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SCIENCE MEDICINES HEALTH

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Patient Health Protection

Assessment report for Tienam and associated names

Pursuant to Article 30 of Directive 2001/83/EC, as amended

International Non-proprietary Name: Imipenem monohydrate/Cilastatin sodium

Procedure No. EMEA/H/A-30/1187

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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1. Background information on the procedure

1.1. Background information on the basis of the grounds for referral

On 18 May 2009 The Netherlands presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, as amended, in order to harmonise the national summary of product characteristics, labelling and package leaflet of the medicinal products: Tienam and associated names (see Annex I of CHMP opinion).

Further to the CHMP's consideration of the matter, the referral procedure was initiated at the May 2009 meeting. The marketing authorisation holder was informed of the start of the procedure.

Tienam medicinal products are registered in the following EU Members States: Austria, Belgium, Bulgaria, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden and United Kingdom and also in Iceland and Norway.

2. Scientific discussion during the referral procedure

2.1. Introduction

A referral under Article 30 of Directive 2001/83, as amended was triggered by a Member State with the aim of harmonising the SPC for Tienam and associated names (imipenem and cilastatin sodium). The reference member state therefore triggered the referral procedure, which started in May 2009. During the May 2009 CHMP meeting, the CHMP adopted a list of questions (LoQ) to be addressed by the MAH, followed by a number of Lists of Outstanding Issues. During the course of the procedure, a Drafting Group meeting was convened by the CHMP in order to gain input from European Experts.

Tienam (also referred to as imipenem/cilastatin) is a broad spectrum antibacterial agent that belongs to the group of carbapenems and consists of a fixed combination (1:1 ratio) of imipenem (a carbapenem antibiotic which is a derivative of thienamycin) and cilastatin (an inhibitor of dehydropeptidase I, a renal enzyme which metabolizes and inactivates imipenem). Imipenem exerts a bactericidal action by inhibiting cell-wall synthesis in aerobic and anaerobic Gram-positive and Gram-negative bacteria. Cilastatin blocks the metabolism of imipenem by dehydropeptidase I on the brush borders of renal tubular cells. The concomitant administration of imipenem and cilastatin allows antibacterial levels of imipenem to be attained in the urine, and this combination may also protect against proximal renal tubular necrosis that can occur when imipenem is used alone. Imipenem has activity against a wide variety of bacteria, including Gram-positive aerobic cocci (including some bacteriostatic activity against enterococci), Gram-positive aerobic bacilli (including static activity against *Listeria*), Gram-negative aerobic bacteria (*Haemophilus*, *Enterobacteriaceae*, many strains of *Pseudomonas aeruginosa*), and anaerobes (including some strains of *Bacteroides*).

In its responses, the MAH evaluated the nationally approved SPCs and suggested appropriate changes in the text where divergences exist. For a number of sections, the MAH proposed to retain the wording currently used in the MAH EU SPC. To support the proposed harmonised SPC, the MAH provided a review of the data available for imipenem/cilastatin from the original Worldwide Marketing Applications (WMA) and available literature data, in particular regarding the four indications under question (i.e., gynaecological infections, septicaemia, bone and joint infections, and endocarditis) and the use in paediatric patients less than 3 years of age.

Tienam was approved in the EU beginning in 1985 and currently, 27 European countries (Norway, Iceland and all EU countries with the exception of Denmark and Cyprus) have active registrations. Tienam has a quite long history of well established efficacy and safety in adults and has been also used in children. Tienam is approved as an intravenous (IV) formulation: Powder for solution for infusion 500 mg/500 mg. The Committee was informed that the MAH is currently deleting the intramuscular formulation and the 250 mg/250 mg strength across Europe.

2.2. Critical Evaluation

Section 4.1 - Therapeutic indications

Indications proposed by the MAH:

- *intra-abdominal infections*
- *lower respiratory tract infections*
- *gynaecological infections*
- *septicaemia*
- *genitourinary tract infections*
- *bone and joint infections*
- *skin and soft-tissue infections*
- *endocarditis*

Prophylaxis:

Tienam is also indicated for the prevention of certain post-operative infections in patients undergoing contaminated or potentially contaminated surgical procedures or where the occurrence of post-operative infection could be especially serious.

Mixed Infections:

Tienam can be used for the treatment of mixed infections caused by susceptible strains of aerobic and anaerobic bacteria and initiating therapy prior to identification of the causative organisms. The majority of these infections are associated with contamination by faecal flora, or flora originating from the vagina, skin, and mouth. In these mixed infections, Tienam is usually effective against *Bacteroides fragilis* sp., the most commonly encountered anaerobic pathogen, which is usually resistant to the aminoglycosides, cephalosporins and penicillins.

Tienam is not indicated for the treatment of meningitis.

4.1.1 Intra-abdominal infections

The CHMP noted that the MAH did not discuss nor provide any supporting data for the general "intra-abdominal infections" indication, which is currently approved in almost all European countries. The CHMP noted that the use of imipenem/cilastatin should be reserved for severe bacterial infections suspected or due to pathogens resistant to other beta-lactams and susceptible to imipenem/cilastatin. Intra-abdominal infections differ from other infections because they can have a variety of causes, severities and mortalities, they are often polymicrobial, their microbiology results are often difficult to interpret and surgical intervention is sometimes required. The CHMP noted the main clinical studies available with imipenem/cilastatin regarding this indication which included patients with complicated intra-abdominal infections. In these studies, imipenem/cilastatin (500 mg every 6 hours) was successfully used in cIAIs and was comparable to meropenem. Consequently, taking into account the microbiological activity of penems, the current microbiological context, the clinical practice, and the medical need of penems in some situations, it is considered that the indication may be considered appropriate if amended to "Complicated intra-abdominal infections", in line with the indications approved for meropenem in another recent harmonisation referral. The MAH was requested to provide an exhaustive update of available data on the efficacy and associated posology of Tienam.

The MAH provided an overview of the limited data (112 patients) from the original WMA, showing that 21 patients (19%) had a diagnosis of intra-abdominal abscess and 36 patients (32%) had a diagnosis of peritonitis. Overall, 17 of 21 (81%) patients with intra-abdominal abscess and 35 of 36 (97%) patients with peritonitis had a favourable response to imipenem/cilastatin. Among the other diagnoses of intra-abdominal infection seen in at least 3 patients, imipenem/cilastatin resulted in a favourable response in all cases (31/31): 4 of 4 patients with gall bladder empyema, 6 of 6 patients with perirectal abscess, 6 of 6 patients with cholecystitis, 7 of 7 patients with appendicitis with peritonitis, and 8 of 8 patients with appendiceal abscess. The MAH considered that data provide convincing evidence that imipenem/cilastatin is efficacious in treating intra-abdominal infections including the treatment of complicated intra-abdominal infections e.g., intra abdominal abscess, peritonitis, gall bladder empyema, appendicitis with peritonitis.

The MAH also carried out a comprehensive literature review, which revealed 19 articles reporting at least 50 patients treated with imipenem/cilastatin monotherapy for intra-abdominal infections. Overall,

18 of 19 (95%) articles were comparative studies of imipenem/cilastatin with another antibiotic or combination of antibiotics. The vast majority of patients in these intra-abdominal infection studies had complicated IAIs. The MAH provided detailed information from all 19 studies and discussed in particular the three major comparative studies. The first study, by Oliva et al, (2005) was a randomised, double-blind multinational trial comparing tigecycline (100 mg initial dose, then 50 mg every 12 hours) versus imipenem/cilastatin (500/500 mg q.i.d) in patients with complicated intra-abdominal infections for 5-14 days. A favourable clinical response was seen in 81% (199/247) of patients treated with tigecycline as compared to 82% (210/255) of patients treated with imipenem/cilastatin at the TOC visit (14-35 days after therapy) in the microbiologically evaluable population (ME). The second study, by Erasmo et al (2004) was another open randomised, comparative study (in 6 Asian countries) of patients with intra-abdominal infections, the majority of which were appendicitis (49%) or peritonitis (25%). A favourable response was seen in 97% (108/111) of patients treated with piperacillin/tazobactam (4 g/500 mg t.i.d) and 97% (100/103) of patients treated with imipenem/cilastatin (500/500 mg q.i.d). Mean duration of treatment was approx. 6 days in both groups. Finally, the third study, by Basoli (1997) was an open randomised, multicentre trial comparing meropenem (3.0 grams daily) versus imipenem/cilastatin (1.5 grams daily) for treatment of complicated IAI (requiring surgical intervention within 24 hrs of diagnosis/enrolment into the study) of mild to moderate severity (around 80% of patients had Apache II score ≤ 10). Clinical cure was noted in 95% (95/100) of meropenem-treated patients as compared with 98% (99/101) of the imipenem/cilastatin treated patients. Mean duration of treatment was approx. 7 days in both groups.

The MAH noted that overall, for the 19 studies, the favourable clinical response rates for imipenem/cilastatin ranged from 68% to 98%, while the favourable clinical response rates for the comparator agents (18 studies) ranged from 69% to 98%. The comparator agents included meropenem (4 studies), piperacillin/tazobactam (3 studies), tigecycline (2 studies), cefepime and metronidazole (2 studies), clindamycin and aminoglycoside (2 studies), cefazolin and ceftazidime (1 study), ciprofloxacin and metronidazole (1 study), cefuroxime and metronidazole (1 study), clinafloxacin (1 study), and trovafloxacin (1 study). The use of imipenem/cilastatin was generally safe and well tolerated.

The CHMP considered that the data provided by the MAH included sufficient evidence that imipenem/cilastatin is efficacious in most studies in treating complicated intra-abdominal infections including e.g., intra-abdominal abscesses, peritonitis, complicated appendicitis, gall bladder empyema. However, not all relevant quoted studies were discussed by the MAH and the optimal dosing regimen for this indication was not discussed. Dose regimens of 500/500 mg q.i.d or 1 g t.i.d (by 30-60 min infusion) have been evaluated in the studies and the CHMP requested the MAH to further discuss the optimal dosage for moderate to severe complicated cases especially in cIAI which is usually of polymicrobial nature. The MAH should take into consideration the previous MAH statement that the dosage for treatment of infections with fully susceptible organisms should be 2.0 g/day, of 4.0 g/day for infections with moderately susceptible organisms (primarily some strains of *P. aeruginosa*).

The MAH discussed the available dosage data based on the 112 patients receiving treatment with imipenem/cilastatin for intra-abdominal infections in the Merck clinical trials (as part of the original WMA). In the comparative trials, the imipenem total daily doses ranged from 1 to 2 g daily, with the most commonly administered dose being 500 mg every 6 hours (500 mg q6h). Overall, favourable outcomes were seen in 105 of these 112 (94%) patients. Among patients receiving imipenem at 2 g daily in the comparative studies, the success rate was 93% (42/45). Among patients receiving <2 g daily in the comparative studies, the success rate was 87% (13/15). A comprehensive literature search identified 19 studies with at least 50 patients treated with imipenem/cilastatin monotherapy for intra-abdominal infections. Overall, 18 articles were comparative studies. In the majority of these studies (11 of 19), patients received 2 g daily (500 mg q6h) of imipenem, with favourable clinical response rates for imipenem/cilastatin ranging from 68% to 97%. In another 3 studies, patients received imipenem as 1.5 g daily (500 mg q8h), with generally similar efficacy results to that seen with 2 g daily. In 2 studies, the dose of imipenem/cilastatin was administered at 3 grams (as 1 g q8h), with favourable clinical response rates of 84% and 94%. Based on the studies reported in the literature, doses ranging between 1.5 and 3 g daily (500 mg q8h, 500 mg q6h, and 1 g q8h) of imipenem all demonstrate favourable clinical outcomes in the treatment of intra-abdominal infections. Data from an ongoing surveillance study of intra-abdominal pathogens (the Merck-sponsored Study to Monitor Antimicrobial Resistance Trends, or SMART study) confirm that *Enterobacteriaceae* are the most prevalent gram-negative pathogens identified in patients with intra-abdominal infections, with *E. coli* and *K. pneumoniae* representing over 60% of all gram-negative pathogens. A PK/PD analysis was performed using over 5,000 isolates each of *E. coli* and *K. pneumoniae* isolates collected between 2005 and 2009 in the SMART study. Data from Monte Carlo simulations at the accepted efficacy target (i.e., time above MIC target of 40%) suggest that imipenem doses of 500 mg every 6 hours or 1 g every 8

hours provide very similar coverage for *E. coli* and *Klebsiella* spp. Thus, these two doses could be viewed as essentially interchangeable in the treatment of complicated intra-abdominal infections.

In summary, the MAH considered that data from the original WMA and the comprehensive literature search, coupled with the supportive PK/PD data, are consistent with a dosing recommendation for imipenem of 500 mg every 6 hours or 1 g every 8 hours for the indication of complicated intra-abdominal infections.

The CHMP noted the MAH response providing additional information in the form of abstracts or very brief publications together with interim findings from the ongoing SMART project. The CHMP was of the opinion that in light of the present clinical and PK/PD data, a standard dose of 500 mg every 6 hours or 1g every 8 hours can be accepted, provided that a recommendation is inserted in the SPC stating that for infections suspected or proven to be due to less susceptible organisms (e.g. *P. aeruginosa*,) and for very severe infections (e.g. in neutropenic patients with a fever), the 1000 mg q.i.d should be used. In conclusion, the CHMP adopted the following harmonised indication:

"*complicated intra-abdominal infections*"

4.1.2 Lower respiratory tract infections

The CHMP noted the proposed indication "lower respiratory tract infections", which is currently approved in 24 of 30 European countries, but remarked that the MAH did not provide any discussions or supporting data. The CHMP considered the indication to be non-specific and therefore no longer appropriate, as according to the Guideline on Antibacterial agents, general statements are not acceptable as indications and should be replaced by specific indications according to the available clinical studies. In addition, the use of imipenem/cilastatin should be reserved for severe bacterial infections suspected or due to pathogens resistant to other beta-lactams and susceptible to imipenem/cilastatin. The CHMP noted that several studies are available which may support the indication "nosocomial pneumonia". However, the other LRTIs need to be justified based on the available evidence from the clinical studies.

Community acquired pneumonia (CAP):

CAP is a common diagnosis in clinical practice. Most patients are treated empirically because a definite etiologic diagnosis is not made in up to 50% of cases or because the bacteriological data are not available until 48-72 hours or even later if to be confirmed by serology. For all patients with CAP, pneumococcus is the most common pathogen. Although the incidence of drug-resistant *Streptococcus pneumoniae* is increasing, available data show that mortality in CAP is adversely affected by drug-resistant pneumococci only when MIC values to penicillin is ≥ 4 mg/L. The impact of organisms at lower levels of resistance remains uncertain. Other common bacterial causes of pneumonia are *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* (the "atypical" pathogens), either alone or as part of a mixed infection. The antibacterial spectrum of imipenem/cilastatin does however not cover *C. pneumoniae* and *M. pneumoniae* as many other beta-lactams. On the other hand, imipenem/cilastatin is a broad spectrum antibiotic and should only be used in the treatment of severe bacterial infections suspected or due to pathogens resistant to other beta-lactams. Consequently, the CHMP was of the opinion that the use of imipenem/cilastatin to treat CAP is not appropriate.

Cystic fibrosis (CF):

No documentation was submitted in support of an indication on the management of patients with cystic fibrosis. The antibacterial activity of imipenem/cilastatin against *P. aeruginosa* has decreased during the last decades. According to the proposed SPC, the EUCAST MIC breakpoints for *P. aeruginosa* was increased from 2 to 4 ug/ml to avoid dividing the wild distribution, and this pathogen relates to high dose frequent therapy. In addition, this pathogen is listed under species for which acquired resistance may be a problem. The proposed posology for severe and/or life threatening infections due to less susceptible organisms (primarily *P. aeruginosa*) is 1000 mg every 6 or 8 hours. The maximum daily dosage should not exceed 50 mg/kg/day or 4 g/day, whichever is lower. However, cystic fibrosis patients with normal renal function have been treated up to 90 mg/kg/day in divided doses, not exceeding 4 g/day. In the proposed posology, it is also stated that "The higher doses (up to 90 mg/kg/day in divided doses in older children) have also been used in patients with cystic fibrosis".

Consequently, the MAH is requested to provide an exhaustive update of available data in order to substantiate this indication and discuss the suitability of imipenem/cilastatin for use in the treatment of CF considering the increasing resistance of *P. aeruginosa* to this antibiotic. In addition, the proposed posology for this indication should be discussed, and especially the higher doses of up to 90 mg/kg/day in divided doses both in adults and in older children needs to be justified. A PK/PD analysis should be

performed with respect to both components of this product in order to reassure that the proposed posology would adequately cover the main pathogen and also to justify the safety at higher doses. Imipenem/cilastatin is known to be associated with seizures at higher doses in children, and hence this high dose regimen needs to be justified from a safety perspective.

The MAH reviewed the clinical trial database of the original WMA for imipenem/cilastatin collected in the late 1970s to early 1980s but noted that the data does not enable specific division of pneumonias into the more modern designations of community-acquired pneumonia (CAP), nosocomial pneumonia or ventilator associated pneumonia. However, it can be inferred that both CAP and nosocomial pneumonia were observed, since the pathogens that were isolated from these cases included pathogens that would be more typically associated with CAP (such as *Streptococcus pneumoniae* and *Haemophilus influenzae*), as well as pathogens that would be more typically associated with nosocomial pneumonia (such as *E. coli*, *Klebsiella spp.* and *Pseudomonas aeruginosa*). Overall, the clinical trial database included 137 patients with lower respiratory tract infections (LRTIs). The success rate of imipenem/cilastatin in LRTIs was 85%.

In addition, the MAH reviewed data from the literature and identified at least 16 studies with at least 50 or more patients treated with imipenem/cilastatin monotherapy for LRTIs. Overall, 11 randomised comparator controlled clinical trials, 1 non-comparator trial, 3 observational studies and 2 publications reporting the compilation of several studies were identified. Several studies provide data on the treatment of imipenem/cilastatin for ventilator-associated pneumonia: 1 randomised clinical trial, a subgroup analysis of another randomised clinical trial and 2 retrospective observational studies. The results across all these studies consistently show the value of imipenem/cilastatin in the treatment of LRTIs, and, in particular, nosocomial pneumonia (and ventilator-associated pneumonia). In the prospective, clinical trials, the clinical response rate for imipenem/cilastatin ranged between 53% to 85% and the microbiologic response rate ranged from 50% to 76%. The most common pathogens reported in the clinical trials included the following: *S. aureus*, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *E. coli*, and *Haemophilus influenzae*. The observational studies support the findings from the clinical trials. In addition, several studies published within the last 10 years were designed to evaluate other treatments (i.e., doripenem, piperacillin/tazobactam, levofloxacin, cefepime, and meropenem) versus imipenem/cilastatin. The MAH considered that these studies demonstrated that these treatments were similar to imipenem/cilastatin in treating nosocomial pneumonia, including ventilator-associated pneumonia and discussed them in detail.

