertapenem but showed varying levels of resistance to cefotetan. Additionally, *Clostridium innocuum* and *Eubacterium lentum* were generally susceptible to ertapenem but generally resistant to cefotetan.

Overall, the majority of pathogens (66.7%) isolated and tested in the cefotetan group were resistant to cefotetan, whereas only 16.3% of the isolates tested in the ertapenem group were resistant to ertapenem. The prominence of *Enterococci* spp, *S. aureus*, *Bacteriodes* spp. & *E.coli* are entirely within the expected range of pathogens associated with post-colorectal surgical infection. *Enterococci* are always resistant to ertapenem and cefotetan. There was a notable difference in the sensitivities of the pathogens in the 2 groups: 67% of the pathogens identified in the cefotetan group were resistant to cefotetan, whereas only 16% of the pathogens in the ertapenem group were resistant to ertapenem. Also, *Clostridium innocuum* and *Eubacterium lentum* were observed to a greater degree in the cefotetan group (principally from superficial incisional infections); these isolates were uniformly resistant to cefotetan but susceptible to ertapenem.

Statistical Assessment of Efficacy

Although the study title claims this is an ‘in-house’ blinded study the study is, to all intents and purposes, double blind. In order to maintain the blind, assignment to treatment group and preparation of IV study antibiotics was performed by someone other than the person who administered and monitored product infusions and evaluated the patient for clinical response and presence of adverse experiences. The study pharmacist received open-label clinical supplies and an appropriate allocation schedule was provided by a central computerised system IVRS. The allocation schedules were not released to anyone else involved with the study, and the IV study antibiotics were “blinded” against visual discrimination as they were prepared by the pharmacist.

The primary analysis used a non-inferiority margin of 10% as suggested in the CPMP/EWP/558/95 note for guidance on evaluation of new anti-bacterial medicinal products. The MAH then switched the objectives of the trial to superiority once non-inferiority had been shown which is considered appropriate, even though it was not pre-specified (as discussed in the CPMP/EWP/482/99 points to

consider document on switching between superiority and non-inferiority). The analysis methods used are also considered to be appropriate for the endpoints used.

For the overall analysis, superiority of ertapenem over cefotetan was shown for both the EPP and MITT populations. A slightly larger treatment effect was seen in the EPP than the MITT population, which is as expected. The confidence interval presented was also slightly larger, which is due to the smaller number of patients included in the EPP population.

The results of this study indicate that, for the prophylaxis of surgical site infection following elective colorectal surgery in adults, ertapenem is superior to cefotetan. This is shown in both the EPP and MITT populations at 4 weeks post-treatment.

- **Choice of the dose**

Further to the assessment of data submitted originally in November 2005, the MAH was requested, in February 2006, to better justify the rationale of the proposed dose (1g single dose). In the supplementary information submitted, the MAH presented new data on the concentrations of ertapenem in colon, which confirm that sufficient active substance is present for the duration of most colorectal procedures (tissue concentrations exceeding the MIC90 for all relevant aerobic and anaerobic pathogens at >4 hours). In addition, presentation of results by time from administration of product and also by duration of surgery continues to support the primary results of Protocol 039 using 1g dose. The MAH's responses submitted in April 2006 are not judged fully satisfactory to resolve the concern on the inadequacy of the posology in case of surgical interventions of long duration. The MAH provided a post-hoc efficacy analysis by time slot of duration of surgical intervention and considered this analysis as reassuring insofar that results are in favour of ertapenem whatever the time duration of the intervention. The MAH's response that univariate analysis demonstrating duration of surgery as a predictor for development of postoperative infection was not specific of ertapenem. These results were consistent with known risk factors for infectious as well as non-infectious complications of intra-abdominal surgery. It should be highlighted that for other antibiotics (especially for the comparator, cefotetan), it is recommended to re-administer the product in cases where duration of the colorectal procedure lasts more than 4 hours (to avoid the risk of suboptimal concentrations).

Moreover, the MAH stated that the percentage of patients where duration of the colorectal procedure lasts more than 4 hours is expected to be low (estimated to 7%) and therefore the feasibility of an additional study to further substantiate the dose was questioned.

In summary, although colorectal procedures of duration greater than 4 hours may be expected rarely, it remains particularly worrying that such patients might be exposed to sub-optimal concentrations, based on the data submitted. **The CHMP agreed that this critical concern should not be ignored and requested that the section 4.4 of the SPC should be amended to reflect this point.**

As the potential difficulties in performing an additional study for substantiating the dose in patients experiencing long surgery (>4hours) are recognised, the MAH should be advised to adopt a step by step approach i.e. **the MAH should commit to collect PK/PD and efficacy data (treatment response) with the currently recommended dose in patients experiencing long surgery (>3 hours) in clinical practice (as a follow-up measure) and depending on the signal emerging from these data, the need for an additional study will be re-considered. The CHMP requested the MAH to submit a proposal by the end of September 2006.**

Despite the distribution data presented were reassuring, the MAH was requested, in April 2006, to further discuss the adequacy of the recommendation of the 1 hour time lag between the administration of ertapenem and the beginning of surgery, in light of eventually available PK data for colon distribution earlier than 120 minutes.

The supplementary data submitted in June 2006 support the expected fact that the ideal timing for administration of ertapenem for prophylactic reasons should be between 30 and 60 minutes before surgery. Since the present analysis is irrespective of surgery duration, and notwithstanding the fact that a further multivariate analysis should be conducted considering both these risk factors, it may be admitted that the delay from antibiotic administration and the beginning of surgery could be an

independent risk factor, as it is to be expected. **The CHMP agreed that this recommended timeframe between administration of ertapenem and surgery should be reflected in section 4.2 of the SPC.**

These supplementary data also support the fact that the prophylactic effectiveness of the currently proposed dosage for ertapenem for surgery procedures with duration > 4h, and possibly even after 3 hours, cannot be considered acceptable based only on the results of the study 039, even though other factors may significantly contribute to the failure rate observed in this group of patients. As the value of an additional 1g dose was not evaluated, the CHMP agreed that a precautionary statement should be added to section 4.4 of the SPC regarding this issue. **Furthermore, the MAH should explore the efficacy of a further 1g dose in colorectal surgical procedures with more than 3 hours duration. The CHMP requested the MAH to submit a proposal by the end of September 2006.**

- **Conclusion on clinical efficacy**

The data from the single pivotal study 039 supports the claim for *prophylaxis of surgical site infection elective colorectal surgery*.

For the overall analysis, superiority of ertapenem over cefotetan was shown for both the EPP and MITT populations. A slightly larger treatment effect was seen in the EPP than the MITT population, which is as expected. The confidence interval presented was also slightly larger, which is due to the smaller number of patients included in the EPP population. The results of this study indicate that, for the prophylaxis of surgical site infection following elective colorectal surgery in adults, ertapenem is superior to cefotetan. This is shown in both the EPP and MITT populations at 4 weeks post-treatment.

The use of the single dose of 1g has been properly justified. The ideal timing for administration of ertapenem for prophylactic reasons being between 30 and 60 minutes before surgery, the section 4.2 of the SPC has been updated to reflect it.

As the currently proposed dose of 1g for surgery procedures >3hours are not acceptable on the basis of this study 039 and as the value of an additional 1g dose was not evaluated, the CHMP agreed that a precautionary statement should be added to section 4.4 of the SPC regarding this issue.

2.2 Clinical safety

- **Safety data from the main study: Protocol 039**

Adverse experiences were recorded from the day a patient signed informed consent up to and including 14 days after administration of study therapy (safety follow-up period). Of the 1002 patients enrolled, 952 received their scheduled dose of study therapy and are included in the analysis of adverse experiences.

- **Patient exposure**

Of the 1002 randomised patients, 952 patients (476 in the ertapenem group and 476 in the cefotetan group) received their scheduled dose of study therapy. Fifty (50) patients (24 in the ertapenem group and 26 in the cefotetan group) were randomised but did not receive any study drug. These patients were excluded from the safety analyses. All patients were to receive one dose of study medication one hour prior to surgery infused over 30 minutes. The number of patients who received ertapenem was updated in section 4.8 of the SPC to add the 476 adults from this study 039.

- **Adverse events during study therapy and 14-day follow-up period**

Overall 738 out of 952 patients (77.5%) experienced clinical adverse experiences during study therapy and 14-day follow-up period. There were 31 patients (6.5%) in the ertapenem group and 33 patients (6.9%) in the cefotetan group with drug related adverse experiences; 3 patients (0.6%) in the

ertapenem group and 3 patients (0.6%) in the cefotetan group experienced drug related serious adverse experiences. One patient in the cefotetan group discontinued study therapy due to a drug related adverse experience. No patients in the ertapenem group discontinued due to drug related serious adverse experiences.