The first study, by Chastre et al (2008) was the largest Phase III, randomised, open-label (with in-house blinding), prospective, multicenter, multinational trial ever conducted in patients (mainly in North America, Western Europe, Australia) with ventilator-associated pneumonia, doripenem was found to be clinically non-inferior to imipenem/cilastatin. Doripenem was administered at a dosage of 500 mg every 8 hrs via a 4-hr intravenous infusion. Depending on the standard practice at each site, imipenem was given at a dosage of either 500 mg every 6 hrs via a 30-min infusion or 1000 mg every 8 hrs via a 60-min infusion. Patients were started on intravenous study drug treatment before baseline respiratory tract cultures were known. Patients were withdrawn from the study if the culture was negative and the patient had not received antibiotic therapy for 72 hrs before collection or if MRSA was the only pathogen identified. Vancomycin or amikacin were also to be withdrawn within 48 hrs if the baseline culture failed to confirm MRSA or *P. aeruginosa*, respectively. Adjunctive anti-pseudomonal therapy (required in imipenem-treated patients with *P. aeruginosa* at baseline, but only under specific conditions in doripenem treated patients) and prevented patients with a baseline lower respiratory tract organism resistant to imipenem from being excluded from the doripenem treatment arm. Only 22% of the patients received adjunctive anti-pseudomonal (amikacin) therapy, and consequently, this study provides primarily a direct comparison of carbapenem monotherapy (used in 80% of the patients) in treating nosocomial pneumonia caused by Gramnegative pathogens. To minimize bias, in house handling and analysis of data (e.g., determination of patients' evaluability) were blinded. Clinical investigators were responsible for the determination of clinical outcomes and safety assessments. In the clinical modified intent-to-treat (cMITT) population, the clinical cure rates were 59.0% (N=249) for patients receiving doripenem and 57.8% (N=252) for patients receiving imipenem/cilastatin. In the clinically evaluable (CE) population, the clinical cure rates were 68.3% (N=126) for patients receiving doripenem and 64.2% (N=122) for patients receiving imipenem/cilastatin. In the microbiologic evaluable (ME) population, the microbiologic response rates were 73.3% (N=116) for patients receiving doripenem and 67.3% (N=110) for patients receiving imipenem/cilastatin. Approximately 10% of all patients (from both arms of the study) had *P. aeruginosa* isolated as a baseline pathogen in the lower respiratory tract. None of the 53 *P. aeruginosa* isolates had a doripenem MIC >8 g/mL, but 13.2% had an imipenem MIC >8 g/mL. The clinical cure rates for doripenem and imipenem in *P. aeruginosa* infections were 80.0% (16 of 20) and 42.9% (6 of 14) (not significant), respectively, and the microbiological cure rates were 65.0% (13 of 20) and 35.7% (five of 14) (not significant),

respectively. Emergence of resistant *P. aeruginosa* during therapy with imipenem (pooled clinical trials) was 33% in respiratory tract infections (28), similar to the results reported here. In the cMITT population, there were 20 emergent (i.e., nonbaseline) infections (8%) in the doripenem arm, compared with 28 (11%) in the imipenem arm. The most common pathogens responsible for new post treatment infections were *P. aeruginosa* (doripenem three, imipenem six) and *K. pneumoniae* (doripenem none, imipenem six). *P. aeruginosa* was also responsible for two and four infections while patients were undergoing doripenem or imipenem therapy, respectively. At the LFU visit, there was only one patient with recurrent pathogens in each treatment arm.

The second study, by Schmitt et al was a randomised, double-blind, prospective, multicenter trial conducted in Europe, comparing the efficacy and safety of piperacillin/tazobactam with imipenem/cilastatin in patients with established nosocomial pneumonia. Due to difficulties in recruiting sufficient patients it was terminated prematurely. In all, 221 patients were randomly assigned to either piperacillin/tazocin at 4 g/0.5 g (n = 110) or I/C at 1 g/1 g every 8 hrs (n = 111). Additional aminoglycoside therapy was mandatory if *P. aeruginosa* was present. The ITT population (107 P/T and 110 I/C patients) was used for the analysis of efficacy. Patients had a mean APACHE II score of approx. 14. The predominant pathogens were members of the Enterobacteriaceae (27%) and only 4% were *P. aeruginosa*. The clinical efficacy of piperacillin/tazobactam was found to be similar to imipenem/cilastatin at the end of therapy and at days 3 and 14 post-therapy. The clinical response rates were the following: 71.0% (76/107) for patients receiving piperacillin/tazobactam as compared to 77.3% (85/110) for patients receiving imipenem/cilastatin at the end of therapy; 66.4% (71/107) for piperacillin/tazocin and 70.0% (77/110) for imipenem/cilastatin at day 3 post-therapy; and 59.8% (64/107) for piperacillin/tazobactam and 66.4% (73/110) for imipenem/cilastatin at day 14 post therapy.

The third study, by West et al (2003) was a randomised, open-label, prospective, multicenter, comparator-controlled trial conducted in North America, the efficacy and safety of levofloxacin was compared with imipenem/cilastatin followed by ciprofloxacin in adult patients with nosocomial pneumonia. A subgroup analysis of this study was performed by Schorr et al (2005). Patients were randomised 1:1 to either levofloxacin at 750 mg QD given IV and then orally for 7 to 15 days or imipenem/cilastatin 500 mg to 1 g IV every 6 to 8 hours, followed by oral ciprofloxacin 750 mg every 12 hours, for 7 to 15 days. Patients had a mean APACHE II score of approx. 15. Patients with suspected or documented *P. aeruginosa* infection received adjunctive therapy. In patients randomised to receive levofloxacin, adjunctive therapy consisted of ceftazidime 2 g IV every 8 hours (or another non-carbapenem betalactam); in those randomised to receive the comparator regimen, adjunctive therapy consisted of amikacin 7.5 mg/kg IV every 12 hours (or another aminoglycoside). Adjunctive therapy was to be discontinued if *P. aeruginosa* infection was not confirmed by culture. In patients with suspected or documented infection caused by methicillin-resistant *S. aureus*, adjunctive therapy with vancomycin was to be instituted regardless of treatment assignment. Vancomycin was to be discontinued if suspected infection was not confirmed by culture. Levofloxacin was at least as effective as imipenem/cilastatin followed by ciprofloxacin as demonstrated by comparable clinical and microbiologic response rates. Clinical response rates were 58.1% (54/93) for patients receiving levofloxacin and 60.6% (57/94) for patients receiving imipenem/cilastatin followed by oral ciprofloxacin. In the 187 patients evaluable for microbiologic efficacy, eradication was achieved in 66.7% (62/93) of patients receiving levofloxacin and 60.6% (57/94) of patients receiving imipenem/cilastatin followed by ciprofloxacin. Clinical success rates in patients with positive respiratory cultures for *P. aeruginosa* were 64.7% (11/17) and 41.2% (7/17), respectively. The subgroup analysis focused on the group of patients with VAP. Clinical success results were similar to those described above. Clinical success rates in patients with positive respiratory cultures for *P. aeruginosa* were 87.5% and 61.1% for patients receiving levofloxacin or imipenem-cilastatin, respectively.

The fourth study, by Zanetti et al (2003) was a randomised, open-label (with evaluator-blinding), prospective, multicenter, comparator-controlled trial conducted in Europe, the efficacy and safety of cefepime (2 g t.i.d) was compared to imipenem/cilastatin (500 mg/500 mg q.i.d) . Nosocomial pneumonia was documented microbiologically in 148 (71%) of 209 patients, 77 of 108 (71%) in the cefepime group and 71 of 101 (70%) in the imipenem-cilastatin group. The most frequent pathogen was *P. aeruginosa*, which was present in 59 (40%) patients with microbiological documentation of pneumonia. An extended-spectrum beta-lactamase (ESBL)-producing causative organism was documented in 23 (16%) patients (cefepime group, 13 patients; imipenem group, 10 patients): *K. pneumoniae* was found in 22 patients (19 of whom were hospitalised in the same participating centre), *Enterobacter aerogenes* was found in 1 patient, and *Acinetobacter baumannii* was found in 1 patient (together with *K. pneumoniae*). Patients had a mean APACHE II score of 15-16. The clinical efficacy of cefepime was found to be non-inferior to imipenem/cilastatin. The clinical response rates were 70% (76/108) for patients receiving cefepime and 74% (75/101) for patients receiving imipenem/cilastatin.

Therapy of pneumonia caused by an organism producing an extended spectrum-lactamase (ESBL) failed in 4 of 13 patients in the cefepime group but in none of 10 patients in the imipenem group. The clinical response rates of patients with *P. aeruginosa* infection were 23 of 27 (85%) patients in the cefepime group and 23 of 32 (72%) patients in the imipenem-cilastatin group. Primary and secondary resistance to imipenem was more common for *P. aeruginosa*. The propensity of *P. aeruginosa* to develop secondary resistance during therapy with imipenem-cilastatin has been reported previously, and this propensity was not reduced by the simultaneous use of aminoglycosides in one study.

The fifth study, by Verwaest (2000) was a randomised, open-label, prospective, multicenter, parallel-group trial, conducted in Belgium, empirical monotherapy was evaluated comparing treatment with meropenem to imipenem/cilastatin (both with 1g every 8 hr by I.V infusion) in intensive-care unit (ICU) patients with one or more of the following infections caused by sensitive pathogens: LRTI in ventilated patients, intra-abdominal infections or sepsis. Meropenem was found to be at least as efficacious (clinically and bacteriologically) as imipenem/cilastatin for the empirical treatment of serious bacterial infections in ICU patients. The clinical response rates for LRTI were 68.3% (41/60) for patients receiving meropenem and 68.6% (35/51) for patients receiving imipenem/cilastatin. The microbiologic response rates for LRTI were 61.5% (32/52) for patients receiving meropenem and 57.1% (24/42) for patients receiving imipenem/cilastatin.

The MAH also noted 6 publications including between 30 and 50 patients treated with imipenem/cilastatin for nosocomial pneumonia or ventilator associated pneumonia. These publications were also reviewed to evaluate the consistency of the reported findings and the findings were consistent with the findings of the larger studies. Overall, the MAH considered that the data from the literature provide supportive evidence for the efficacy of imipenem/cilastatin in the treatment of nosocomial pneumonia, including ventilator associated pneumonia. In addition, imipenem/cilastatin was generally well tolerated and safe to use in patients with these infections. Adverse events reported for the imipenem/cilastatin were, for the most part, similar to comparators and support the known safety profile of imipenem/cilastatin.

Regarding cystic fibrosis, the MAH acknowledged the CHMP comment, and presented the available data from the Merck compassionate use trials (submitted as part of the original adult and supplemental paediatric WMA) for 10 cystic fibrosis patients treated with imipenem/cilastatin for broncho-pulmonary infections. Eight (80%) showed clinical improvement following imipenem/cilastatin use. The MAH also provided supplementary data submitted to the FDA in 1986, which showed clinical improvement in 20 of 26 (77%) cystic fibrosis patients treated with imipenem/cilastatin for pneumonia. Patients received high doses of imipenem/cilastatin (approximately 90 mg/kg per body weight/day or more). The total daily dose ranged from 1.75 g to 4 g of imipenem, with most of the patients (69%) having received between 3 to 4 g/day. Lastly, data from a comprehensive literature review identified 8 non-comparative studies and 5 case reports of cystic fibrosis patients receiving imipenem/cilastatin as monotherapy or as part of combination therapy for broncho-pulmonary infections. The non-comparative studies enrolled only a small number of children and adult patients (6 to 20) with respiratory infections, mostly broncho-pulmonary infections. *P. aeruginosa* was the primary pathogen in these infections. The dosage of imipenem/cilastatin ranged from 30 to 100 mg/kg per body weight/day. In most (6) studies, imipenem/cilastatin was administered as monotherapy. The majority of patients in each of the 8 studies demonstrated clinical improvement during treatment with imipenem/cilastatin; in fact, the clinical improvement rate ranged from 55-100% across these 8 studies. However, several studies reported that *P. aeruginosa* may persist and resistance to *P. aeruginosa* emerged over the course of treatment. In these non-comparative studies, imipenem/cilastatin was generally safe and well-tolerated by cystic fibrosis patients. However, one study of the combination treatment of imipenem/cilastatin plus tobramycin reported that 7 of 10 patients experienced adverse reactions, mainly gastrointestinal, and treatment of 3 patients was discontinued due to rash or nausea and vomiting. These side effects were considered to be due to imipenem/cilastatin.

The MAH also presented five case reports from a single or a few patients (2 or 3) with cystic fibrosis and associated broncho-pulmonary infections. All patients in these 5 reports demonstrated some improvement following imipenem/cilastatin therapy. Overall, the case reports provide additional data supporting the efficacious use of imipenem/cilastatin against various pathogens in broncho-pulmonary infections in cystic fibrosis patients. The MAH acknowledged the limited comparator-controlled data available, which prevents a definitive evaluation of the efficacy of imipenem/cilastatin in the treatment of broncho-pulmonary infections in cystic fibrosis patients. The MAH also recognised that the concomitant use of an appropriate aminoglycoside may be indicated when *P. aeruginosa* infections are suspected or proven to be involved (as is often the case in cystic fibrosis).

The CHMP endorsed the MAH position with regard to the very limited and non-comparative data in support of this indication. The original WMA mainly included patients with pneumonia (mainly due to *P. aeruginosa*) secondary to CF. Patients received high doses of imipenem/cilastatin (approximately 90 mg/kg per body weight/day or more), with most of the patients having received between 3 to 4 g/day. The published literature described around 120 CF patients, mainly with broncho-pulmonary infections due to *P. aeruginosa* cases; this included 37 patients who used combination therapy with aminoglycosides. Improvement is reported for most cases. Persistence of the *P. aeruginosa* infection has been reported (which can be expected in this CF condition) and development of resistance to this pathogen has also been reported. The need to combine or replace Tienam with an aminoglycoside can also be expected, which complicated the assessment of efficacy even more difficult in the uncontrolled reported data. Overall, the CHMP considered the appropriate assessment of efficacy based on these qualitatively and quantitatively poor data to be impossible. The uncertainty about the benefit of Tienam in this indication is further increased by the known lower susceptibility of the predominant pathogen *P. aeruginosa* to imipenem/cilastatin and the potential failures due to importantly increased frequencies of resistance of the pathogen to imipenem. The CHMP was of the opinion that the data does not support the use of Tienam in the treatment of broncho-pulmonary infections in CF patients and therefore deleted the indication.

The CHMP noted the revised MAH proposal to limit the indication to "nosocomial pneumonia (including ventilator-associated pneumonia)" as suggested by the CHMP and that the claim for the CAP indication was retracted as the antimicrobial spectrum of imipenem/cilastatin does not cover *C. pneumoniae* and *M. pneumoniae*. Regarding the dosage, doses of imipenem -cilastatin used in the described studies were generally 500 mg-500 mg q.i.d or 1g t.i.d. These imipenem -cilastatin doses have shown appreciable efficacy in nosocomial pneumonia but in several studies the concomitant use of vancomycin and an aminoglycoside were used as indicated when MRSA or *P. aeruginosa* infections respectively were suspected or involved due to the antibacterial spectrum of imipenem and low susceptibility of *P. aeruginosa* to the product. In addition, an increased risk of failure and emergence of resistant strains of *P. aeruginosa* was reported after therapy with mentioned dosing regimens of the product in infections due to *P. aeruginosa* in several studies in nosocomial pneumonia and ventilator associated pneumonia. The CHMP inserted a statement in section 4.4 concerning the limited susceptibility of specific pathogens and the concomitant use of an appropriate anti-MRSA agent or of an aminoglycoside.

The MAH was requested to optimised the dosing regimen in patients with nosocomial pneumonia, including also an advice on the need of appropriate antibiotic concomitant therapy in order to align the therapeutic results with optimal management of such life threatening nosocomial infections with available recent therapeutic options (such as carbapenems). The MAH was also requested to discuss in the light of present data whether the standard dose for sought life-threatening infections should be set at 1 g t.i.d or q.i.d. The MAH agreed to the inclusion of guidance in the SPC for regarding the use of appropriate antibiotic concomitant therapy in order to align the therapeutic results with optimal management of life-threatening nosocomial infections, such as pneumonia. The MAH also agreed to state the option to use a higher imipenem dose of 1 g q6h when treating pneumonia caused by susceptible *P. aeruginosa*. The following paragraph was inserted in Section 4.4:

"The selection of imipenem/cilastatin to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria."

In addition, the MAH carefully reviewed the dosage information for this indication from a variety of available sources, including data from all prospective Merck clinical trials (submitted with the original WMA) and from the available clinical data in the literature. Furthermore, the MAH performed a PK/PD analysis using a Monte Carlo simulation approach for the targeted efficacy parameter (i.e., time above MIC), using recent isolates collected from an ongoing surveillance study in an effort to help confirm the optimal dose for imipenem/cilastatin for this indication. A total of 145 patients with respiratory tract infections, including 137 with lower respiratory tract infections (LRTIs) received treatment with imipenem/cilastatin in Merck clinical trials (as part of the original WMA). Overall, favourable outcomes were seen in 85% of the patients with LRTIs treated with imipenem/cilastatin. In the comparative trials, the imipenem total daily doses ranged from 1 to 2 g daily, with the most commonly administered dose being 500 mg every 6 hours (500 mg q6h). Among patients receiving imipenem at 2 g daily in the comparative studies, the success rate for respiratory tract infections was 98% (40/41). Among patients receiving imipenem at < 2 g daily in the comparative studies, the success rate was 82% (33/40). In non-comparative studies, the success rate at <2 g daily and >2 g daily was 86% (18/21) and 74% (32/43), respectively. A comprehensive literature search identified 18 publications in

which at least 50 patients were treated with imipenem/cilastatin for nosocomial pneumonia or ventilator-associated pneumonia. Of these 18 publications, 11 randomised comparator-controlled clinical trials and 1 subgroup analysis of one of these trials have been reported in the literature since 1990. In some studies, the concomitant use of vancomycin or an aminoglycoside was allowed for suspected or documented infections with methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*, respectively. In 5 clinical trials, patients who received imipenem at 2 g daily (500 mg q6h) had favourable clinical response rates of 63% to 82%. In 2 clinical trials, patients who received imipenem at 3 g daily (1g q8h) had favourable clinical response rates of 69% and 77%. The remaining 5 clinical trials focused on severe (nosocomial) pneumonia or ventilator-associated pneumonia, and the imipenem daily dosages varied within each study (with ranges between 2 and 4 g daily); favourable clinical response rates for imipenem ranged from 53% to 79% in these studies. As reported in the literature, the epidemiology of bacterial pathogens most commonly seen in hospital and ventilator-associated pneumonia include a variety of pathogens, namely *S. aureus*, non-fermentative gram-negative pathogens (*P. aeruginosa* or *Acinetobacter baumannii*), and Enterobacteriaceae, especially *E. coli*, *Klebsiella* spp., and *Enterobacter* spp. The MAH performed a PK/PD analysis with Monte Carlo simulations using recent isolates collected from an ongoing surveillance study of intra-abdominal and urinary tract pathogens (the Merck-sponsored Study to Monitor Antimicrobial Resistance Trends, or SMART study) in an effort to help discern the optimal dose for imipenem in the treatment of infections caused by *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. This PK/PD analysis was performed using over 5,000 isolates each of *E. coli* and *K. pneumoniae* isolates collected between 2005 and 2009 in the SMART study, as well as over 5,000 isolates of *P. aeruginosa* collected between 2002 and 2009 in the SMART study. Additionally, although *Enterococcus* spp. are rarely associated with pneumonia, the MAH included approximately 5,000 isolates of *Enterococcus* in the PK/PD simulation. The data suggests that imipenem doses of 500 mg every 6 hours or 1 g every 8 hours provide very similar coverage for *E. coli* and *Klebsiella* spp. in the simulation. Thus, these two doses could be viewed as essentially interchangeable in the treatment of infections against these pathogens. Against organisms with higher MICs (e.g., especially for *P. aeruginosa*, and to a lesser extent *Enterococcus* spp.), imipenem doses of 1 g every 6 hours (4 g daily) provided a moderate numerical increase in the % above MIC in the Monte Carlo simulation, as compared to the two lower imipenem doses (500 mg q6h and 1 g q8h). Thus, in seriously ill patient populations against susceptible organisms with higher MICs (e.g., *Pseudomonas aeruginosa* with MIC=4 mg/L), the MAH is proposing language in the revised SPC for physicians to consider a dose of 1 g q6h as another possible option. However, the benefit-risk ratio of this higher dose must be carefully considered in each individual clinical setting.