Of the patients treated, 357 patients (75.0%) in the ertapenem group and 381 patients (80.0%) in the cefotetan group had one or more adverse experience during study therapy and the 14-day follow up period (Incidence $\geq 3\%$ in One or More Treatment Groups). The most common adverse experiences were **gastrointestinal disorders** with 95 patients (20.0%) in the ertapenem group and 121 patients (25.4%) in the cefotetan group reporting nausea and 54 patients (11.3%) in the ertapenem group and 52 patients (10.9%) in the cefotetan group reporting **vomiting**. Ileus was also frequent with 55 patients (11.6%) in the ertapenem group and 45 patients (9.5%) in the cefotetan group reporting **ileus**. Another common adverse experience was **pyrexia** with 72 patients (15.1%) in the ertapenem group and 64 patients (13.4%) in the cefotetan group reporting this event. The incidence of clinical adverse experiences was generally similar between the two treatment groups. However, consistent with the primary efficacy endpoint, the number of patients with infections and infestations was higher in the cefotetan group. One hundred patients (21.0%) in the ertapenem group and 142 patients (29.8%) in the cefotetan group experienced an infection during study therapy and 14-day follow-up period. These infections included **pneumonia, postoperative infection, urinary tract infect, and wound infection**.

Clinical adverse experiences occurring in 5% or more of patients in either treatment group were defined as frequently occurring clinical adverse experiences either treatment group during study therapy and the 14 day follow-up period. The treatment difference for these clinical adverse experiences and the 95% CI about the treatment difference are also displayed in the table. **Nausea** was reported by 95 patients (20.0%) in the ertapenem group and 121 patients (25.4%) in the cefotetan group. This confidence interval for the difference indicates that ertapenem had significantly lower incidence of nausea than cefotetan. An additional significant difference exists with respect to **wound infection**. Thirty-one patients (6.5%) in the ertapenem group and 59 patients (12.5%) in the cefotetan group experienced a wound infection during study therapy and the 14-day follow-up period.

Thirty-one (31) patients (6.5%) in the ertapenem group and 33 patients (6.9%) in the cefotetan group had one or more drug related adverse experiences during study therapy and the 14-day follow-up period (Incidence $\geq 0\%$ in One or More Treatment Groups). The incidence of drug related clinical adverse experiences were similar between the 2 treatment groups. Three (3) patients (0.6%) in the ertapenem group and 4 patients (0.8%) in the cefotetan group experienced a drug related clinical adverse event on the day of initial operative procedure.

- **Serious adverse events and deaths**

Three (3) patients in the ertapenem group and 7 patients in the cefotetan group experienced adverse experiences resulting in death. None of these deaths were considered to be drug related.

Amongst patients with serious adverse experiences with incidence $>0\%$ by body system occurring during therapy and the 14-day follow-up period (including fatal and nonfatal serious clinical adverse experiences), 98 patients (20.6%) in the ertapenem group and 121 patients (25.4%) in the cefotetan group experienced serious clinical adverse experiences. As expected in this surgical population, the most frequently occurring serious clinical adverse experiences were **ileus** and **wound infection**. Nineteen patients (4.0%) in the ertapenem group and 10 patients (2.1%) in the cefotetan group experienced ileus. Wound infection considered to be serious adverse events occurred in 10 patients (2.1%) in the ertapenem group and 20 patients (4.2%) in the cefotetan group.

Three patients in the ertapenem group experienced a serious clinical adverse experience of **cerebrovascular accident**. One experienced a **severe stroke** on the day of initial operative procedure. One experienced a **mild cerebrovascular** event on Study Day 8 and one experienced a **moderate cerebrovascular** event on Study Day 13. All three events were determined to be definitely not or probably not related to study medication.

Amongst the patients with serious drug-related adverse experiences with incidence $>0\%$ by body system occurring during study therapy and the 14-day follow-up period, 3 (0.6%) in the ertapenem group and 3 (0.6%) in the cefotetan group experienced serious drug related clinical adverse

experiences during study therapy and 14 day follow up period. These events can be found in the table below:

Number (%) of Patients With Serious Clinical Adverse Experiences
During Study Therapy and 14-Day Follow-Up Period
(Incidence >0% in One or More Treatment Groups) by System Organ Class—
(Treated Population)
Drug Related

| | Ertapenem (N=476) | | Cefotetan (N=476) | |
|---|----------------------|--------------|----------------------|--------------|
| | n | (%) | n | (%) |
| Patients With One Or More Adverse Experiences | 3 | (0.6) | 3 | (0.6) |
| Patients With No Adverse Experience | 473 | (99.4) | 473 | (99.4) |
| Cardiac Disorders | 1 | (0.2) | 0 | (0.0) |
| Sinus Bradycardia | 1 | (0.2) | 0 | (0.0) |
| Infections and Infestations | 2 | (0.4) | 3 | (0.6) |
| Clostridium Colitis | 2 | (0.4) | 0 | (0.0) |
| Wound Infection | 0 | (0.0) | 3 | (0.6) |
| Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories. | | | | |

Since this was a single dose study, patients discontinued from study therapy due adverse experience had to have a discontinuation of their study therapy during the infusion. One patient in the cefotetan group began experiencing **hypersensitivity symptoms** (a flushed face, watery eyes, sneezing, coughing, wheezing, and a splotchy chest) after receiving 12 ml of study drug. The drug was discontinued and the patient was discontinued from the study. No patients in the ertapenem group discontinued study therapy due to a clinical adverse experience.

- **Laboratory findings**

Nine hundred thirty-four (934) out of 952 treated patients had a least one laboratory test postbaseline during study therapy and the 14-day follow-up period. Two hundred twenty-four (224) of these patients had laboratory adverse experiences, 101 (21.7%) in the ertapenem group and 123 (26.3%) in the cefotetan group. There were 9 patients with serious laboratory adverse experiences, 2 in the ertapenem group and 7 in the cefotetan group. None of these serious adverse experiences were considered drug related and no patients discontinued as a result of a laboratory adverse experience. The incidence of laboratory adverse experiences was similar between the 2 treatment groups. The most common laboratory adverse experiences in both treatment groups were **decreases in blood potassium and blood magnesium** and an **increase in white blood cell count**.

No patients in either treatment group experienced a serious drug related laboratory adverse experience during study treatment and 14-day follow-up period.

No patients discontinued study therapy or study due to laboratory adverse experiences.

- **CSLAs During Hospitalisation**

In addition to reviewing investigator-reported laboratory adverse experiences, assessment of the relative laboratory safety of each treatment group was accomplished by predefining clinically significant laboratory abnormalities (CSLAs) for specified tests and then identifying patients whose worst laboratory value represented a worsening from baseline and met the criteria for a CSLA. Additionally, a review of shift in laboratory values was performed for specified tests. The combination of these 3 approaches to the analysis of laboratory abnormalities provides a more complete overview of the profile of laboratory safety.

In order to be considered in the population for CSLAs, patients had to have a baseline laboratory value, at least 1 postbaseline laboratory test, and normal ranges in the database. For platelet count, absolute neutrophil count, hematocrit, and hemoglobin, the CSLA criteria were defined in terms of a fixed bound. For total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase and serum creatinine, the CSLA criteria were defined in terms of a function of the upper limit of the normal range

(ULN). Patients whose baseline laboratory value exceeded the CSLA criteria were included in the count of patients with CSLAs if any of their postbaseline tests worsened compared to the baseline value. Hospitalisation was defined as the period of time from the time of initial dose to the time the patient was discharged from the hospital after the initial operative procedure. Overall, the proportion of patients with CSLAs was low and generally similar between the 2 treatment groups.

The most common CSLAs during hospitalisation were **elevated total or direct serum bilirubin**. During hospitalisation 20/403 patients (5.0%) in the ertapenem group and 18/407 patients (4.4%) in the cefotetan group experienced an elevation in total serum bilirubin of > 1.5 x ULN. Fourteen (14) of 129 patients (10.9%) in the ertapenem group and 12/130 patients (9.2%) in the cefotetan group experienced an increase in serum direct bilirubin 1.5 x ULN. In the ertapenem group, 10/403 patients (2.5%) experienced a total serum bilirubin elevation >2.5 x ULN and 9/129 patients (7.0%) experienced a serum direct bilirubin >2.5 x ULN (four patients experienced both total bilirubin >2.5 x ULN and serum direct >2.5 x ULN).

- **Adverse events added to the SPC**

The MAH did a comprehensive evaluation of the clinical and laboratory safety information from this new single dose double-blinded colorectal prophylaxis study in adults (Protocol 039), the basis of the current submission, in order to ascertain whether there were new additional investigator determined drug-related adverse events (AE) or concerns not presently reported in the EUSPC. Two new clinical AEs (sinus bradycardia, urticaria) and one new laboratory AE (increased prothrombin time) were identified as possibly drug-related.