Overall, the CHMP agreed with the MAH response and the proposed dose of 500 mg every 6 hours or 1g every 8 hours. The CHMP also agreed with the inclusion of advice on the need of appropriate antibiotic concomitant therapy in order to align the therapeutic results with optimal management of such life threatening nosocomial infections with available recent therapeutic options (such as carbapenems). The CHMP slightly revised the proposed statement and inserted the following statement: "*It is recommended that infections suspected or proven to be due to less susceptible bacterial species (such as Pseudomonas aeruginosa) and very severe infections (e.g. in neutropenic patients with a fever) should be treated with 1000 mg administered every 6 hours.*" In conclusion, the CHMP adopted the following harmonised indication:

"severe pneumonia including hospital and ventilator-associated pneumonia"

4.1.3 Gynaecological infections

The MAH proposed the indication "gynaecological infections", which is currently approved for imipenem/cilastatin in 23 of the 28 European countries according to the MAH. In the original application, data from gynaecological infections were summarised together with genitourinary tract infections, showing that 48 of 51 (94%) patients with gynaecological infections had favourable clinical outcomes with imipenem/cilastatin. The original application also included clinical studies comparing imipenem/cilastatin to moxalactam. In the comparison of imipenem/cilastatin and moxalactam, 59 evaluable patients, including 29 receiving imipenem/cilastatin and 30 receiving moxalactam, were diagnosed with gynaecological infections. 27 (93%) of the 29 imipenem/cilastatin-treated patients and 27 (90%) of the 30 moxalactam-treated patients had favourable clinical outcomes to these gynaecological infections. There were 2 clinical failures in the imipenem/cilastatin-treated group and 3 clinical failures in the moxalactam-treated group. One of the imipenem/cilastatin-treated patients with the failure had two primary infections. Three patients with failure in the moxalactam group had polymicrobial infections with a resistant *Enterococcus* spp.

In addition, data from published studies were provided (involving a total of 273 imipenem/cilastatin-treated patients) and including three randomised, controlled trials and three non-controlled trials. In

the 3 randomised comparator-controlled clinical trials (Berkeley 1986, Gonik 1992, Larsen 1992), the overall percentage of patients who improved (clinically cured and improved) with imipenem/cilastatin was similar or higher than the various comparators. In the 3 non-comparative clinical studies (Sweet 1985, Berkeley 1985, Calandra 1985), imipenem/cilastatin cured 88% to 97% of gynaecological (pelvic) infections. Imipenem/cilastatin was generally well tolerated and safe in women with gynaecologic infections. The rate of adverse events (AEs) possibly related to imipenem/cilastatin was less than 5%.

Based on the available data from the original Worldwide Marketing Application and the medical literature for the efficacy and safety of imipenem/cilastatin in the treatment of gynaecological infections, the MAH therefore considered that "gynaecological infections" should be retained as an indication for imipenem/ cilastatin.

The CHMP noted that no pivotal study was submitted in support of this indication and that instead the summary discussion of Original Worldwide Marketing Application's data, gynaecological infections were summarised together with genitourinary tract infections. No further specification of investigated infections is given. The MAH submitted only three small randomised controlled studies, in which the total number of the patients receiving imipenem/cilastatin was 84. In the largest available randomised study by Larsen (1992), the most important pathogens isolated included *N. gonorrhoeae*, *S. epidermidis*, *Gardnerella vaginalis*, diptheroids, and *E. coli*. This spectrum of pathogens are not considered to adequately reflect the clinical situation, and both diptheroids and *S. epidermidis* would be considered as rather irrelevant pathogens for gynecological infections. On the other hand, chlamydia has not been isolated in any of the above studies while only 1 species of bacteroides was isolated. Both of these bacteria are expected to be more commonly isolated in clinical setting. In the study by Larsen (1992), 32 patients were enrolled at a site that did not do routine chlamydia testing while at the other study sites, laboratory methods included attempts to identify this bacteria but none was found. This study was carried on between 1988-1989, and since then there have been improvements in methodology (culturing and PCR) for the detection of *Chlamydia* spp. The CHMP considered that the above-mentioned pathogens are not representative of gynecological infections, especially pelvic inflammatory disease (PID). *C. trachomatis* is estimated to be the cause in about 60% of cases of salpingitis, which may lead to PID. Salpingitis is often used synonymously with PID, although PID lacks an accurate definition and can refer to several diseases of the female upper genital tract, such as endometritis, oophoritis, myometritis, parametritis and infection in the pelvic peritoneum. Consequently, PID may comprise many different gynecological infections, and chlamydia is a significant pathogen in these infections. Beta-lactams are known not to be efficacious against chlamydia and hence, imipenem/cilastatin is not considered an appropriate agent for the treatment of these infections. In the reference article of Berkeley et al, 17 patients with pelvic inflammatory disease (PID), postoperative, post-abortal and postpartum infections were investigated in imipenem/ cilastatin group. The tested patients received 500 mg every 6 hours IV imipenem/ cilastatin for 4 days. The same dosage (500 mg every 6 or 8 hours IV) of this drug was used in 23 patients with postpartum endometritis in the randomised controlled trial of Gonik et al and 44 patients with serious pelvic infections such as acute salpingitis, pelvic abscess, or postoperative pelvic cellulitis (Larsen et al). Patients (n=72) with pelvic infections such as PID, endometritis, endomyometritis, pelvic cellulitis, community-acquired tubo-ovarian or postoperative abscess, and pelvic peritonitis were investigated in the non-comparative trial of Sweet. Of these, 79% (34/43) infections were developed after cesarean section. The dose of imipenem ranged from 1g to 4g per day, IV for 4-15 days. In the non-comparative trial of Berkeley et al, 55 cases of soft tissue pelvic infections were treated with 500 mg IV every 6 hours imipenem/ cilastatin for minimum of 4 days. In the study of Calandra et al (in 52 centres) 62 patients with gynaecological infections were included. Dosage of imipenem/ cilastatin ranged from 1g to 4g per day, for 5 to 42 days. No further specification of infections is given. In summary, the CHMP considered the submitted data from the Original Worldwide Marketing Application to be insufficient and the references provided to be inadequate and outdated. Due to the fact that the data supporting the use of imipenem/cilastatin in different types of gynecological infections are limited, and the antimicrobial spectrum of imipenem/cilastatin does not cover chlamydia, the general wording of the proposed indication is not considered acceptable. In the recently finalised harmonisation referral for meropenem, the following wording was agreed upon: "Intra- and postpartum infections". The MAH was requested to re-evaluate the available data and to discuss whether the indication "Intra- and postpartum infections" would be applicable to imipenem/cilastatin.

The MAH performed a detailed review of both clinical trial data from the original Worldwide Marketing Application (WMA) and data from a comprehensive literature review with regard to the use of imipenem/cilastatin in the treatment gynaecological infections, specifically "Intra- and post-partum infections". Information was obtained from the original WMA in the broad category of genitourinary infections. The clinical trial database included data from 148 patients treated with imipenem/cilastatin

for genitourinary infections. Although the data did not specifically classify genitourinary infections as either intra- or post-partum infections, the database includes several types of infections seen in the clinical trials that would be consistent with intra- and post-partum infections, namely endometritis, endomyometritis, and puerperal endometritis. These specific infections were associated with favourable clinical outcomes in a total of 24 of 25 (96%) patients treated with imipenem/cilastatin. The efficacy of imipenem/cilastatin was comparable to that seen with the comparators in the respective comparator-controlled clinical trials. Furthermore, the MAH reviewed data from the literature and identified 5 studies totalling 232 patients treated with imipenem/cilastatin monotherapy for gynaecologic infections, including those consistent with intra- and post-partum infections.

In a randomised, controlled trial of imipenem/cilastatin versus moxalactam in the treatment of serious obstetric and gynaecological infections, 17 of 17 (100%) evaluable patients treated with imipenem/cilastatin were clinically cured, as compared to 8 of 13 (62%) evaluable patients treated with moxalactam. Of patients with post-caesarean endometritis, 6 of 6 (100%) patients treated with imipenem/cilastatin were clinically cured compared to 3 of 6 (50%) patients treated with moxalactam. Of patients with post-abortal endometritis, 2 of 2 patients in imipenem/cilastatin group (100%) and 1 of 1 patients in moxalactam group (100%) were clinically cured. A prospective, multicenter, open-label randomised trial focused solely on postpartum endometritis, and compared imipenem/cilastatin monotherapy with clindamycin + aminoglycoside combination therapy. Patients treated with imipenem/cilastatin had an overall clinical response rate of 91% (21/23), as compared with an overall clinical response rate of 73% (19/26) in the patients treated with clindamycin + aminoglycoside. In the 3 non-comparative clinical studies, the clinical response rate for imipenem/cilastatin ranged between 88% and 97% of gynaecological (pelvic) infections, and in one of the trials, the clinical response rate was 98% for patients with endomyometritis and treated with imipenem/cilastatin.

The MAH concluded that the totality of the data from the original WMA, combined with the overall data from the literature review, provide support for the use of imipenem/cilastatin in the treatment of intra- and postpartum infections. Nevertheless, the MAH acknowledged that the antimicrobial spectrum of imipenem/cilastatin does not cover *Chlamydia trachomatis*, and there is insufficient evidence that *Neisseria gonorrhoeae* is a good target for therapy with imipenem/cilastatin. As a result, based on the microbiological spectrum and this detailed review of imipenem/cilastatin, the MAH revised the indication of "gynaecological infections" to the more limited and specific indication "intra- and post-partum infections". Importantly, this limited indication is consistent with the approach used for several other agents in the EU, including agents from the same therapeutic class (i.e., carbapenems).

The CHMP noted that no new documentation was submitted by the MAH, however the discussion of the available documentation focuses primarily on intra- and post-partum infections. The MAH acknowledges the view expressed by the CHMP, that the spectrum of imipenem/cilastatin does not cover *Chlamydia trachomatis*, and that there is insufficient evidence that *Neisseria gonorrhoeae* is a good target for therapy with this agent. Although data supporting this indication is limited, the CHMP considered the indication to be acceptable.

The MAH did not discuss the optimal dosage regimen for this indication. The posology in the submitted studies was mostly 500 mg every 6 hours. However, these studies also covered other gynaecological infections such as pelvic infections. Since an intra- or post-partum infection is likely to be a more serious infection, a posology up to 1 g every 6 hours may be required. The CHMP was of the opinion that in light of the present clinical and PK/PD data, a standard dose of 500 mg every 6 hours or 1g every 8 hours can be accepted, provided that a recommendation is inserted in the SPC stating that for infections suspected or proven to be due to less susceptible organisms (e.g. *P. aeruginosa*,) and for very severe infections (e.g. in neutropenic patients with a fever), the 1000 mg q.i.d should be used. No posology was specified in children for this indication as children above 40 kg would receive the adult dose. In conclusion, the CHMP adopted the following harmonised indication:

"intra- and post-partum infections"

4.1.4 Septicaemia

The MAH proposed the indication "septicaemia" which is currently approved in 26 of the 28 European countries according to the MAH. In the original Worldwide Marketing Application, patients who were identified and treated for systemic infections had either a diagnosis of septicaemia (if there was no associated primary infection site) or bacteraemia (if there was an associated primary infection site). If the same organism was cultured from the blood and another site of infection (prime site), the patient was reported to have a diagnosis of prime site infection with bacteraemia. Septicaemia was reserved for cases where there was no associated, evaluable prime site infection due to the same organism. Therefore, in the original Worldwide Marketing Application, the term septicaemia encompassed

septicaemia, endocarditis, and catheter-associated bacteraemia. Favourable overall clinical outcomes were demonstrated in 93% of imipenem/cilastatin-treated patients with septicaemia. A broad range of infections were treated, including infections caused by Gram-negative organisms, Gram-positive organisms, and anaerobes. Catheter-associated bacteraemia and endocarditis were also successfully treated with imipenem/cilastatin (with 83% and 100% cured or improved, respectively). Studies regarding septicaemia included both comparator-controlled and non-comparative studies. The comparators concerned cefazolin, cephalothin, cefotaxime, moxalactam, and gentamicin/clindamycin. Overall clinical outcomes for imipenem/cilastatin ranged between 79 and 100%.

In the comparator-controlled study of imipenem/cilastatin and cefazolin, 7 evaluable patients, including 5 treated with imipenem/cilastatin and 2 treated with cefazolin, were diagnosed with septicaemia. Favourable bacteriological outcomes were demonstrated for all identified pathogens. Of note, one of the imipenem/ cilastatin-treated patients had a polymicrobial infection.

In the comparator-controlled study of imipenem/cilastatin and cephalothin, 7 evaluable patients, including 3 treated with imipenem/cilastatin and 4 treated with cephalothin, had septicaemia as a primary diagnosis. All patients were cured or improved for their respective infections. One patient who received cephalothin died; however, the infection was considered "clinically cured." Notably, in this study, two patients who received imipenem/cilastatin had bacteraemia associated with a primary diagnosis other than septicaemia. Both had urinary tract infections due to *E. coli*; both infections were cured, and their bloodstream pathogen (*E. coli*) was successfully eradicated.

In the controlled study with cefotaxime, 31 evaluable patients, including 19 imipenem/cilastatin-treated patients and 12 cefotaxime-treated patients, were diagnosed with septicaemia. Clinical efficacy was demonstrated in 79% of the imipenem/cilastatin-treated patients (15 of 19), and in 100% of the cefotaxime-treated patients (12 of 12). Overall, there were four clinical failures (3 were also bacteriologic failures) in the imipenem/cilastatin group. Two of these 4 clinical failures had undocumented intra-abdominal abscesses in addition to the septicaemia. The intra-abdominal abscess was possibly responsible for a breakthrough bacteraemia in one case. The second patient had a resistant *S. epidermidis* as the primary pathogen. Both patients had venous catheters in place. One patient most likely represented a case of endocarditis which relapsed ten days after a four-week course of methicillin. In spite of sterilization of blood by Day 3 of imipenem/cilastatin therapy, this patient remained febrile. All 15 pathogens isolated in the cefotaxime group and 17 of the 20 pathogens isolated in the imipenem/cilastatin group were successfully eradicated.

In the comparator-controlled study of imipenem/cilastatin and gentamicin/clindamycin, 17 evaluable patients had septicaemia. All 6 imipenem/cilastatin-treated patients (100%) and 9 of the 11 gentamicin/clindamycin-treated patients (82%) were cured or improved. Among the two clinical failures in the gentamicin/clindamycin group with septicaemia, one patient was also a bacteriological failure with persistence of the original *E. coli*. Both had breakthrough bacteraemia on the fourth day of treatment with gentamicin/clindamycin-resistant enterococci. In one case, the investigator switched to cefotaxime therapy before receiving the final blood culture results. Although the cultures were negative, the investigator considered this case a failure. The second patient was later found to have a sub-hepatic abscess which the investigator felt was the initial focus of the infection. By this time, the patient had been switched to another antibiotic. In this study of, all 11 strains isolated from the imipenem/cilastatin-treated patients were successfully eradicated. Of the 13 strains isolated from the gentamicin/clindamycin-treated patients, 12 were eradicated.

In the non-controlled studies, imipenem/cilastatin demonstrated favourable overall clinical response in all 22 patients (100%). In the controlled study with moxalactam, 24 evaluable patients, including 16 imipenem/cilastatin-treated patients and 8 moxalactam-treated patients, had septicaemia. Fifteen (94%) of the 16 imipenem/cilastatin-treated patients and all 8 of the moxalactam-treated patients were cured or improved. All isolated pathogens were eradicated.

The MAH also provided data from several more recent studies in the peer-review medical literature, ultimately demonstrating the utility of imipenem/cilastatin in the treatment of septicaemia and bacteraemia (involving over 500 imipenem/cilastatin-treated patients), including 5 non-comparative trials and 3 randomised comparator-controlled trials. The clinical response rate for imipenem/cilastatin from these studies ranged between 59% to 100%, and the bacteriologic response rate for imipenem/cilastatin ranged between 71% and 98%. In all 3 comparator-controlled studies, imipenem/cilastatin compared favourably to the comparator agent. Imipenem/cilastatin was generally well tolerated and safe to use in patients with septicaemia and bacteraemia.

Furthermore, in a German national guideline, imipenem/cilastatin is also listed for use in an empirical situation for severe and /or nosocomial sepsis without known origin, and with origin from the following: respiratory tract, urinary tract, gut, gynaecologic tract, biliary tract, skin and soft tissue; directed treatment for *P. mirabilis*, *Citrobacter freundii*, *Enterobacter* spp., *Bacteroides fragilis*; in combination with a fluoroquinolone or an aminoglycoside for *P. aeruginosa*, *S. marcescens*, *Acinetobacter* spp (Vogel F et al, Chemotherapie Journal 13, 46-105, 2004).

Based on the available data from the original Worldwide Marketing Application and the medical literature for the efficacy and safety of imipenem/cilastatin in the treatment of septicaemia/bacteraemia, the MAH considers that septicaemia should be retained as an indication for imipenem/cilastatin.

The CHMP noted the large, randomised and controlled clinical study by Geddes et al, 1999, in which 260 patients with bacteraemia/septicaemia received imipenem/cilastatin and high cure rates (85%) and bacteriological eradication rates (87%) were obtained in the PP population. The comparator was in this study was levofloxacin, which showed a clinical cure rate of 89%. However, the data were considered inadequate. Septicaemia (likewise sepsis and bacteraemia) is generally a complication (secondary condition) to the primary site infection and can therefore not be considered as a specific indication. In the indicated primary conditions imipenem /cilastatin is of course effective with or without bacteraemic complications. Accordingly, and in the light of current CHMP NfG on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95) "Septicaemia" is considered unacceptable as an indication; this is also in line with recent European assessments of antibiotics. Furthermore, insufficient data were presented and discussed. The MAH was requested to summarise the evidence that might support a possible indication for use of imipenem-cilastatin in the management of patients with a suspected or proven bacteraemia in association with clinical signs and symptoms of systemic infection. The response should include whatever data are available from clinical studies regarding characteristics of the treated cases, pathogens, dose regimens used (including use of monotherapy or combination therapy) and clinical and microbiological outcomes by indication. Regarding posology, the proposal presented by the MAH was questioned due the severity and life-threatening character of the bacteraemic condition. The MAH was requested to further justify the dosage in this indication.

The MAH acknowledged that there is limited (and very old) clinical trial data and agreed carry out a new literature search for more recent comparator-controlled clinical trials which evaluate the use of imipenem/cilastatin in the management of patients with a suspected or proven bacteraemia in association with clinical signs and symptoms of systemic infection, which also include mortality/morbidity data. The MAH provided responses to the CHMP, noting that the response documentation mentions the terms *bacteraemia*, *septicaemia* and *sepsis*. Especially in the old clinical studies/literature, septicaemia has been used as a synonym for bacteraemia or bacteraemia leading to sepsis; it is not a well defined term and should be avoided. According to the CHMP guideline on the clinical development of new medicinal products in the treatment of patients with sepsis (CHMP/EWP/4713/03), *sepsis* is a severe and complex form of infection associated with a systemic inflammatory response syndrome (SIRS). However, in numerous patients with signs of sepsis, a source of infection cannot be confirmed. The management of sepsis is complex and includes several interventions, among others the use of adequate anti-infective agents. The severity of sepsis is also diverse, ranging from mild systemic inflammation without significant clinical consequences to multi-system failure resulting in septic shock with a high mortality rate. Therefore, it is important to have information on the clinical sepsis-status of a bacteraemic patient with any signs of sepsis. This should be taken into account in the discussion of any qualification of an antibiotic like Tienam for a possible indication. Globally, for the antibiotic to qualify for the treatment of the infectious condition in patients with (severe) sepsis status the following characteristics of the agent and data are considered necessary:

- Broad-spectrum antibiotic appropriate that makes at least initial/empiric treatment of gram-negative and gram-positive infections possible.
- Agent has an approved broad spectrum of indications and in particular indications that include the most common foci of septicaemia, i.e. pneumonia, urinary tract infections, intra-abdominal infections, and skin and soft tissue infections.
- Adequate data, preferably from appropriate designed controlled trials, including data on starting treatment within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained. Evaluation of the adequacy of the antibiotic choice (e.g. including supporting bacteriological and clinical evidence). The wrong choice could be deadly. Appropriate combination therapy should be recommended whenever indicated by the antibacterial susceptibility.