Sinus Bradycardia: An adverse event of bradycardia was reported in 3 patients in Protocol 039: one patient who had received ertapenem and 2 patients who received cefotetan. None of these events were considered related to study therapy by the investigator. There was 1 adverse event of sinus bradycardia in the study, occurring in the immediate pre-operative period in a patient who received ertapenem prophylaxis. This 76-year-old male with a previous history of A-V conduction disorder, also on treatment for hypertension, experienced transient worsening of sinus bradycardia and onset of transient low blood pressure as the study drug pre-operative infusion was completed. He had been receiving a number of other medications, including atenolol, fosinopril and citalopram that may have contributed to the bradycardia and blood pressure changes. Because of the temporal relationship to the administration of ertapenem the MAH considered this to be possibly a drug related event.

To the MAH's knowledge there is no known or reported mechanism, either for ertapenem, or for other drugs in the carbapenem class, resulting in sinus bradycardia. Other than the single report in this study which is confounded by pre-existing conditions and medications with potential cardiac effects, review of both the clinical trial and the post-marketing safety environment reveal no direct association between ertapenem and sinus bradycardia. However, because of the temporal association to ertapenem administration in the patient in this study and because the event was ascribed by the investigator as possibly related to study therapy, the MAH proposed for completeness to include the term 'sinus. The CHMP agrees with the proposal.

Urticaria: In Protocol 039 an adverse event of urticaria was reported in 1 (0.2%) patient who had received ertapenem and 1 (0.2%) patient who had received cefotetan as single dose prophylaxis. This is a 66-year-old Asian female with a medical history positive for Crohn's disease and colon adenocarcinoma (primary diagnosis for study entry), as well as a history significant for osteoporosis, arthritis, low back pain as well as bilateral cataracts, experienced some mild laboratory adverse experiences (decreased phosphorus and potassium) as well as headache, fever, and lower back pain. She also had diarrhea, blood in stool and some abdominal distension. On study day 10, the patient experienced transient "groin hives" which were noted to resolve spontaneously later in the day. Concomitant medications at the time of the urticaria were potassium chloride, metamucil, and percocet. These events were considered possibly related to study therapy by the MAH.

Rash and hypersensitivity reactions are currently included in the ertapenem SPC. The term urticaria is not. Both the time to onset and the course observed in the single case of urticaria reported in Protocol 039 strongly suggest an etiology other than the dose of ertapenem received 10 days previously as the

cause of urticaria. Examination of the post-marketing safety of ertapenem does not provide compelling evidence to support the addition of this term to the SPC. Because the event (urticaria) in Protocol 039 was reported by the investigator as possibly drug-related, the MAH has included the term in the proposed SPC for completeness and consistency with the previous approach for reporting undesirable effects in the SPC. The CHMP agrees with this proposal.

Increased Prothrombin Time: For patients in Protocol 039 who had at least one laboratory test performed post-baseline, one or more laboratory adverse event (AE) was reported in 21.7% of patients in the ertapenem group and 26.3% of patients who received cefotetan. As would be expected, the large majority of these events were attributed to surgical management or complications of surgery. Only 3 (0.6%) and 9 (1.9%) patients in the ertapenem and cefotetan group respectively experienced a drug-related laboratory AE; none of these AEs were considered serious. Prolonged prothrombin time was reported in 4/386 (1.0%) patients who received a single prophylactic dose of ertapenem and 5/385 (1.3%) patients who received cefotetan. One patient in the ertapenem group and 4 patients in the comparator group had this reported as possibly drug-related.

Prolonged Prothrombin Time (PT) was reported uncommonly in Protocol 039 occurring post-operatively in 1.0% of 386 patients who received a prophylactic dose of ertapenem and 1.3% of 385 patients who received cefotetan. These increases were noted days after the dose of ertapenem would have been cleared from the body, were generally mild and none were considered serious. In one case the PT increase was considered by the investigator to have been possibly related to ertapenem. Review of the post-marketing safety data base revealed rare reports of PT increase but these reports were confounded by other medications or incomplete data and alone do not support a causative association between ertapenem PT prolongation. Because, however, this event (increased PT) in Protocol 039 was reported by the investigator as possibly drug-related, the MAH has included the term in the proposed SPC for completeness and consistency with the previous approach for reporting undesirable effects in the SPC. The CHMP agrees with this proposal.

- **Conclusion on clinical safety**

The frequently occurring clinical adverse events during study therapy and the 14-day follow-up period were: **gastrointestinal disorders, vomiting, ileus, pneumonia, postoperative infection, urinary tract infect, and wound infection.**

Three (3) patients in the ertapenem group and 7 patients in the cefotetan group experienced adverse experiences resulting in death. None of these deaths were considered to be drug related.

The most common clinically significant laboratory abnormalities during study therapy and the 14-day follow-up period were **decreases in blood potassium and blood magnesium and an increase in white blood cell count.**

With respect to the above data, **sinus bradycardia, urticaria and increased prothrombin time** were added in section 4.8 of the SPC.

Further to the assessment of the data submitted, no major new safety issues have been identified that needed to be added to the SPC.

2.3 Conclusion on clinical aspects

Study 039 provided evidence to support the indication *prophylaxis of surgical site infection elective colorectal surgery in adults.*

The use of a single dose of 1g is supported for this indication with a statement to reflect that the ideal timing for administration of ertapenem for prophylactic reasons to be completed within the hour before surgery.

As the currently proposed dose of 1g for surgery procedures > 4hours are not acceptable on the basis of this study 039 and as the value of an additional 1g dose was not evaluated, a precautionary statement should be added to section 4.4 of the SPC regarding this issue.

Further to the assessment of the data submitted, no major new safety issues have been identified. With respect to the above data, sinus bradycardia, urticaria and increased prothrombin time were added in section 4.8 of the SPC.

The overall benefit/risk assessment is positive for an extension of the therapeutic indication to the use in Invanz to *prophylaxis of surgical site infection elective colorectal surgery in adults*.

3. Changes to the Product Information directly linked to study 039

- **Section 4.1 “Therapeutic indications” of the SPC**

To reflect the added indication, the following statement was added:

Prevention

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

- **Section 4.2 “Posology and method of administration” of the SPC**

To reflect the optimal use of Invanz, i.e. administration to be completed within 1 hour prior to surgery, the following statement was added:

Prophylaxis of surgical site infection following elective colorectal surgery in adults: To prevent surgical site infections, the recommended dosage is 1 g administered as a single intravenous dose to be completed within 1 hour prior to the surgical incision.

- **Section 4.4 “Special warnings and precautions for use” of the SPC**

To reflect that the currently proposed dose of 1g for surgery procedures > 4hours are not acceptable on the basis of this study 039 and as the value of an additional 1g dose was not evaluated, the following statement was added:

Based on the data available it cannot be excluded that in the few cases of surgical interventions exceeding 4 hours, patients could be exposed to sub-optimal Ertapenem concentrations and consequently to a risk of potential treatment failure. Therefore, caution should be exercised in such unusual cases.

- **Section 4.8 “Undesirable effects” of the SPC**

To update the number of adults 18 years of age and older who received ertapenem, the following statement was added:

An additional 476 patients received ertapenem as a single 1 g dose prior to surgery in a clinical study for the prophylaxis of surgical site infections following colorectal surgery.

Sinus bradycardia, urticaria and increased prothrombin time were added in section 4.8 of the SPC as follows:

Cardiac disorders: *Uncommon: Sinus bradycardia*

Skin and subcutaneous tissue disorders: *Uncommon: urticaria*

Haematology: *Uncommon: increased prothrombin time*

The Package Leaflet has been updated accordingly in its sections 1, 3 and 4.

4. Further changes to the Product Information

- **Section 2 “Qualitative and quantitative composition”**

The following information of the quantity of sodium in Invanz as excipients was added:

Excipients: each 1.0 g dose contains approximately 6.0 mEq of sodium (approximately 137 mg).

This information was as well reflected in section 4.4 of the SPC as follows:

This medicinal product contains approximately 6.0 mEq (approximately 137 mg) of sodium per 1.0 g dose, which should be taken into consideration by patients on a controlled sodium diet.

- **Section 4.2 “Posology and method of administration” of the SPC**

The MAH proposed to add *Infants* to better reflect the group of age concerned, meaning from 3 months of age and replaced *INVANZ is not recommended in children under 3 months of age, as no data are available* by *There is no experience in children under the 3 months of age*. These updates were accepted by the CHMP.

For infants and children (3 months to 12 years of age): The dose of INVANZ is 15 mg/kg given twice daily (not to exceed 1 g/day) by the intravenous route (see section 6.6). There is no experience in children under the 3 months of age (see section 4.4).

- **Section 4.7 “Effects on ability to drive and use machines” of the SPC**

The MAH proposed to add:

No studies on the effects on the ability to drive and use machines have been performed.

This has been accepted by the CHMP.