In addition, the draft for the second revision of the Guideline on the Evaluation of Medicinal Products indicated for the Treatment of Bacterial Infections (CPMP/EWP/558/95 rev 2) states that in order to qualify for an indication in the treatment of bacteraemia (which could still require qualification by specific pathogens), the antibacterial agent must have shown to be efficacious and be indicated for use in a range of infections that collectively account for a substantial proportion of cases of bacteraemia observed in clinical practice (e.g. including community and/or hospital-acquired pneumonias, urinary tract infections, skin and soft tissue infections and intra-abdominal infections). The studies must also include a sufficient number of bacteraemic cases in each indication.

The MAH stated that in the studies from the original WMA, patients who were identified and treated for systemic infections could have either a diagnosis of septicaemia (if there was no associated primary infection site) or bacteraemia (if there was an associated primary infection site). Septicaemia was

reserved for cases where there was no associated, evaluable prime site infection due to the same organism. Therefore, the term septicaemia encompassed septicaemia, endocarditis, and catheter-associated bacteraemia. In the comparative trials, the imipenem total daily doses were 1-2 g/day; in non-comparative trials, imipenem doses were 1 to 4 g/day. Favourable overall clinical outcomes were demonstrated in 70 of 75 (93%) of imipenem/cilastatin-treated patients with septicaemia. Catheter-associated bacteraemia and endocarditis were also successfully treated with imipenem/cilastatin (with 83% and 100% cured or improved, respectively). A broad range of infections were successfully treated, including infections caused by Gram-negative organisms, Gram-positive organisms, and anaerobes. Overall, the data from these studies provide evidence for the use of imipenem/cilastatin in the treatment of septicaemia (or bacteraemia). In addition to the data from the original WMA, data were summarised from several studies (involving over 500 imipenem/cilastatin-treated patients) in the peer-review medical literature. Five non-comparative trials and 3 randomised comparator-controlled trials were identified. These studies were all conducted prior to the year 2000. Two of the non-comparative trials focused solely on the treatment of bacteraemia and septicaemia and one randomised comparator-controlled trial focused on the empirical treatment of suspected bacteraemia/sepsis. The remainder of the studies report on a subset of patients with bacteraemia or septicaemia. In the non-comparative trials, the patient populations had a mean age of ~50 years, with a predominance of males (>50%). The imipenem dose ranged between 1 to 4 g daily. The majority of patients have significant underlying diseases such as: cardiovascular, cancer, diabetes mellitus, and immunologic diseases. The primary sites of infection studied include urinary tract infections, intra-abdominal infections, respiratory tract infections, and skin/skin structure infections. The most common organisms isolated were Gram-negative organisms. The most common organisms included *E. coli*, *Kleibsellia pneumoniae*, *Kleibsellia spp.*, *P. aeruginosa*, *S. aureus*, and *S. pneumoniae*. In the 3 randomised comparator-controlled trials, the mean age of the patient populations was ~60 years, with male gender in the majority (57%-76%). The imipenem dose was 500 mg every 6 hours in one study and 1000 mg three-times daily in two studies. The severity of illness of the patients varied between studies. Garau et al. included severely ill patients, with a mean APACHE II score of 16.5 with most patients required intensive care (90%) and mechanical ventilation (72%), while in Norrby et al. the patient population had a mean APACHE II score of 4. Geddes et al. studied the empirical treatment of suspected bacteraemia/sepsis and the most common underlying diseases included renal/genitourinary, respiratory and cardiovascular. The primary site of infections in these 3 studies included: pneumonia/lower respiratory tract infections (46%-65%), pyelonephritis/urinary tract infections (range: 3%-28%), intra-abdominal infection (10%-15%) and sepsis (6%-23%). Gram-negative organisms predominated. The most common organisms included *E. coli*, *Kleibsellia pneumoniae*, *Kleibsellia spp.*, *P. aeruginosa*, *S. aureus*, and *S. pneumoniae*. The clinical response rate for imipenem/cilastatin from the non-comparative and the randomised-comparator-controlled trials ranged between 59% to 100%, and the bacteriologic response rate for imipenem/cilastatin ranged between 71% and 98%. In all 3 comparator-controlled studies, imipenem/cilastatin compared favourably to the comparator agent. Imipenem/cilastatin was generally safe and well tolerated to use in patients with these severe infections, namely septicaemia and bacteraemia. Overall, the MAH concluded that the data from the literature provides supportive evidence for the use of imipenem/cilastatin in the treatment of septicaemia (or bacteraemia).

The CHMP noted that there is only one published open large randomised controlled trial imipenem/cilastatin (1g t.i.d) versus levofloxacin (i.v. 0.5 g b.i.d) focused on the empirical treatment of *suspected bacteraemia/sepsis* (Geddes et al 1999). It enrolled adult patients with clinical evidence of infection e.g. respiratory tract infection (RTI), urinary tract infection (UTI), intra-abdominal infection; and a systemic response to infection manifested by two or more SIRS (Systemic inflammatory response syndrome)-criteria. The primary efficacy analysis was based on the clinical and bacteriological response at clinical endpoint. Clinical and bacteriological assessments were performed at clinical endpoint (1-5 days after the last day of treatment) but only a clinical assessment was performed at follow-up (10-30 days after the last day of treatment). This assumes a success rate of 80% in both treatment arms and a δ of 15% (maximum difference between treatments to be accepted as equivalent). The characteristics of the basic illness were similar for both treatment groups. The study enrolled a total of 499 subjects, of which 260 received imipenem/cilastatin. Pneumonia/RTI was the most common condition (47%, $n = 232$), either alone or in combination with other infections. The majority of all patients had community-acquired infections (82%, $n = 409$). The median APACHE III score was 46 (range 6-106). A pathogen was isolated at baseline in 308 patients (62%). The most common pathogens isolated from blood cultures were *E. coli*, *S. pneumoniae* and *K. pneumoniae*. Of 365 aerobic isolates, eight (2%) were resistant to imipenem/cilastatin and 15 (4%) to levofloxacin. *Clinical cure rates* at clinical endpoint in the intent-to-treat population and per-protocol population were 77% (184/239) and 89% (125/140), respectively, for levofloxacin and 68% (178/260) and 85% (125/147), respectively, for imipenem/cilastatin. At follow-up, the cure rates in the per-protocol population were 84% for levofloxacin and 69% for imipenem/cilastatin (95% CI was -3.5;12.0). The

satisfactory bacteriological response rate, in the per-protocol population at clinical endpoint, was similar in both levofloxacin (96/110; 87%) and imipenem/cilastatin (97/116; 84%). The CHMP acknowledged that the delta value of 15% chosen for this study may be criticised as being too large. In addition, the comparator is not approved for this indication. Furthermore, sepsis condition with unknown primary focus was enlisted to be present only in 15-16 patients per arm (6-7% of the study subjects); the infection site was thus known for the overwhelming majority of the tested population. Pneumonia/RTI and pyelonephritis/UIT were the predominant diagnoses (46% and 28% of the patients respectively) followed by patients with IAI (10%). On the other hand, as can be expected, the bacteraemia associated with the approved indications was favourably affected as reflected in the high clinical cures reported for the known primary site infection. However, at follow-up, cure rates were lower for imipenem/cilastatin (69% vs. 84% for levofloxacin).

The MAH carried out an additional comprehensive clinical literature review, to identify clinical studies, including clinical trials and observational studies, to summarize the efficacy/effectiveness, safety, or mortality of intravenously administered imipenem/cilastatin monotherapy, in the treatment of suspected or proven bacteraemia. No comparator-controlled clinical trials were identified that were both conducted and published between the years of 1-Jan-2000 to 28-Jun-2010 and had a primary objective to evaluate the efficacy and safety imipenem/cilastatin for the treatment of suspected or proven bacteraemia. One article was identified and selected for inclusion in the pooled analysis to compare the safety and efficacy of intravenous tigecycline in subjects with secondary bacteraemia with various comparators from 8 Phase III clinical trials. Based on the review of this article, two additional articles were identified summarizing the two, Phase III clinical trials in patients receiving either tigecycline or imipenem/cilastatin for the treatment of complicated intra-abdominal infections with or without concomitant bacteraemia. Five epidemiologic studies reporting the impact of imipenem/cilastatin treatment on patient outcome were found. These were all single-centre, retrospective studies, providing data on the use of imipenem/cilastatin in patients with the treatment of suspected or proven bacteraemia. The MAH provided a detailed summary of these studies and stated that due to the lack of controlled trials to adequately assess the efficacy of empirical or definitive therapy for bacteraemia, research over the last decade has focused on conducting epidemiologic studies evaluating the association between appropriate antibiotic therapy for suspected or proven bacteraemia with outcome from infection such as morbidity, mortality, and clinical response to treatment. The majority of these studies are single-centre, retrospective studies focused on bacteraemia associated with particular pathogens. In order to obtain an adequate number of bacteraemia cases, the studies cover many years, but may still not be sufficiently powered to address the study objectives. In addition, assessment of individual antibiotic treatments with outcome is seldom described. The majority of the epidemiologic studies are retrospective and the cautious interpretation of study results is required due to the inherent biases associated with this particular study design. Nevertheless, the studies discussed above do provide supportive data on the impact of imipenem/cilastatin on outcomes, including mortality, for bacteraemia associated with various pathogens.

Therefore, the MAH considered that overall, the available data support the efficacy and safety of imipenem/cilastatin in the treatment of septicaemia or alternately, bacteraemia. The MAH believed that the retention of bacteraemia as an indication for imipenem/cilastatin is scientifically justified.

The CHMP noted the updated review of the data from the original dossier and available relevant literature sources in support of efficacy and safety of imipenem/cilastatin in the treatment of bacteraemia. There were no useful comparator-controlled clinical trials conducted and published in the peer-review literature from 2000 through 2010 in this indication while the epidemiological studies are of questionable quality and not sufficiently informative, in particular with regards to the used imipenem/cilastatin dosage. However, the CHMP acknowledged that high clinical cure rates were often reported in a large number of patients with bacteraemia associated with the approved indications. The reported lower cure rates may be attributed to the severity of the infection (as in the study by Norby, 1993). The described evidence was considered to be supportive of the originally approved indications specified by site of infection and thus implied in these approved indications. Imipenem, like other carbapenems, is generally regarded as the drug of choice for treatment of extended-spectrum β -lactamase (ESBL)-producing bacteria. They are more effective than fluoroquinolones for serious infections, since ESBL-producing bacteria may carry determinants that confer low- or high level resistance to fluoroquinolones. However, specific data for use of imipenem against ESBL-associated infections are limited, although generally supportive of their effectiveness in patients with bacteraemia (Endimiani *et al.*, 2004; Paterson *et al.*, 2004). Regarding the dosage, the CHMP was of the opinion that in light of the present clinical and PK/PD data, a standard dose of 500 mg every 6 hours or 1g every 8 hours can be accepted, provided that a recommendation is inserted in the SPC stating that for

infections suspected or proven to be due to less susceptible organisms (e.g. *P. aeruginosa*,) and for very severe infections (e.g. in neutropenic patients with a fever), the 1000 mg q.i.d should be used. In conclusion, based on the presented data, the CHMP considered the indication to be acceptable but revised the wording according to that agreed in the drafting group for anti-infectives. In conclusion, the CHMP adopted the following harmonised indication:

"Tienam may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection."

4.1.5 Genitourinary infections

The CHMP noted the proposed indication "genitourinary infections", which is currently approved in 25 of 30 European countries, but remarked that the MAH did not provide any discussions or supporting data. Imipenem/cilastatin is targeted only in severe bacterial infections suspected or due to pathogens resistant to other beta-lactams and susceptible to imipenem/cilastatin. In addition, the term "genitourinary tract infections" was considered outdated. The CHMP therefore proposed the following wording for a potential indication: "complicated urinary tract infections".

The MAH agreed with the CHMP proposal to limit the indication to "complicated urinary tract infections" and provided a succinct summary of the clinical trial data from the original worldwide marketing application (WMA), as well as a succinct summary of a comprehensive literature review with regard to the use of imipenem/cilastatin in the treatment of urinary tract infections (UTIs). The original WMA (late 1970s to early 1980) comprised 94 UTI cases: cystitis (37) or unspecified "urinary tract infection" (6), and 47 had a diagnosis of pyelonephritis. Overall, all 37 (100%) patients with cystitis and all 6 (100%) patients with "urinary tract infection" (unspecified) had a favourable overall response to imipenem/cilastatin. In addition, 87% (41/47) of the patients with pyelonephritis had a favourable overall response to imipenem/cilastatin. The remaining 4 cases were recorded as different types of complicated urinary tract infection: 1 bladder abscess, 1 prostatitis, and 2 renal abscesses. In all four of these cases, the patients had favourable overall responses to imipenem/cilastatin. Taken together, 88% (45/51) of the patients with a complex urinary tract infection had a favourable response to imipenem/cilastatin. A literature search generated 39 journal articles for further screening, 8 articles reported at least 20 patients treated with imipenem/cilastatin monotherapy for urinary tract infections. The majority of patients in these published reports had a diagnosis of *pyelonephritis* or *cUTI*. Overall, in these 8 studies, the favourable clinical response rates for imipenem/cilastatin ranged from 80% to 100%. The use of imipenem/cilastatin was generally safe and well tolerated. The MAH described in particular details 3 studies.

The first study, by Hou et al (2002) was a randomised, controlled clinical trial in 182 hospitalised patients with infections in China; it compared meropenem (0.5g or 1g b.i.d) versus imipenem/cilastatin (500mg/500 mg or 1g b.i.d) given for 7-14 days. A favourable clinical response was seen in all 22 patients treated with meropenem for a UTI, and in all 26 patients treated with imipenem/cilastatin for a UTI. Notably, 16 (73%) of the 22 meropenem-treated patients and 22 (85%) of the 26 imipenem/cilastatin treated patients had pyelonephritis or a complicated UTI. The second study, by Sheehan et al (1985) was a comparative study of UTI where the majority of cases were due to pyelonephritis. A favourable response was seen in 84% (48/57) of patients treated with imipenem/cilastatin, and in 91% (64/70) of patients treated with cephalothin, moxalactam, cefazolin, or cefotaxime. The third study, by Naber (2002) was a randomised, double-blind, trial (in DE) comparing piperacillin/tazobactam 2g/0.5g t.i.d versus imipenem/cilastatin (500mg/500 mg t.i.d) for treatment of acute uncomplicated pyelonephritis (11-13% of the patients) and complicated urinary tract infection in 161 and 166 patients per treatment group respectively. Clinical success was noted in 83% (122/147) piperacillin/tazobactam-treated patients as compared to 80% (123/154) of the imipenem/cilastatin-treated patients at TOC (5-9 days after antibiotic therapy). Microbiological success at the early follow-up was 78 135 (57.8%) for piperacillin/tazobactam and 70 144 (48.6%) for imipenem cilastatin. Piperacillin/tazobactam was more efficient at eradicating *E. coli*, *Enterobacter cloacae* and *P. aeruginosa* and a better bacteriological response was documented.

In summary, the MAH considered that data obtained from the review of both clinical trial data from the original WMA and data from a comprehensive literature review with regard to the use of imipenem/cilastatin in the treatment of urinary tract infections provided convincing evidence for the use of imipenem/cilastatin in the treatment of complicated UTIs.

The CHMP noted the review carried out by the MAH and also the MAH agreement to limit the indication, which is consistent with the approach used for several other agents in the EU, including carbapenems. The CHMP considered that most studies were outdated and/or of poor quality. The most informative

and relevant study was the recent study of Naber KG et al (2002) which showed that the daily dose of Tienam 500mg/500 mg t.i.d for treatment of acute uncomplicated pyelonephritis and cUTI is efficacious, however, clinical success and microbiological was higher in piperacillin/tazobactam treated patients as compared to 80% (123/154) of the imipenem/cilastatin-treated patients. Piperacillin/tazobactam was more efficient at eradicating *E. coli*, *Enterobacter cloacae* and *P. aeruginosa* and a better bacteriological response was documented. The MAH was requested to further clarify the proposed dosage.

The MAH provided summarised data from the Merck clinical trials (submitted as part of the original WMA), on gynaecological infections together with genitourinary tract infections. Overall, 94 patients received treatment with imipenem/cilastatin for UTIs. A total of 51 of these 94 patients had infections categorised as cUTIs. In the comparative trials, the imipenem total daily doses ranged from 1 to 2 g daily for UTI, but the most common dose, administered to 71% of the patients, was 500 mg every 6 hours (500 mg q6h). Among patients with genitourinary tract infections receiving imipenem at 2 g daily in comparative studies, the success rate was 94% (58/62). Among patients receiving imipenem at <2 g daily in comparative studies, the success rate was 88% (22/25). Doses higher than 2 g daily were not frequently administered in the Merck trials. A comprehensive literature search identified 8 studies with at least 20 patients treated with imipenem/cilastatin monotherapy for UTI. Four of the 8 articles were comparative studies of imipenem/cilastatin versus another antibiotic. In 3 of these comparative studies, the imipenem doses ranged from 1 to 2 g daily. The success rates for imipenem/cilastatin ranged from 80% to 100% in these 3 studies. In the 4 non-comparative studies, the daily dose of imipenem ranged between 1 to 4 g with generally similar efficacy results as those seen in the comparative studies. In 2009, the ongoing surveillance study of intra-abdominal pathogens (the Merck-sponsored Study to Monitor Antimicrobial Resistance Trends, or SMART study) was expanded to collect pathogens from UTI. The SMART surveillance data confirm that Enterobacteriaceae are the most prevalent gram-negative pathogens identified in patients with UTI, with *E. coli* and *K. pneumoniae* representing over 70% of all gram-negative pathogens. A PK/PD analysis was performed using over 5,000 isolates each of *E. coli* and *K. pneumoniae* recently collected in the SMART study. Data from Monte Carlo simulations at the accepted efficacy target (i.e., time above MIC target of 40%) suggest that imipenem doses of 500 mg every 6 hours or 1 g every 8 hours provide very similar coverage for *E. coli* and *Klebsiella* spp. Thus, these two doses could be viewed as essentially interchangeable in the treatment of cUTI. In summary, the MAH considered that the data from the original WMA and the comprehensive literature search, coupled with the supportive PK/PD data are consistent with a dosing recommendation for imipenem of 500 mg every 6 hours or 1 g every 8 hours for the indication of cUTI. Since both doses are commonly used in clinical practice, and provide similar drug exposure, the MAH considered it important to provide flexibility for clinicians to choose either dose when treating cUTI.

The CHMP noted the revised dosing recommendation of 500 mg every 6 or 1g every 8 hours for cUTI, as proposed by the MAH, and also that the MAH did not propose the higher dose of 1 g q6h. The CHMP stated that severe cUTI, the pathogen(s) involved and the degree of susceptibility of these pathogen(s) are often not identified at initiation of therapy but can be life-threatening, for example in "urosepsis". In the nosocomial setting, pathogens such as *Enterococcus faecalis*, *P. aeruginosa* and *Klebsiella* spp. are frequent, as is (the predominant) *E. coli*. Therefore, when determining the dosage to be used for therapy with Tienam, the less susceptible pathogens must also be taken into account. The presently revised dosing recommendation by the MAH for adults is 500 mg every 6 or 1g every 8 hours. The CHMP was of the opinion that in light of the present clinical and PK/PD data, a standard dose of 500 mg every 6 hours or 1g every 8 hours can be accepted, provided that a recommendation is inserted in the SPC stating that for infections suspected or proven to be due to less susceptible organisms (e.g. *P. aeruginosa*,) and for very severe infections (e.g. in neutropenic patients with a fever), the 1000 mg q.i.d should be used. In conclusion, the CHMP adopted the following harmonised indication:

"complicated urinary tract infections"

4.1.6 Bone and joint infections

The MAH proposed the indication "bone and joint infections", which is currently approved indication in 26 of 28 European countries and stated that studies in bone and joint infections for imipenem/cilastatin included both comparator-controlled and non-comparative studies. The comparators used in the comparator-controlled studies included cefazolin, moxalactam, and gentamicin/clindamycin. In the original Worldwide Marketing Application for imipenem/cilastatin, data from 35 patients with bone and joint infections were included. 94% of patients treated with imipenem/cilastatin (33 of 35 patients)

was cured or improved. These infections included primarily osteomyelitis and septic arthritis. In addition to *S. aureus*, some cases of *P. aeruginosa* osteomyelitis were successfully treated.

Studies regarding bone and joint infections included both comparator-controlled and non-comparative studies. The comparators included cefazolin, moxalactam, and gentamicin/clindamycin. The overall clinical outcomes for imipenem/cilastatin-treated patients ranged between 91 and 100%. Although the number of cases was limited, similar efficacy was observed for imipenem/cilastatin when compared to cefazolin and moxalactam. In the comparator-controlled study of imipenem/cilastatin and cefazolin, 10 evaluable patients, including 5 treated with imipenem/cilastatin and 5 treated with cefazolin, had infections involving the bone or joint. This includes 3 cases of osteomyelitis (2 imipenem/cilastatin, 1 cefazolin) and 7 cases of septic arthritis (3 imipenem /cilastatin, 4 cefazolin). All 3 cases of osteomyelitis were cured; of note, 1 of the 2 imipenem /cilastatin-treated patients with osteomyelitis had a polymicrobial infection. Among the 7 cases of septic arthritis, all 3 (100%) imipenem/cilastatin-treated patients and 3 (75%) of the 4 cefazolin--treated patients were cured or improved. Four patients with septic arthritis, including 1 treated with imipenem/cilastatin and 3 treated with cefazolin, had poly-microbial infections; all but one (cefazolin) had a favourable outcome. Six of the 8 pathogens isolated in the imipenem/cilastatin group (75%) and 9/12 pathogens isolated in the cefazolin group (75%) were successfully eradicated. In the comparator-controlled study of imipenem/cilastatin and moxalactam, 5 evaluable patients, including 4 receiving imipenem/cilastatin and 1 receiving moxalactam, had osteomyelitis. All five patients were cured. All had poly-microbial infections. In the comparator-controlled study of imipenem/cilastatin and gentamicin/clindamycin, one imipenem/cilastatin-treated patient had an infected bursa, which was cured with the pathogens eradicated. One gentamicin/clindamycin-treated patient had septic arthritis and was a clinical and bacteriologic failure, with *B. fragilis* persisting in the knee joint fluid. The investigator considered the septic arthritis due to seeding from an undocumented intra-abdominal abscess. In addition, this patient had bacteraemia and a urinary tract infection. In the non-comparative studies, overall clinical response was 92% (22 of 24 patients). The MAH also provided additional data from several more recent studies (involving over 200 imipenem/cilastatin-treated patients), including two randomised controlled trials and seven non-comparative trials. In these studies, the clinical cure rates for imipenem/cilastatin ranged between 61.8% and 100% while the microbiologic response (i.e. bacteriological eradication) ranged between 57.1% and 93%. In the two controlled studies, imipenem/cilastatin provided comparable efficacy to ampicillin/sulbactam and cefazolin. Imipenem/cilastatin was generally well tolerated in these studies. Adverse events possibly related to imipenem/cilastatin in 10% or more of the study population included diarrhoea, nausea, elevated alkaline phosphatase or transaminase levels, neutropenia, phlebitis, and abnormal hepatic function levels. These AEs are consistent with the proposed harmonised EU SPC for imipenem/cilastatin.

Based on the submitted data from the original Worldwide Marketing Application and the medical literature for the efficacy and safety of imipenem/cilastatin in the treatment of bone and joint infections, the MAH considered that bone and joint infections should be retained as an indication for imipenem/cilastatin.

The CHMP considered the data submitted to substantiate the broad indication in the treatment of "Bone and joint infections" to be insufficient and noted that osteomyelitis is an infection difficult to treat, and data from controlled studies are considered necessary to support this indication. Information from the original Worldwide Marketing Application is very scarce and very few patients were investigated in the provided comparative and non-comparative studies. In the original dossier, there is data from a total of 35 patients with bone and joint infections and primarily *osteomyelitis* and *septic arthritis* were the identified infections.

Of these patients, 25 had osteomyelitis while 9 had septic arthritis, and 94% was cured or improved. These data were obtained however from 3 controlled small studies (n=2-5 in each study) and two non-controlled studies (n=24). Nearly all additional documentation submitted consists of non-controlled studies. In one randomised, double-blind, controlled study (Grayson 1994), diabetic patients with limb-threatening foot infection were treated with imipenem/cilastatin or ampicillin/sulbactam. The frequency of osteomyelitis in association with soft-tissue infections was 56% in imipenem/cilastatin group and 68% in ampicillin/sulbactam group, and cure rates were 85% and 81%, respectively. The most commonly isolated pathogens were *S. aureus*, enterococci, streptococci and non-fragilis bacteroides. There is a risk that these pathogens might have originated from the infected tissue cultures, and not from the bone.

Gram-positive organisms, particularly staphylococci and streptococci, are responsible for the majority of bone and joint infections. Therefore, imipenem/cilastatin is not considered to be an appropriate antibiotic for the empiric treatment of osteomyelitis which is frequently caused by staphylococci since the risk of selecting for MRSA is quite high, especially in certain European countries, with an inherent risk of therapeutic failure. Likewise, prosthesis-hip infections are often caused by coagulase-negative staphylococci for which imipenem/cilastatin would not be an appropriate agent. Lower-limb infections in diabetic patients are frequently caused by a mixture of Gram-negative bacteria and anaerobes that often require the use of a combination of antibiotics. Due to its broad antibacterial spectrum covering the above-mentioned bacteria and relative lack of renal toxicity (e.g. compared to aminoglycosides), imipenem/cilastatin could be an appropriate agent for the treatment of such infections in diabetic patients.

The CHMP also considered data from literature sources. The monograph of Gentry reports the use of imipenem/cilastatin in 34 patients with osteomyelitis. The mean daily dose was 3.5g for 32.5 days mean therapy duration. However, Grayson et al described treatment of serious limb pedal infections in diabetic patients (aged >18 years) where imipenem/cilastatin was given 500 mg every 6 hours. Of 48 patients, 56% were with osteomyelitis. Amputations were performed on 28 (58%) patients. Only 8 patients with bone and joint infections were enrolled in the comparative study of Marier et al. Of these, 3 patients received 250 mg every 6 hours IV imipenem/cilastatin. Infections were identified as mild and moderate and were further not specified. Ketter et al investigated 61 patients with chronic post-traumatic osteitis in their non-comparative study. Of all cases, 90% were localised in the lower limbs, and 6% at the upper extremity. Imipenem was given 500 mg TID for 10 days. *S. aureus* was the most commonly isolated pathogen. Only 7 patients over 13 years of old with osteoarticular infections were enrolled in the non-comparative study of Garau et al. One patient had osteomyelitis, one patient with osteoarthritis of the right shoulder required surgery to drain the humeral osteomyelitic focus, three patients with haematogenous arthritis and for two patients not mentioned. Imipenem/cilastatin generally was given 500 mg IV, ranged 2g-3g/daily for 3-55 days (mean duration: 13 days). In the study of MacGregor et al, 34 patients with osteomyelitis were treated for a mean of 32.5 days with 2 to 4 g /day IV of Imipenem/ cilastatin. Of these, 26 infections involving the lower extremities associated with accidents and prosthesis implantation. The review article of Trumbore et al reports 5 cases of osteomyelitis treated with imipenem/cilastatin 2-4 g daily for 34-70 days. One patient with sternal osteomyelitis was treated in combination with tobramycin. Therapy for one diabetic patient with osteomyelitis was failed after treatment with 2 g /d of imipenem/ cilastatin for 34 days due to a super-infection. In the non-comparative study of Zajac et al, 31 patients (over 12 years of age) with several infections were enrolled and treated with imipenem/ cilastatin 1g IV every 6 hours for 5 to 56 days. Of these, 7 patients had osteomyelitis. Dosages used in osteomyelitic cases are not mentioned. One patient was failed due to the sterile bone culture, 5 was cured and no relapse after >12 months of follow-up, one was improved. In another non-comparative trial of Calandra et al, 717 adult patients were treated with imipenem/ cilastatin 1-4g daily in 3-4 divided doses IV, for 5-43 days. Of these, 57 cases were identified as bone and joint infections. No further specification is given. Fourteen of 73 adult patients were with osteomyelitis reported in the non-comparative trial of Freimer et al. All patients with several infections received imipenem/ cilastatin generally IV every 6 hours in doses ranging from 250 mg to 1g. But the authors found that doses of 500 mg every 6h exceeded the MIC for all initial bacterial isolates.

In summary, the CHMP did not agree with the claimed broad indication in the treatment of bone and joint infections. The submitted data from the original Worldwide Marketing Application was considered insufficient and the references provided by the MAH were regarded as outdated. In the submitted studies, a variety of infections were investigated at the same time and the studies were mainly uncontrolled and with a very low number of enrolled patients in each infection group. In the few comparative trials, the number of cases was too small to allow appropriate conclusion on the efficacy in the claimed indication. Furthermore, imipenem/cilastatin is not considered to be an appropriate agent to treat staphylococcal infections. Finally, this general indication is not in line with the current CHMP NfG on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95) and needs further specification. Since osteomyelitis was the commonest infection type in the studies, the CHMP requested the MAH to discuss limiting the indication to "*Osteomyelitis*" or "*limb-threatening diabetic foot infections*" and to substantiate any claimed indication by providing substantial relevant data. The MAH was also requested to further discuss its dose recommendation of 500 mg in 6 hours (2 g/day) for severe infections, considering this serious infection and the higher dosage used in several studies (up to 4 g daily for longer periods).

The MAH performed a detailed review of both clinical trial data from the original Worldwide Marketing Application (WMA) and data from a comprehensive literature review with regard to the use of imipenem/cilastatin in the treatment of bone and joint infections, specifically osteomyelitis. Data from the WMA were presented in the broad category of bone and joint infections. A total of 35 patients who were treated with imipenem/cilastatin for bone and joint infections were included in the WMA. Among these 35 patients, 25 patients had osteomyelitis. The success rate of imipenem/cilastatin in the treatment of osteomyelitis was 92% (23 of 25 patients). The efficacy of imipenem/cilastatin was comparable to that seen with the comparators (cefazolin, moxalactam and gentamicin/clindamycin). Most of the data in osteomyelitis were obtained at the dose of 2 to 4 g/day of imipenem/cilastatin. Therefore, the MAH believed that the data from clinical trials submitted in the original WMA support the proposed dose in the SPC: 500 mg or 1 g administered every 6 or 8 hours, thereby translating to a maximal dose of 4 g/day. The MAH also summarised the data from the literature review, which identified 10 studies with over 200 patients treated with imipenem/cilastatin monotherapy with bone and joint infections, including osteomyelitis, and 2 reviews of studies. Of the 10 studies submitted, 3 were randomised controlled trials and 7 were non-comparative. In 7 of the 10 studies, the bone and joint infection diagnosis was exclusively osteomyelitis. In these 7 studies, the clinical cure rates for osteomyelitis in patients treated with imipenem/cilastatin ranged between 50% and 83%. The microbiologic response (i.e. eradication) for imipenem/cilastatin ranged between 50% and 93%. Across the studies reviewed, the 3 most common pathogens isolated in patients with osteomyelitis were *S. aureus*, *P. aeruginosa*, and *Enterococcus spp.* In general, imipenem/cilastatin was efficacious against these 3 pathogens. Other less common pathogens seen in patients with osteomyelitis were *Staphylococcus epidermidis*, *E. coli*, *Proteus spp.*, and anaerobes. In the 7 studies that included the specific diagnoses of osteomyelitis, imipenem/cilastatin dosages ranged from 1-4 g/day, with the majority between 2-4 g/day. Overall, the data from the literature support the evidence for the use of imipenem/cilastatin monotherapy to successfully treat osteomyelitis.

The MAH concluded, based on this detailed review, that the CHMP proposal to modify the indication of "bone and joint infections" to the more limited and specific indication "osteomyelitis" was acceptable. The MAH proposed that the standard daily dose be used to treat osteomyelitis. Data from clinical trials submitted in the original WMA and from the literature demonstrate favourable efficacy consistent with the proposed dose in the SPC and the MAH therefore proposed 500 mg or 1 g administered every 6 or 8 hours, which translates to a maximal dose of 4 g/day. The MAH acknowledged that much of the data for imipenem/cilastatin was generated at a time when either a sub-classification of *S. aureus* into MRSA or MSSA was not performed or the incidence of MRSA was not sufficiently high to warrant significant concern. Thus, it is likely that the large majority of *S. aureus* described in the earlier studies were MSSA. Nevertheless, efficacy was reported against those *S. aureus* isolates causing bone infections, albeit most to all were due to MSSA. Following the review of the available data, the MAH considered that there have not been enough cases of imipenem/cilastatin monotherapy in patients with limb-threatening diabetic foot infections and/or infections in joint prosthesis & orthopaedic devices, specifically in relation to multi-resistant Enterobacteriaceae spp., to support those particular indications.

The CHMP noted the data submitted by the MAH and the agreement to limit the indication. Of the data from the literature review, only two clinical trials and one review article are new, compared to the documentation submitted previously. Of the 3 randomised controlled trials submitted in total, the one reported by Gomis et al (1999) contributed most patients, 16 treated with imipenem/cilastatin and 16 with ofloxacin. Two bacteriological failures to imipenem-cilastatin consisted of persistence (isolation of the causative organism from culture of diseased bone during therapy) and super-infection (isolation of a new pathogen from infected bone during therapy), respectively. In the first case, *P. aeruginosa* susceptible to imipenem-cilastatin *in vitro* could not be eradicated, and in the second case the initial pathogen was *S. aureus* and super-infection was due to *Staphylococcus epidermidis*. Most of the submitted studies were non-controlled, and only the studies by Ketterl and Garau contributed more than a very few patients with osteomyelitis, 61 and 34 respectively. Thus, although it is accepted that the majority of patients in the submitted documentation had osteomyelitis, the numbers per study is considered too limited to support this difficult-to-treat-infection. Imipenem/cilastatin is generally not considered to be a good staphylococcal agent, which is confirmed by e.g. the microbiological data in the study by Ketterl who reported a MIC value in *S. aureus* of 0.28 µg/ml, which is considerably higher than what is normally found for preferred anti-staphylococcal agents. Regarding the dosage, the MAH did not propose an optimal dosage regimen for this indication. In the studies submitted by the MAH on bone- and joint infections, the dosage varied over the proposed interval of 0.5 to 1 g every 6 to 8 hours depending on the severity of the infection and the infecting organism. However, since almost all submitted literature cover a variety of indications and only a few cases of osteomyelitis, a discussion is needed on the optimal posology in osteomyelitis. In the study by Gomis et al, including only cases of

osteomyelitis, the posology was 0.5 g every six hours. Furthermore, regarding the possible indication of limb-threatening foot infections, in the study by Grayson et al on this indication, the posology was 0.5 g every 6 hours.

In conclusion, the CHMP considered that there are not enough data to support an indication for osteomyelitis or septic arthritis and requested the MAH should provide and discuss all available evidence on the efficacy and safety of imipenem/cilastatin for the treatment of osteomyelitis and septic arthritis considering especially the microbiological spectrum and also, in the light of the present data, whether the standard dose should be 500 mg q.i.d. or whether 1 g t.i.d. is more appropriate.

The MAH performed an additional (confirmatory) literature search (up till July 2010) focused on all available literature for the use of imipenem in the treatment of osteomyelitis. No additional studies were identified and it was noted that 3 published, independent systematic reviews evaluating available data from published clinical trials of antibiotic therapy of osteomyelitis over the last 3 decades have identified only a few, small randomised, controlled-clinical trials of various antibiotic therapies. These reviews confirm the paucity of adequate, high-quality, evidence to determine the best antibiotic treatments for osteomyelitis. However, the MAH presented in its responses, the results from a single-centre, double-blind, randomised trial evaluating the use of ampicillin/sulbactam (3 g every 6 hours) versus imipenem/cilastatin (500 mg every 6 hours) in the treatment of limb threatening foot infections in diabetic patients. Among a subset of patients with osteomyelitis who were treated with aggressive ablative surgical debridement, including foot-sparing amputations, 65% (17/26) and 73% (16/22) had been cured by relatively abbreviated courses of ampicillin/sulbactam and imipenem/cilastatin, respectively, and remained free of osteomyelitis during a one year follow-up. The MAH also recognised that the limited information available prevents a definitive evaluation of the efficacy of imipenem/cilastatin in the treatment of osteomyelitis.

Regarding the dosage, the MAH proposed imipenem doses of 500 mg q6h or 1 gm q8h, and not the higher dose of 1 gm q6h, for treatment of osteomyelitis for several reasons. Firstly, osteomyelitis is typically not a serious, potentially life-threatening infection compared to other syndromes such as hospital- and ventilator associated pneumonia. Thus, the benefit-risk ratio of using a higher dose may not be as compelling for osteomyelitis as it would be for nosocomial pneumonia. Secondly, antibiotic therapy for osteomyelitis is often adjunctive, and primary treatment usually involves surgical debridement, or in some cases, even amputation, in order to optimize therapeutic success. Thirdly, since *S. aureus* and *P. aeruginosa* are common pathogens isolated from patients with osteomyelitis, and the MAH recommends the concomitant use of an appropriate anti-MRSA agent or an aminoglycoside when MRSA or *P. aeruginosa* infections (including osteomyelitis) are suspected or proven to be involved, this may not necessitate using the highest dose of imipenem.

In summary, the MAH considered that the data from the original WMA and the comprehensive literature search, coupled with supportive PK/PD data, support osteomyelitis as an indication, with a dose of 500 mg every 6 hours or 1 g every 8 hours.

The CHMP noted that the MAH acknowledged the limited information available from randomised controlled-clinical trials which prevent a definitive evaluation of the efficacy of imipenem/cilastatin in the treatment of osteomyelitis. There is a paucity of adequate, high-quality, evidence in the literature to determine the best antibiotic treatment for osteomyelitis. The studies identified in the literature review provide some support for the use of imipenem/cilastatin in osteomyelitis, but are also not fully conclusive. Imipenem/cilastatin is generally not considered to be a good anti-staphylococcal agent. In addition imipenem/cilastatin is not efficacious against MRSA and methicillin resistant coagulase-negative staphylococci. The CHMP also noted that potential failure of the therapy with Tienam might lead to impacting surgical interventions or amputations which should be considered as serious adverse outcomes, although not life-threatening. In conclusion, the CHMP was of the opinion that the available documentation remains inadequate to substantiate the indication and posology for Tienam in the treatment of osteomyelitis. Therefore, the CHMP deleted this indication.

4.1.7 Skin and soft tissue infections

The CHMP noted the proposed indication "skin and soft tissue infections" (SSTI), which is currently approved in 25 of 30 European countries, but also that the MAH did not provide any discussions or supporting data. Skin and soft tissue infections are mostly caused by Gram-positive bacteria, *S. aureus* being the most important pathogen. Imipenem/cilastatin is not considered to be the best anti-staphylococcal agent, as other agents like semi-synthetic penicillins are generally considered to be more effective. Furthermore imipenem/cilastatin has no activity against MRSA and is therefore not considered to be an appropriate antibiotic for the empiric treatment of SSTIs caused by staphylococci

since the risk of selecting for MRSA is quite high. The CHMP also noted that the prevalence of resistant Gram-positive bacteria has increased in last two decades. The less favourable in vitro activity of imipenem/cilastatin against relevant Gram-positive species found in SSTI gives rise to concern regarding its effectiveness in these infections. Finally, imipenem/cilastatin is a broad spectrum antibiotic and is therefore not considered appropriate for use in uncomplicated infections. The CHMP noted a number of publications on the use of imipenem/cilastatin in complicated SSTIs (cSSTIs), including sources from the Cochrane Library. From the searched documentations, imipenem/cilastatin (mainly 500 mg every 8 hours) appears to be effective and well tolerated in the treatment of "Complicated Skin and soft-tissue infections".

In conclusion, the CHMP requested the MAH to substantiate the indication SSTIs, and discuss the suitability of this agent in relation to the currently high incidence of MRSA, describing the antibacterial activity of imipenem/cilastatin against *S. aureus* and taking into account the fact that imipenem/cilastatin is targeted only in severe bacterial infections. The MAH was requested to provide an exhaustive update of available data on efficacy and associated posology.

The MAH performed a detailed review of both clinical trial data of the original WMA from the original Worldwide Marketing Application (WMA) and data from a comprehensive literature review with regard to the use of imipenem/cilastatin in the treatment of skin and soft tissue infections (SSTIs). Regarding the original WMA, the information from the clinical trial database for imipenem/cilastatin was collected in the late 1970s to early 1980s. The clinical trial data for imipenem/cilastatin from the original WMA in the mid 1980s did not sub-classify *Staphylococcus aureus* into either methicillin-resistant (MRSA) or methicillin-sensitive (MSSA). Nevertheless, the clinical trial database included data from 217 patients treated with imipenem/cilastatin with SSTIs. Moreover, the database includes cases of SSTIs which would be considered "complicated SSTIs" based on more modern designations including abscess, cellulitis, fasciitis, and necrotizing soft tissue infection. The success rate of imipenem/cilastatin in SSTIs was 93%. In particular, favourable clinical responses for imipenem/cilastatin were seen in 32 of 34 (94%) patients with abscesses and 61 of 67 (91%) patients with cellulitis. Only one or two cases each of the following types of SSTI are listed: erysipelas, fasciitis, gangrene, infected decubitus ulcer, infected prosthetic graft, lymphadenitis, mediastinitis, necrotizing soft tissue infection, suppurative panniculitis, and psoas abscess. However, it is noteworthy that favourable clinical responses were seen in 92% (12 of 13) of these patients. Studies in SSTIs included both comparator-controlled and non-comparative studies. The comparators used in the 5 comparator-controlled studies included cefazolin, moxalactam, cefotaxime, and gentamicin/clindamycin. The efficacy of imipenem/cilastatin was comparable to that seen with the comparators, with favourable overall clinical outcomes for patients treated with imipenem/cilastatin ranging between 90 and 100% in the respective comparator-controlled clinical trials. Furthermore, the efficacy of imipenem/cilastatin was confirmed for many of the pathogens traditionally associated with SSTIs, including *Streptococcus* spp. (including Group A streptococcus), *S. aureus*, and *S. epidermidis*.

The literature review conducted by the MAH identified several studies with at least 40 or more patients treated with imipenem/cilastatin monotherapy for SSTIs. Among these studies were several large, multicenter, randomised studies. Since the mid-1990s, imipenem/cilastatin has been chosen as the comparator for 2 randomised comparator controlled clinical trials evaluating meropenem and 1 randomised comparator-controlled clinical trial evaluating ampicillin/sulbactam for the treatment of SSTIs. In several studies, the efficacy/safety of imipenem/cilastatin was compared to cefazolin, moxalactam, and other unspecified antibiotics. The literature review also identified several studies which included patients with complicated SSTIs, including complex abscesses, complicated cellulitis, and ulcers. Overall, the clinical response rate for imipenem/cilastatin for SSTIs ranged between 72% and 98% and the clinical cure rate ranged between 47% and 96%. The microbiologic response rate ranged between 70% and 91%. The pathogens isolated from SSTIs reported in a limited number of studies, that cover approximately 2 decades of experience, were found to be representative of the pathogens originally reported to be susceptible to imipenem/cilastatin. In one recent study, the clinical response rate for imipenem/cilastatin-treated patients with infections caused by MSSA was 84%. In a second study, imipenem/cilastatin was reported to eradicate 78% (36/46) of the *S. aureus* pathogens, but, as expected, only 33% (1/3) of the MRSA pathogens.

The MAH agreed, based on this detailed review, to limit and specify the indication to "complicated skin and soft tissue infections". The MAH also agreed with the CHMP that the current incidence of MRSA in complicated SSTIs is higher than what it was 25 to 30 years ago, when the original studies for the WMA were performed.

The CHMP noted that the MAH agreed to restrict the indication. The CHMP considered that Tienam may not be suitable for empiric initiation of the treatment in specific conditions and that microbiological

data and the resistance profile of the causative bacteria should be available prior to treatment. Similarly, concomitant use of an appropriate anti-MRSA agent or an aminoglycoside may be indicated when MRSA or *P. aeruginosa* infections are suspected or proven to be involved. The CHMP therefore inserted a statement in section 4.4 concerning the limited susceptibility of specific pathogens and the concomitant use of an appropriate anti-MRSA agent or of an aminoglycoside.

Regarding the dosage, the CHMP noted that both of the two more recent studies (Fabian et al, 2005 and Embil et al, 2006) studied the use of imipenem/cilastatin in complicated cases of skin and soft tissue infections, with a posology of 0.5 g every 8 hours. However, in some of the older studies (e.g. Marier et al 1985), up to 1 g every 6 hours was used. The CHMP was of the opinion that in light of the present clinical and PK/PD data, a standard dose of 500 mg every 6 hours or 1g every 8 hours can be accepted, provided that a recommendation is inserted in the SPC stating that for infections suspected or proven to be due to less susceptible organisms (e.g. *P. aeruginosa*,) and for very severe infections (e.g. in neutropenic patients with a fever), the 1000 mg q.i.d should be used. In conclusion, the CHMP adopted the following harmonised indication:

"complicated skin and soft-tissue infections"

4.1.8 Endocarditis

The MAH proposed the indication "*endocarditis*", which is currently approved in 23 of 28 European countries. 2 cases of endocarditis were reported; both patients were treated with imipenem/cilastatin and were successfully cured. In both cases, the pathogens (*S. aureus* and *Streptococcus sanguis*) were eradicated. The MAH also provided a literature review of the clinical efficacy/effectiveness studies of imipenem/cilastatin in the treatment of endocarditis. Two non-comparative studies (involving 38 patients) showed rates of clinical cure, overall improvement, and microbiologic cure among patients receiving imipenem/cilastatin of 100%. Imipenem/cilastatin was generally well tolerated in these patients with these severe infections. Adverse events possibly related to imipenem/cilastatin in more than 1 patient in the first study included shortness of breath and hypertension (2 patients), mild diarrhoea (4 patients), and positive direct Coombs' test (4 patients).

Based on the submitted data from the original Worldwide Marketing Application and the medical literature for the efficacy and safety of imipenem/cilastatin in the treatment of endocarditis, the MAH considered that endocarditis should be retained as an indication for imipenem/cilastatin.

The CHMP noted that the clinical documentation derived from the original Worldwide Marketing Application was entirely non-informative as only 2 cases of endocarditis were reported, without any mention of the used dosage. Data from literature sources was also scarce. Only one non-comparative study (Dickinson et al, 1985) on endocarditis was conducted. Of 29 patients enrolled in this study, 12 patients were excluded. One patient with staphylococcal endocarditis left the hospital during the first day of the treatment, 4 patients did not meet the criteria for endocarditis, and the other 7 patients had negative results of blood cultures. Seventeen patients, including 14 who used intravenous drugs were treated with IV imipenem/cilastatin in a dose of 500 mg every 6 hours. The mean duration of treatment was 29 days with a range of 21 to 56 days. Eleven patients reported prior episodes of endocarditis and 10 of these were drug abusers. The criteria for diagnosis were two or more positive blood culture results for the same organism plus one of the following: the presence of a cardiac murmur, echocardiographic abnormalities consistent with valve infection or radiographic abnormalities consistent with septic pulmonary emboli. *S. aureus* was the predominant pathogen (in 11 patients). All patients were reported to be cured and no relapse was demonstrated in 16 patients in 3 months follow up. The authors reported that complications were infrequent once treatment was instituted; 2 patients had embolisation to the brain and one patient had a late pulmonary embolism. Cultures of blood obtained on the second to 4th day of treatment showed growth in 8/16 patients and 7 of these in whom culture was repeated between day 6 and 7 were not bacteraemic. The authors concluded that imipenem/cilastatin appears to be a relatively safe and highly effective treatment of staphylococcal endocarditis in intravenous drug abusers. The second reference is the non-comparative study of Calandra et al which included also 9 patients with endocarditis. These 9 patients were treated with imipenem/cilastatin $\leq 2\text{g/d}$ in 3-4 divided doses. In 6/9 patients, the pathogen was *S. aureus*. No further details are available. Serious infections due to *S. aureus* are associated with excessive morbidity and mortality and the presence of *S. aureus* bacteraemia is associated with high rates of endocarditis. Infections due to both methicillin-susceptible and methicillin-resistant strains may arise in a variety of health care settings or the community. Among those with *S. aureus* bacteraemia the prognosis is worse for those infected with MRSA. Infective endocarditis is mostly caused by MSSA whereas nosocomial endocarditis is mostly caused by MRSA. Prosthetic valve endocarditis is frequently caused by *S. epidermidis* (MSSE or MRSE). The large International Collaboration on Endocarditis (ICE)

merged database study (n=1779) has suggested that *S. aureus* has become the most common microbiologic cause of endocarditis observed in tertiary referral centres, occurring in 31.4% of cases of endocarditis (Fowler 2005). This study showed also that endocarditis was associated with MRSA in 23.7% of the patients treated in Europe.

In summary, the claimed indication in the treatment of endocarditis was insufficiently substantiated. The presented data are very scarce (rather consistent with the epidemiology of the infection) and imipenem/cilastatin is not considered one of the most effective agents against staphylococci and methicillin-resistant staphylococci are known to be resistant to imipenem/cilastatin. Moreover, the use of imipenem in the management of any type of endocarditis has not been mentioned in the EU endocarditis Guideline, 2004. Therefore, the CHMP did not consider imipenem/cilastatin to be an appropriate antibiotic for the empiric treatment of this life-threatening infection as the risk of selecting for MRSA is especially high and therefore concluded that the provided data could not support an indication for use in endocarditis. However, *S. aureus* was the predominant pathogen in the present data and dosages of 500 mg every 6 hours for 4-6 weeks seems to be effective in the treatment of *staphylococcal endocarditis* in intravenous drug abusers. The MAH was therefore requested to discuss any specific indication and specific posology in the treatment of endocarditis as well as the suitability of this agent in relation to the currently high incidences of MRSA, and also in relation to the presence of prosthetic valve endocarditis due to MRSE.

The MAH agreed that the available data was insufficient to support the indication in endocarditis and the CHMP therefore deleted the indication.

4.1.9 Prophylaxis

The MAH proposed the indication "prevention of certain post-operative infections in patients undergoing contaminated or potentially contaminated surgical procedures or where the occurrence of post-operative infection could be especially serious" and provided data to support the indication, including several published studies evaluating imipenem or imipenem/cilastatin as prophylaxis antibiotic therapy to prevent post-surgical infections as a result of colorectal surgery, appendectomy, and endoscopic sclerotherapy. The indication is currently approved in 9 of 28 European countries. The MAH submitted data to support the retention of the prophylaxis indication in the harmonised label.

Colorectal surgery:

Three studies assessing the use of imipenem/cilastatin as prophylaxis have been conducted in colorectal surgical populations (Kager et al 1989, Pacelli et al 1991, Karran et al 1993). In the first study, two doses of imipenem/cilastatin were tested (500 mg and 1 g) in 20 patients undergoing colorectal surgery (Kager et al 1989). The concentrations of imipenem in sera showed a large increment between the doses (Mean concentrations at 1 hour for 0.5-g dose: $15.9 \pm 1.7 \mu\text{g/ml}$; for 1.0-g dose: $68.2 \pm 8.2 \mu\text{g/ml}$). The half-lives, however, were similar. The imipenem concentrations in the intestinal mucosa varied between <0.1 and 3.6 mg/kg for the 500-mg dose and 3.2 and 13.4 mg/kg for the 1.0-g dose. The imipenem concentrations also varied in the faecal samples between <0.1 and 5.0 mg/kg for the 500-mg dose and 0.7 and 11.3 mg/kg for the 1.0-g dose. Faecal specimens were collected during the study to assess aerobic and anaerobic bacteria. Both aerobic and anaerobic bacteria were significantly suppressed, most likely due to the relatively high concentrations obtained in the intestinal mucosa and faeces. No new colonizing imipenem-resistant bacteria were observed in this study. The micro-floras were normalised after 2 weeks of follow-up. No post-operative infections occurred in this study. In a small randomised, controlled trial of 61 elective colorectal surgery patients, a single dose of imipenem/cilastatin (n=31) was compared with three doses of cefuroxime plus metronidazole (n=30) as prophylaxis therapy (Pacelli et al 1991). No significant differences in surgical-infection rates were found. Infections of non-surgical origin were only found in the cefuroxime plus metronidazole group. In a large, randomised controlled trial of 411 elective colorectal surgery patients, two different doses of imipenem were compared with cefuroxime/metronidazole (Karran et al 1993). There were no differences in the ability of the three regimens to prevent all infections or to prevent infections related to surgery. A similar number of bacteria were isolated from each group, with different distribution of aerobic and anaerobic from each group. All surgical-site isolates in the imipenem groups were found to be susceptible to imipenem. These data suggest that both regimens of imipenem and the cefuroxime/metronidazole regimen provided equivalent protection. In addition, the two-dose course of imipenem was as effective as the triple-dose cefuroxime plus metronidazole or triple-dose imipenem. The MAH argued that data from these three studies provide support for the use of short-course imipenem prophylaxis in non-contaminated patients undergoing elective colorectal surgery.

Appendectomy:

In addition to the 3 studies in colorectal surgery prophylaxis, a single-preoperative dose of imipenem/cilastatin was compared with metronidazole in a randomised controlled trial for the prevention of infectious complications following emergency appendectomy. The study enrolled 300 patients (Burkitt et al). In this study, 268 patients were evaluable. Wound infection rates did not differ in low-risk patients with a normal or inflamed appendix (8% in the imipenem/cilastatin group and 9% in the metronidazole group). However, when sepsis was already established intraperitoneally (i.e., gangrenous or perforated appendix), the wound infection rate was 8% for imipenem/cilastatin and 24% for metronidazole. There was a trend favouring imipenem/cilastatin over metronidazole in those patients with a perforated appendix.

Acute pancreatitis:

Supportive information for surgical prophylaxis was also obtained in the setting of prophylaxis antibiotic therapy for acute pancreatitis where the gastrointestinal bacterial pathogens are similar to those found in infections complicating abdominal surgery. Several studies have evaluated the effectiveness and safety of imipenem/cilastatin as prophylaxis antibiotic therapy for acute pancreatitis. Acute pancreatitis can range from a mild to a severe, fatal disease. The mortality of severe pancreatitis increases with the occurrence of infection and resulting pancreatic necrosis. Data from 8 studies with imipenem/cilastatin used as prophylaxis or early treatment to prevent the infection of pancreatic necrosis suggest imipenem/cilastatin to be effective and safe in patients with acute pancreatitis (Pederzoli 1993, Bassi 1998, Ho 1997, Nordback 2001, Rokke 2007, Manes 2003, Maravi-Poma 2003, Xue 2009).

The MAH considered that the data from the literature provides compelling evidence for the use of imipenem/cilastatin as prophylaxis for the prevention of post-operative infections and support for the retention of the prophylaxis indication in the harmonised SPC.

The CHMP noted the MAH proposal for the prophylaxis against post-surgical infections indication in adults, with a 1000 mg intravenous dosage on induction of anaesthesia and 1000 mg three hours later. For high-risk (e.g. colorectal) surgery, two additional 500 mg doses can be given at 8 and 16 hours after induction. The CHMP considered that the relevant large controlled studies that evaluated the clinical efficacy of Imipenem/cilastatin in the claimed indication had severe limitations. In addition, imipenem/cilastatin is a broad spectrum antibiotic which should be used in the treatment of severe/life-threatening infections accompanying with microbial resistance and/or when microbial resistance is demonstrated. Unjustified and non-substantiated prophylactic use is not acceptable. The CHMP therefore considered the use of this antibiotic to be inappropriate for the prevention of post-operative infections. The MAH was requested to delete the indication or provide an exhaustive update of available data (i.e. appropriately controlled studies) on the efficacy and associated posology to justify the prophylactic use in a specific high risk indication. If the prophylactic use of imipenem is indicated it should be specified very carefully in which surgical interventions this drug would be indicated e.g. *contaminated surgical procedures like in colorectal surgery*.

The MAH agreed with the CHMP proposal. The CHMP therefore deleted this indication.

4.1.10 Management of bacterial infections in patients with febrile neutropenia

Despite the fact that the MAH has not proposed the above indication, the CHMP was of the opinion that there are grounds to consider this indication, which is currently authorised in a number of member states, under the current harmonisation procedure. First of all, there are several published studies which may support this indication. In a recent meta-analysis (Paul et al 2006), the authors concluded that ceftazidime, piperacillin/tazobactam, imipenem/cilastatin and meropenem appear to be suitable agents for monotherapy in the empirical treatment of febrile neutropenia. Consequently, the MAH is requested to discuss the suitability of this antibiotic for the above-mentioned indication, taking into account the fact that some studies indicate increased rate of seizures in children with cancer (Karadeniz et al 2000).

The MAH stated that the original WMA, contains no information on the use of imipenem/cilastatin in the management of bacterial infections in patients with febrile neutropenia. The MAH performed a literature review on the subject, identifying a total of 28 publications, including 22 publications reporting the use of imipenem/cilastatin as monotherapy in the treatment of febrile neutropenic patients in a randomised, controlled, comparative setting. The following comparators were used as monotherapy: ceftazidime, cefepime, meropenem, piperacillin/tazobactam, or cefoperazone/sulbactam; or imipenem/cilastatin monotherapy compared to combination antibiotic therapy. All of the

22 trials were open-label and non-blinded. In addition, 6 publications reporting outcome data for imipenem/cilastatin monotherapy in non-comparative studies were found. Overall, approximately 2500 patients received imipenem/cilastatin in these 28 studies. When examining overall clinical response rates across all comparator-controlled studies, outcomes numerically favoured imipenem/cilastatin in 18 of the 22 studies (reaching statistical significance in favour of imipenem/cilastatin in 6 studies). The data from the 6 non-comparative studies provide additional supportive evidence for the efficacy of imipenem/cilastatin for management of bacterial infections in patients with febrile neutropenia.

Two studies included paediatric patients and one of these was exclusively a paediatric study, including patients between 1 and 16 years of age. This study showed imipenem/cilastatin to be statistically superior ($P < 0.05$) to ceftazidime plus vancomycin with an 82% (37 of 45 evaluable episodes) success rate for imipenem/cilastatin compared to a 59% (26 of 44 evaluable episodes) success rate with the combination of ceftazidime plus vancomycin. In this study, imipenem/cilastatin was "well tolerated, non-toxic, and safe". None of the patients experienced seizures. These data, in conjunction with data in adult studies, support the paediatric use of imipenem/cilastatin in febrile neutropenia. The dosage regimen (15 mg/kg x 4 doses daily) used in that study is consistent with the paediatric dose in the proposed SPC (15-25 mg/kg dosed every 6 hours). The MAH acknowledged that imipenem can lower the threshold of seizure activity and should be used with caution in patients with medical conditions or on medications that may potentiate the risk of seizure. However, the supporting data has not identified any notable increased risk of seizures with the empirical use of imipenem/cilastatin in the setting of febrile neutropenia. In fact, the safety profile for imipenem/cilastatin in these studies appeared generally similar to that reported for the comparators. Children with cancer may become neutropenic during chemotherapy, and occurrences of febrile neutropenia suspected to be due to a bacterial pathogen may require administration of an empirical antibiotic therapy such as imipenem/cilastatin. It is possible that some of these children may be at increased risk of seizure, for example, if they have central nervous system metastases, or other underlying conditions that may lower their threshold for seizures. In these clinical situations, the physician must make an individual assessment as to the benefit-risk of administering imipenem/cilastatin compared to other antibiotics. The MAH noted that the vast majority of these studies tended to show numerically higher response rates with imipenem/cilastatin relative to the comparators and that imipenem/cilastatin was well tolerated and had a safety profile similar to that seen for the comparators.

In conclusion, the MAH considered, based on this detailed review, that the benefit-risk ratio is appropriate to recommend the use of imipenem/cilastatin in the "management of neutropenic patients with fever that is suspected to be due to a bacterial infection".

The CHMP noted that, overall, although no high quality, double blind studies were submitted, the MAH provided a substantial number of randomised, comparative open-labelled studies. Some of the submitted studies enrolled a quite high number of patients and treated with imipenem/cilastatin monotherapy. The posology of imipenem/cilastatin was in accordance with the one applied for and the comparators used in the clinical trials of the literature review presented by the MAH were considered adequate. Also, in a recent meta-analysis (Paul et al 2006), the authors concluded that imipenem/cilastatin appears to be suitable for the management of neutropenic patients. The MAH acknowledged that imipenem can lower the threshold of seizure activity and should be used with caution in patients with medical conditions (e.g., underlying central nervous system abnormalities) or on medications that may potentiate the risk of seizure. The MAH was also requested to discuss increased rate of seizures in children with cancer as a consequence of therapy with imipenem/cilastatin. In the study by Riikonen (1991), submitted by the MAH, the author assessed two antibiotic regimens, imipenem as monotherapy and ceftazidime plus vancomycin as combination therapy, for initial empiric therapy in febrile neutropenic children with cancer. The author concluded that imipenem was well-tolerated, non-toxic and safe as first line therapy in febrile neutropenic children with cancer and compared favourably with the ceftazidime-vancomycin combination therapy. No seizure was reported in imipenem/cilastatin group.

The CHMP noted that the MAH did not discuss the optimal dosage regimen for this indication. In the studies submitted by the MAH, the posology varied from 0.5 g every 6 hours in some studies (Aparicio et al, Liang et al, Winston et al) to up to approximately 0.8 to 1 g every 6 hours in others (Freifeld et al, Rolston et al, Norrby et al, Leyland et al). It should be noted that in the study by Winston et al (*Annals of Internal Medicine*, 1991;115:849-859), the posology for the initial 29 patients was 1 g every 6 hours, but frequent seizures among these patients necessitated a dosage reduction to 0.5 g every 6 hours for the subsequent 106 patients. The CHMP was of the opinion that in light of the present clinical and PK/PD data, a standard dose of 500 mg every 6 hours or 1g every 8 hours can be accepted, provided that a recommendation is inserted in the SPC stating that for infections suspected or proven

to be due to less susceptible organisms (e.g. *P. aeruginosa*,) and for very severe infections (e.g. in neutropenic patients with a fever), the 1000 mg q.i.d should be used.

At the request of the CHMP, the MAH also summarised the case reports published by Karadeniz et al. which describe 3 paediatric patients with systemic malignancies who experienced a seizure during therapy with imipenem/cilastatin. These reports are confounded since seizures are a known adverse reaction for many of the chemotherapies received by these patients. While not discussed by the author, the routine use of intrathecal methotrexate as preventive CNS therapy is common practice during the induction phase of chemotherapy for patients with acute lymphoblastic leukaemia and has a known complication of acute neurotoxicity to include seizures and leukoencephalopathy. In the discussion section of the article, the authors state that the incidence rates of seizures among children with chemotherapy induced neutropenia are "...similar to those reported in adult patients." The imipenem/cilastatin SPC currently lists seizure as an adverse event and includes information under Precautions stating "*CNS adverse reactions such as myoclonic activity, confusional states, or seizures have been reported, especially when recommended doses based on renal function and body weight were exceeded. These experiences have been reported most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function in whom accumulation of the administered entities could occur. Hence, close adherence to recommended dose schedules is urged, especially in these patients.*" Additionally, an analysis of post-marketing seizure events in the paediatric population was provided, which showed no evidence in support of an increased risk of seizures in this patient population. Thus, the MAH did not accept the addition of the CHMP proposed text regarding seizures in children with chemotherapy induced febrile neutropenia. The CHMP accepted the MAH responses. In conclusion, the CHMP adopted the following harmonised indication:

"Tienam may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection."

4.1.11 Mixed infections

The CHMP noted the proposed indication "mixed infections" but that the MAH did not provide any discussions or supporting data. The CHMP was of the opinion that this wording is not in line with the current thinking behind the antimicrobial guidelines and recent European regulatory decisions, which require a site of infection to be specified. The utility of imipenem/cilastatin in polymicrobial infections susceptible to this drug is however not excluded, but should be mentioned only in section 5.1. The CHMP therefore removed the wording from Section 4.1.

4.1.12 Non-indication in the treatment of meningitis.

The CHMP did not consider this to be an indication. As it is mentioned in section 4.4, this information was removed from section 4.1

4.1.13 Paediatric use

Age range

The age range for use of imipenem/cilastatin (whether or not to limit the lower age range to 3 months or 3 years of age) was identified as an area of disharmony among the member states. The use of imipenem/cilastatin in paediatric patients as young as 3 months of age is already approved in 21 of the 28 European countries, while use is limited to 1 year of age or older in 5 member states and to 12 years of age or older in 1 member state. Imipenem/cilastatin is not approved for use in paediatric patients in one member state. At the time of initiation of the clinical development program for imipenem/cilastatin, it was known to the MAH that beta-lactam antibiotics are eliminated more rapidly in infants and young children than in older children or adults. As a result, it was estimated that a larger imipenem/cilastatin dose would be required in paediatric patients than in adults on a mg/kg bodyweight basis. Two small studies on the pharmacokinetics (PK) of imipenem/cilastatin after single dose administration in patients 2 to 12 years old provided preliminary information for choosing a dose. These PK studies suggested that patients aged 3 months to <3 years of age should receive imipenem/cilastatin at 25 mg/kg intravenously (IV) every 6 hours, and patients at ages of ≥3 years should receive imipenem/cilastatin at 15 mg/kg IV every 6 hours. These doses were subsequently evaluated in 2 larger efficacy/safety studies:

Paediatric Study 1

This study, entitled "A Multi-clinic Study of the Efficacy, Safety, Tolerance, and Pharmacokinetics of a Range of Doses of Intravenous Imipenem/Cilastatin in the Treatment of Hospitalised Patients 3 Months to 12 Years of Age with Infections Caused by Susceptible Bacteria", enrolled 178 patients using two

dosages. The distribution of patient ages was 2 patients <3 months of age; 90 patients at least 3 months old, but <3 years of age; and 86 patients ≥ 3 years. Patients aged 3 months to less than 3 years of age received imipenem/cilastatin at 25 mg/kg IV every six hours, and patients aged 3 years and older received imipenem/cilastatin at 15 mg/kg IV every six hours. Ninety-eight of the 178 patients with culture-confirmed bacterial infections were judged evaluable for efficacy. Most patients (n=72) were considered non-evaluable due to lack of bacteriologic confirmation of their infections. All etiologic pathogens for which susceptibility to imipenem was determined were susceptible. The susceptibility results of nine bacterial isolates, including one anaerobic isolate, were not provided. In this study, the most common sites of infection were skin and skin structure (56%), bone and joint (28%), intra-abdominal (5%), respiratory tract (4%) and urinary tract (4%). Overall, 96 of the 98 evaluable patients (98%) had a favourable clinical outcome defined as "cured" or "improved" following treatment with imipenem/cilastatin. Two patients had poor or no clinical response. For paediatric patients ≥3 years of age, 97.8% (44/45) had a favourable clinical outcome, and for paediatric patients <3 years of age, 98.1% (52/53) had a favourable clinical outcome. Pathogens were eradicated in all 21 patients with bacteraemia. The MAH presented the bacteriologic outcome by pathogen for the evaluable patients treated with imipenem/cilastatin. Since some patients had multiple etiologic pathogens, the total number of pathogens is greater than the number of patients included in the efficacy analysis. The clinical outcome was also reported for 77 of the 80 patients (96%) who did not fulfil the criteria for evaluability for efficacy. A favourable clinical outcome was observed in 96% (74 of 77) of these patients. The higher dosage of imipenem/cilastatin (25 mg/kg every six hours) was used in younger infants (<3 years of age) and was expected to compensate for their faster rate of drug elimination. In this study, a total of 43 patients (from 3 study centres) were included in the PK analysis. Trough (5-6 hr) plasma concentrations of imipenem after 25 mg/kg and 15 mg/kg doses were > 1.5 µg/mL and > 0.9 µg/mL, respectively. Trough urinary concentrations of imipenem were in excess of 10 µg/mL for both doses. Regarding safety, 53 of 178 patients developed adverse experiences. Of these, 13 patients had clinical AEs, 29 patients had laboratory AEs, and 11 patients had both clinical and Laboratory AEs. The AEs were characterised as drug related (definitely or probably) in 17 patients (9.5%), including one patient who had both a clinical and a laboratory AEs. In this study, 2 patients developed serious AEs (1 patient with death and 1 patient with hypoglycaemia). Both serious AEs were unrelated to imipenem/cilastatin. Importantly, no AEs previously unreported in adults were found in paediatric patients.

Paediatric Study 2/3

Additional support for the paediatric use of imipenem/cilastatin in the original dossier was obtained from twin studies, both entitled "A Multi-clinic, Open-Label Study of the Clinical Efficacy, Safety, Tolerance, and Pharmacokinetics of a Range of Intravenous Imipenem/Cilastatin Doses in Hospitalised Infants and Children Aged 3 Months to 12 Years", enrolling a total of 106 patients and conducted in 12 centres in 8 countries. The age range was 22 days to 15 years. Fifty-seven were male and 49 were female. The distribution of patients ages were 2 patients < 3 months of age; 27 patients at least 3 months old, but <3 years of age; and 77 patients ≥ 3 years of age. The studies used two dosages, with patients aged 3 months to < 3 years of age receiving imipenem/cilastatin 25 mg/kg IV every six hours, and patients aged 3 years and older receiving imipenem/cilastatin at 15 mg/kg IV every six hours. The data from Paediatric Study 2/3 were obtained and presented as a single study. 74 of the 106 patients (69.8%) with culture-confirmed bacterial infections were judged evaluable for efficacy and 48 (64.9%) of the 74 evaluable treatments (of 106 total patients) were cured and 22 (29.7%) were improved. The overall clinical efficacy (patient cured or improved) of imipenem/cilastatin was 94.6% (70/74) among evaluable patients, and was 94.3% (99/105) among all patients. For patients ≥3 years of age, 94.5% (51/54) had a favourable clinical outcome and for patients < 3 years of age, 95.0% (19/20) had a favourable clinical outcome. Of the 14 evaluable treatments with septicaemia or bacteraemia, all but two were cured or improved following imipenem/cilastatin therapy. 108 strains of pathogens were isolated from the 74 evaluable patients. Fifty-one (69%) and 23 (31%) were in patients with mono-microbial or poly-microbial infections, respectively. In the 51 evaluable patients with mono-microbial infections, the overall bacteriologic efficacy was 92% (46/50). One patient with *Pseudomonas* septicaemia died before the bacteriologic outcome could be assessed. In the 23 evaluable patients with poly-microbial infections, 56 of 57 pathogens were eradicated. One patient with suppurative otitis due to *Proteus mirabilis* had persistence of infection. 14 evaluable patients had septicaemia or bacteraemia/other infection (9 primary, 5 secondary) involving mono-microbial infections. Among these 14 patients, pathogens were successfully eradicated with imipenem/cilastatin in 11 patients. The overall bacteriologic efficacy in these patients with septicaemia or bacteraemia/other infection was 79% (11/14). Regarding safety, 19% of the patients had clinical AEs. None of these experiences were judged probably or definitely related to imipenem/cilastatin treatment by the investigators. Overall, 12% of the patients had clinical AEs possibly related to imipenem/cilastatin. In this study, laboratory AEs were reported in 24% of the patients. Overall, 17% had laboratory AEs were possibly or probably related to imipenem/cilastatin.

The MAH also provided data from a number of studies in the peer-review medical literature demonstrating the utility of imipenem/cilastatin in the treatment of paediatric patients. Outcome measures of interest included clinical and microbiologic response. Overall, 15 clinical studies, including three randomised controlled trials, nine non-comparative trials, and 3 observational studies in paediatric patients (<18 years of age) who were administered imipenem alone, imipenem/cilastatin alone, or imipenem +/- cilastatin in combination with other antibiotics were identified. The 15 studies were conducted in several different countries: 2 in the United States, 2 in Italy, 2 in Germany, 2 in Finland, 2 in Austria and one study was a multi-country study (8 countries), and one each in Egypt, France, Sweden and Switzerland. The age of the study populations varied between the 15 studies. Eight studies included pre-term and term newborns, and infants (less than 3 months of age); thirteen studies included patients less than or equal to 3 years of age. The dose of imipenem monotherapy or imipenem/cilastatin for neonates and children ranged from 15 to 25 mg/kg every 6 hours. Of the 15 clinical studies, 7 studies included doses of approximately 20-25/mg/kg every 6 hours for ages 3 years or greater. Seven studies provided doses of 15 mg/kg every 6 hours for ages 3 years or greater. In patients less than 3 years of age, six studies included doses of 20 to 25 mg/kg every 6 hours. Neonates less than 7 days old were given doses of 20-30 mg/kg every 12 hours (for the first day) and 8 hours thereafter. Doses of 25 mg/kg every 12 hours were provided for patients 25 to 41 weeks of age. The dose of 16.7 mg/kg every 8 hours was given to adolescents in the only study focusing on this age group.

The efficacy of imipenem/cilastatin was impressive in all studies. Clinical cure rates for imipenem/cilastatin, which were reported in 12 studies, ranged from 62% to 100% and bacterial eradication was reported from three studies and ranged between 92% and 100%. Imipenem or imipenem/cilastatin was generally well tolerated and had a similar safety profile as that reported in the adult population. Common symptomatic adverse reactions seen following imipenem +/- cilastatin therapy were gastrointestinal events, such as gastroenteritis, diarrhoea, and vomiting, as well as irritation/rash at IV site and seizures. Laboratory adverse events include eosinophilia and increased creatinine levels. Overall, 13 of the 15 studies included data in patients less than 3 years of age, and the efficacy in this age group was not reported to differ from that in older children (3 years and older). Several studies focusing particularly on patients less than 3 years of age were identified, and the efficacy of imipenem/cilastatin in this younger age group was encouraging.

In summary, the MAH considered that the data from the original Worldwide Marketing Application and the medical literature provide compelling and strong evidence for the efficacy and safety of imipenem/cilastatin in the treatment of paediatric patients less than three years of age and as young as 3 months of age. Favourable clinical outcomes in Paediatric Studies 1 and 2/3, in patients less than 3 years of age, were 98.1% and 95.0% respectively and were similar to the favourable clinical outcomes in patients 3 years of age or older. Currently, 27 of the 28 European countries have an approved indication in paediatric patients, including 21 countries with indications for children as young as 3 months of age and 5 countries with indications for children as young as 1 year of age. Thus, the MAH believes that an indication for paediatric patients age 3 months or older should be retained for imipenem/cilastatin.

The CHMP noted the two main studies presented by the MAH enrolled 4 patients below 3 months, 117 patients between 3 months and 3 years and 163 patients above 3 months. The investigated infections were of moderate or severe intensity. In the first study, the most common sites of infection were skin and skin structure infections (cellulitis, wound infections, lymphadenitis) including periorbital cellulitis (54%), and bone and joint infections (infectious arthritis and osteomyelitis) (27%). Less common infections included intra-abdominal (peritonitis, sub-hepatic abscess) (5%), respiratory tract (lobar pneumonia) (7%) and urinary tract (pyelonephritis) (5%) infections. In the second study, respiratory tract infections (27%) and skin infections (23%) were the commonest. The overall clinical efficacy (patient cured or improved) of imipenem/cilastatin was high and acceptable among evaluable patients. The used dosage was effective and safe.

Nevertheless, the CHMP raised a number of concerns with regards to the use in paediatric patients. In the other studies presented, no precise age groups were provided, making it impossible to identify how many of the patients were <3 years of age and how many were < 1 year of age. 7 of the 15 studies were not relevant for the currently proposed indications and 2 of 3 randomised controlled trials related to old and juvenile patients and were therefore also not relevant at this stage. The only randomised controlled trial from 1992 included doses of 25/mg/kg every 6 hours for ages 2.5 years or greater (to 16.8 years old) included a total of 218 patients with appendicitis associated severe abdominal infections. Of these, the appendix was perforated with or without peritonitis in 54 cases. Furthermore, gangrenous appendicitis and peri-appendicular abscess were also indicated. Patients were 100%

clinically cured. The remaining studies are non-comparative and some are too small to allow any conclusion.

The safety of imipenem/cilastatin should be discussed thoroughly in children <3 years, especially in those <1 year of age. In infants, it is generally difficult to exclude meningitis when diagnosing prior to the start of empiric treatment. These youngest children may be more prone to have serious side effects such as seizures, and the efficacy of imipenem/cilastatin in meningitis has not been documented. It should thus be evaluated whether the use of imipenem/cilastatin should be limited to children above 1 year of age.

In response to the CHMP request, the MAH further categorised paediatric patients from the 2 paediatric studies (Paediatric Studies 1 and 2/3) in the following age groups: 0-3 months, 4-6 months, 7-9 months, 10-12 months, 13-24 months, 25-35 months, and yearly from 3 years to 18 years. Overall, 178 paediatric patients received imipenem in Study 1, and 106 patients received imipenem in Study 2/3. Across the two studies, 56 of the 284 (19.7%) patients were 12 months of age or less; 33 of the 284 (11.6%) patients were between 1 and 2 years of age (13 to 24 months); and 32 of the 284 (11.3%) patients were between 2 and 3 years of age (25 to 35 months). Thus, 121 of the 284 (42.6%) of the patients included in Paediatric Studies 1 and 2/3 were <3 years of age. The remaining 57% of patients were 3 to 18 years of age, with the majority of those patients being in the 3 to 10 year old categories. Overall, the pharmacokinetic parameters of imipenem for the different age groups are consistent with the pooled data analysis, despite the limited number of patients per each age subcategory. Safety and efficacy data were not summarised for the requested age subcategories in the original Merck paediatric clinical trials; thus, these results are not available. The MAH stated that unlike neonatal meningitis where the clinical presentation is indistinguishable from that of neonatal sepsis without meningitis, the majority of children beyond the neonatal period with bacterial meningitis present with fever, and symptoms and signs of meningeal inflammation. While no single sign of meningitis is pathognomonic, the signs and symptoms exhibited by infants with bacterial meningitis are easily recognised and include hyperthermia and hypothermia, lethargy, respiratory distress, poor feeding, vomiting, diarrhoea, seizures, irritability and/or bulging fontanel. Thus, it should be possible to exclude a diagnosis of meningitis in children beyond the neonatal period before beginning treatment with imipenem/cilastatin. The MAH considered the dose and administration recommendations for children 3 months of age and older in Section 4.2 of the current proposed SPC to be appropriate.

The CHMP disagreed with the MAH evaluation on the difficulties in excluding bacterial meningitis in small children. It is incorrect that meningitis can be excluded in children < 1 year based on the symptoms listed by the MAH as many of these symptoms will be present in several other infections. Furthermore, clinical experience is that the frequency of seizures in children < 1 year of age is unacceptably high. A more thorough discussion concerning the safety of children < 3 years, especially in those < 1 year of age is warranted. On the current basis, it seems impossible to accept a posology for children < 1 year of age due to the risk of seizures and the difficulties with excluding the diagnosis of meningitis.

The MAH provided a cumulative review of adverse event reports received for imipenem/cilastatin in paediatric patients between 3 months to 3 years of age, which identified a total of 163 events in 82 (46; 56% serious) reports. This review did not identify new safety issues. Underlying risk factors for seizures were present in the majority of reports containing convulsion terms in ages 3 months to 1 year and ≥ 1 to 3 years. Imipenem/cilastatin use continues to be appropriate in ages greater than 3 months.

Based on the submitted data including the pharmacokinetics in children and extrapolation from the adult population, the CHMP considered that adequate safety and efficacy were demonstrated for imipenem/cilastatin in children > 1 year. However, concerns remained regarding safety in children < 1 year. The frequency of seizures in the paediatric population < 1 year is unacceptably high, possibly as high as 6% and this risk is confirmed by the spontaneous adverse event reports presented by the MAH. The percentage of convulsions/seizures in children 3 months to < 1 year was higher than that in children 1 to 3 years and adults. According to the MAH, a low number of post-marketing reports were received cumulatively in the paediatric population as compared to the adult population. The interpretation by the MAH is that use in paediatric patients 3 months to 3 years is quite limited and is likely reserved for severe infections where alternative antimicrobial therapy may not be available. According to the MAH, imipenem/cilastatin is one of the few therapies available to treat e.g. *Acinetobacter* spp. and *Pseudomonas* spp. However, meropenem has shown a much lower convulsive activity than imipenem whilst retaining the same broad antimicrobial spectrum (Linden P. et al. Drug Saf 2007;30:657-68, Baldwin CM et al. Drugs 2008;68:803-38, Day IP et al. Toxicol Lett 1995;76:239-43). Children with meningitis may be more prone to have serious side effects such as

seizures, and the efficacy of imipenem/cilastatin in meningitis has not been documented. The CHMP considered that extra caution with children is clearly warranted when it comes to risk of seizures, especially as children receive a higher weight-adjusted dose, resulting in a higher exposure. The CHMP therefore confirmed its position that the benefit-risk for imipenem/cilastatin in children under 1 year of age is negative. The CHMP therefore inserted a statement that the clinical data are insufficient to recommend dosing for children under the age of 1 year.

Dose recommendations:

Clinical response was described to be favourable in $\geq 95\%$ of the 73 evaluable patients < 3 years of age who were treated with imipenem/cilastatin 25 mg/kg every six hours in the data from studies 1 and 2/3. The MAH stated that the higher dosage of imipenem/cilastatin (25 mg/kg every six hours) was used in younger infants (<3 years of age) in order to compensate for their faster rate of drug elimination and to obtain higher plasma concentrations than with 15 mg/kg. Some support for this dosage can also be derived from presented literature. The higher plasma concentrations of imipenem/cilastatin were considered desirable and adequate for infants and young children because in this population occult bacteraemia, sometimes associated with unapparent meningitis can occur. Consequently, patients aged 3 months to < 3 years of age received imipenem/cilastatin at 25 mg/kg IV every six hours, and patients aged ≥ 3 years received imipenem/cilastatin at 15 mg/kg IV every six hours in the Paediatric study 1 (n=178) and Paediatric study 2&3 (n=106). According to Uhari et al (1992), even for older children ≥ 3 years of age, treatment with the higher doses should be chosen because of suspicion of bacteraemia. The dosage should be the same independent of the age of the child, i.e. 100 mg/kg/day. This dose regimen was well tolerated also by the older children and was effective in treating serious intra-abdominal infections.

The CHMP noted the observed PK relationship for imipenem between renal and total body clearance and body weight. Observed imipenem plasma trough values were above 0.9 and 1.5 $\mu\text{g/ml}$ for the 25 and 15 mg/kg dose respectively. Furthermore, concentrations in urine were above 10 $\mu\text{g/ml}$. Limited data were available for cilastatin. No comparison was provided with adolescent/adult data, and dose recommendation from a pharmacokinetic point of view was poorly supported and discussed.

The CHMP requested the MAH to further specify the age distributions of children <3 years of age, i.e. the number of children <1 year of age, 1-2 years and 2-3 years, with regards to the pharmacokinetic data in order to support the dose recommendations from a pharmacokinetic point of view.

The MAH provided the demographic data from the CSR for Paediatric study 1 categorising children in 4 age groups, as follows: 2 patients aged 0-2 months, 90 patients aged 3-35 months, 81 patients aged 3-12 years and 5 patients aged over 12 years. In Paediatric study 2/3 CSR, children were not categorised by age group but fifty seven male children between the ages of 2 months and 15 years were enrolled. The median and mean ages for males were 5.5 and 5.7 years, respectively. Forty-nine female children between the ages of 22 days and 11 years were enrolled with median and mean ages of 6.0 and 5.7 years, respectively. Clearance vs. age plots were generated from patient data in the following age categories: less than one year, 10 patients; 12 months to 24 months, 8 patients; 25 months to 36 months, 5 patients. Data from 29 children between the ages of 37 months and 14 years were used to generate these plots as well.

The CHMP was reassured that there is pharmacokinetic and clinical data in each subcategory by the presented breakdown of the paediatric populations by age groups. However, the CHMP remained unconvinced regarding the dose recommendation. The MAH was requested to assess whether the potential posology of 15 mg/kg every 6 hours for children over 3 years is adequate in all relevant indications in the light of heterogeneity of doses used in the literature and taking into account the pharmacokinetic data from Paediatric studies 1 and 2&3 as well as a comparison of pharmacokinetic data with adolescent/adult data.

The MAH provided plasma clearance vs. age plots generated from available paediatric data. Individual plots were made available for children 3 months to 3 years and 3-14 years. In addition, available adult clearance data were plotted vs. age for reference. The MAH observed that weight normalised clearance does not appear to change with age in the paediatric population from 3 months to 14 years. There is also no evidence suggesting a change in clearance for children less than 3 years of age when compared to clearance in older children. Clearance in adults is distributed across the same range as the paediatric population with a trend toward lower clearance values in older adults.

The MAH provided a description of the CL of imipenem according to age. As stated by the MAH there seems to be a possible trend to lower clearance in older adults, whereas there seems to be no change in CL over the age range 3 months to 14 years. There are conflicting data on the pharmacokinetics of imipenem in children. Whereas the MAH's original pharmacokinetic studies concluded on a higher

clearance in children than in adults, the available pharmacokinetic data from paediatric studies 1 and 2/3 suggests that the elimination is similar across the age groups. Two studies from the literature report higher CL in children compared to adults, which was suggested to be related to the involvement of tubular secretion. Discrepancies in the volume of distribution as well as CL of imipenem have been reported in children (Jacobs et al, J Pediatr 1984; 105(6): 996-1001). The CHMP was concerned by the efficacy and safety in paediatric patients, especially children below 1 year of age. The documentation in paediatric patients is limited, and without a thorough documentation of the pharmacokinetics of imipenem in different age groups of children it is difficult to base recommendations in the SPC on extrapolations from the documentation in adults. Since weight normalised clearance does not appear to change with age in the paediatric population from 3 months to 14 years, the higher weight-adjusted dose in children needs to be justified. Although the CHMP acknowledged that the documentation in paediatric patients was based solely on the posology of 15-25 mg/kg every 6 or 8 hours, the MAH was requested to thoroughly discuss the pharmacokinetics in paediatric patients. From clearance and exposure related to mg dose (AUC) data, the MAH was asked to discuss distribution to tissues (V_D) and consequent efficacy of imipenem/cilastatin in the paediatric population. An altered AUC in paediatric patients in combination with increased CL may alter V_D . If there is a reduced distribution of imipenem, this could potentially lead to insufficient drug levels at the site of action, which might affect the effect of the drug. Furthermore, with increased exposure in paediatric patients, there is an increased risk of seizures.

In response, the MAH pooled together pharmacokinetic data from all available paediatric studies to evaluate the effect of age on the clearance (CL), volume of distribution ($V_{d_{ss}}$), and terminal half life ($t_{1/2}$) of imipenem. Neither weight-normalised clearance nor half life for imipenem appeared to change with age in the paediatric population across the age range of 3 months to 14 years. Although the $V_{d_{ss}}$ was only recorded in a limited number of paediatric subjects, the lack of correlation between $V_{d_{ss}}$ and age is consistent with the fact that both CL and $t_{1/2}$ are age-independent. Therefore, $V_{d_{ss}}$ of imipenem is not expected to change with age in paediatric patients. Given the similarity of the pharmacokinetics for imipenem in paediatric patients, the pharmacokinetic data in children were pooled together and compared with the pharmacokinetic results from adults. The pharmacokinetic data of imipenem were presented separately for the various younger age groups (ages 3-6 months, 7-9 months, 10-12 months, 13-24 months, and 25-35 months). In addition, the pharmacokinetic data of imipenem are pooled together for all paediatric patients <3 years of age and all paediatric patients 3-14 years of age. Although the pharmacokinetic data of imipenem for children <3 years of age are limited in the various age subcategories, the pharmacokinetic parameters for imipenem in each subgroup are consistent with the pooled data. The average CL and $V_{d_{ss}}$ for imipenem are approximately 45% higher in paediatric patients as compared to adults, and the $t_{1/2}$ is slightly shorter in paediatric patients as compared to adults. The trend for increased $V_{d_{ss}}$ in paediatric patients is consistent with what has been reported in the literature. The average value of $V_{d_{ss}}$ (0.26 L/kg) in this analysis differs substantially from the values reported by Jacobs (0.63-0.73 L/kg) but is comparable to those reported for children with cystic fibrosis (0.33 L/kg) and critically ill children (0.30 L/kg). Nevertheless, this modestly increased $V_{d_{ss}}$ in paediatric patients indicates that imipenem distributes more extensively to tissues in paediatric patients as compared to adults. The area under the curve (AUC) following administration of 15 mg/kg per body weight of imipenem to paediatric patients is approximately 30% higher than the exposure in adults receiving a 500-mg dose. At the higher dose, the exposure following administration of 25 mg/kg imipenem to children is comparable to the exposure in adults receiving a 1000-mg dose. Overall, imipenem doses of 15 and 25 mg/kg per body weight every 6 or 8 hours in paediatric patients (3 months and older) provides imipenem systemic exposures similar to those seen in adults receiving 500 mg and 1 g every 6 or 8 hours, respectively, thereby indicating an unlikely increase in the risk of seizures in paediatric patients as compared to adults. The MAH agreed that the weight-adjusted dosing should be the same for paediatric patients 3 months to 14 years of age since weight-normalised CL does not change with age. The dosing regimen, however, in paediatric patients should take into account the severity of infection and the MICs of the pathogens. The lower imipenem dose, administered at 15 mg/kg per body weight every 6 or 8 hours, in paediatric patients is sufficient to treat susceptible pathogens with relatively lower MICs (2 mg/L). The higher imipenem dose regimen, administered at 25 mg/kg per body weight every 6 hours, offers modest additional pharmacodynamic benefit for treating susceptible organisms with relatively higher MICs (4 mg/L).

The CHMP considered that the overview provided by the MAH enabled a better understanding of pharmacokinetics in children. The CHMP agreed with the MAH conclusions and amended section 5.2:

"The average CL and $V_{d_{ss}}$ for imipenem was approximately 45% higher in paediatric patients (3 months to 14 years) as compared to adults. The area under the curve (AUC) following administration of 15 mg/kg per body weight of imipenem to paediatric patients was approximately 30% higher than the exposure in adults receiving a 500-mg dose. At the higher dose, the exposure following

administration of 25 mg/kg imipenem to children was 9% higher as compared to the exposure in adults receiving a 1000-mg dose."

Safety

The CHMP considered that with regards to safety, the available documentation supports a similar safety profile of imipenem/cilastatin in children compared to adults. The most common observed adverse events were related to gastrointestinal tract. Imipenem/cilastatin has the potential to induce seizures, especially in those on treatment for central nervous system (CNS) infections. This effect is dose-related and uncommon at lower doses treating other infections. Nevertheless, it is important to choose an optimal dose in children according to the body weight.

The MAH provided a cumulative review of imipenem/cilastatin postmarketing adverse events identified in patients 3 months to < 18 years of age with concurrent conditions or medical history suggesting renal organ impairment or central nervous system (CNS) disorders. From market introduction, a total of 38 reports during imipenem/cilastatin use were received concerning paediatric patients aged > 3 months to < 18 years who were reported to have a medical history or concomitant medical condition suggestive of CNS disorder. More than half of these reports (24; 63%) included adverse events from the Nervous System Disorders SOC. In 20 of the 38 reports (52%), convulsion or clonic convulsion was a reported event. The majority of the cases had risk factors for seizures irrespective of treatment with imipenem/cilastatin. Upon review of these 20 reports across the entire paediatric age group (> 3 months to < 18 years of age), the presence of other factors which could contribute to the risk of convulsion was noted in 17 of 20 reports (85%). Of note, convulsion was reported in 6 of 7 reports of paediatric patients aged > 3 months to < 1 year of age and 3 of 4 reports of paediatric patients aged > 1 year to < 3 years with a history a pre-existing CNS disorder associated with an increase risk for seizures. As mentioned previously, convulsion is a listed event in the EUSPC for imipenem/cilastatin and precautionary statements regarding its use in patients with CNS disorders are also discussed.

The CHMP agreed to add the following statement in section 4.4: "*Special awareness should be made to neurological symptoms or convulsions in children with known risk factors for seizures, or on concomitant treatment with drugs lowering the seizures threshold.*"

4.2 Posology and method of administration

The CHMP noted the MAH proposal. According to the NfG on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95, rev.1), the dose regimen and the duration of treatment courses should be stated by the corresponding indication for both adult and paediatric populations in accordance with the range that was documented to be effective in clinical trial for each acceptable indication.

Adults and adolescents.

The CHMP requested further justifications for the proposed posology and especially the higher doses up to 4 g/day in adults. *P. aeruginosa* is getting increasingly resistant to imipenem/cilastatin, potentially causing treatment failure. The MAH was requested to discuss, in light of the currently available data and for all indications, whether the standard dose should be 500 mg q.i.d and when 1 g t.i.d or q.i.d is more appropriate. The discussion should take into account the PK/PD supportive data and give consideration to adjustments of the dose, to distinguish between treatment of infections with fully susceptible organisms and of infections with moderately susceptible organisms (primarily some strains of *P. aeruginosa*).

The MAH provided a review of the dosage information in adults for the indications agreed, from a variety of available sources, including data from all prospective Merck clinical trials (included in the original WMA) and from the available clinical data in the literature, in an effort to provide evidence supporting the most appropriate dosing regimen for imipenem in adults. Particular emphasis was placed on literature published within the last decade to account for potential changes in the epidemiology of bacterial infections or the availability of newer antibacterial agents. The MAH concluded that the PK/PD data support the conclusions from the clinical trial data submitted with the original WMA, as well as the data from the comprehensive literature search, that imipenem, administered in total daily doses of 2 or 3 g daily (specifically 500 mg q6h or 1 g q8h), is efficacious against susceptible organisms with MICs \leq 2 mg/L. The PK/PD analysis confirms that both of these doses provide similar coverage against the most common organisms, and these 2 dosage regimens can be viewed as essentially interchangeable. Additionally, in seriously ill adult patient populations with certain life threatening infections caused by susceptible organisms with higher MICs (e.g., *Pseudomonas aeruginosa* with MIC=4 mg/L), the MAH is proposing the inclusion of a statement for

physicians to consider a dose of 1 g q6h as another possible option. Clearly, the benefit-risk ratio of this higher dose of imipenem must be carefully considered in each individual clinical setting.

The MAH stated that carbapenems exhibit minimal concentration-dependent killing and produce prolonged *in vivo* post-antibiotic effects with staphylococci and gram-negative bacilli (primarily with strains of *P. aeruginosa*). The literature confirms that the appropriate PK/PD target for the carbapenems is time above the minimal inhibitory concentration ($T > MIC$) for 40% of the dosing interval. Thus, Monte Carlo simulations conducted by outside investigators and the MAH have used this target for the evaluation of the dosage regimen of imipenem. Various PK/PD analyses have been conducted with imipenem using Monte Carlo simulations in the last decade by outside investigators. These analyses support the use of imipenem at 500 mg every 6 hours (500 mg q6h) or 1 g every 8 hours (1 g q8h). As requested, Monte Carlo simulations were also performed by the MAH to obtain probabilities of imipenem pharmacodynamic target attainment for *P. aeruginosa* and *Enterococcus sp.* The MAH included *E. coli* and *K. pneumoniae* in the simulations in order to provide a more comprehensive view of pharmacodynamic target attainment for imipenem. The carbapenems exhibit minimal concentration-dependent killing and produce prolonged *in vivo* post-antibiotic effects with staphylococci and gram-negative bacilli (primarily with strains of *P. aeruginosa*). Therefore, the goal of dosing regimens for the carbapenems (as with the entire class of beta-lactam antibiotics) is to optimize duration of exposure. The time above the MIC is the important pharmacodynamic parameter that correlates with therapeutic efficacy. For maximal bactericidal effect, the concentration of free drug must exceed the MIC for 40% of the dosing interval for carbapenems. This PK/PD analysis was performed using over 5,000 isolates each of *E. coli* and *K. pneumoniae* isolates collected between 2005 and 2009 in the Merck sponsored SMART study (Study to Monitor Antimicrobial Resistance Trends), and over 5,000 isolates of *P. aeruginosa* collected between 2002 and 2009 in the SMART study. Over 4,500 isolates of *Enterococcus spp.* collected between 2004 and 2007 from the TEST study (Tigecycline Evaluation Surveillance Trial) were also used in the PK/PD simulation.

The population pharmacokinetic model for imipenem was developed using the NONMEM program based on imipenem plasma concentrations obtained in 20 adult patients and 34 adult healthy subjects, all with normal renal function. A two-compartment pharmacokinetic model with zero order infusion and first-order elimination adequately described the concentration data available. A Monte Carlo simulation of 6,000 adult subjects was subsequently conducted to estimate the target attainment, $T > MIC$, for each bacterium-regimen combination, where the MIC for a particular bacterium was randomly generated based on MIC distributions. Three imipenem regimens were simulated: 500 mg as a 30-minute infusion every 6 hours (500 mg q6h), 1 g as a 1-hour infusion every 8 hours (1 g q8h), and 1 g as a 1-hour infusion every 6 hours (1 g q6h). The results showed that imipenem doses of 500 mg q6h and 1 g q8h provide very similar pharmacodynamic responses (pharmacodynamic target of free drug at $T > 40\%$, all three doses of imipenem achieved target attainment rates of 98%), and both are adequate against pathogens with relatively low MICs (2 mg/L) such as *E. coli* and *K. pneumoniae*. For *P. aeruginosa*, the same pharmacodynamic target was achieved in ~75%-79% of patients. This is consistent with the EUCAST breakpoint of 4 mg/L for imipenem and reflects the percentage of wild type among 5,038 strains of *P. aeruginosa*, for which 76.4% of all isolates had MICs 4 mg/L. There is no standard in the literature for a pharmacodynamic target for *Enterococcus sp.*, making it difficult to assess appropriate target attainment for any particular dosage regimen. Approximately 68% -72% of patients achieved a PK/PD target of $fT > MIC$ of 40%, which is also consistent with the EUCAST breakpoint of 4 mg/L for *Enterococcus sp.* and the percentage of isolates with MIC 4 mg/L. A higher imipenem dose regimen (1 g q6h) does not offer additional pharmacodynamic benefit for *E. coli* and *K. pneumoniae* in this model. However, for organisms with relatively high MICs (4 mg/L), namely *P. aeruginosa*, a higher dose of 1 g q6h results in modestly higher target attainment. Thus, the higher dose of 1 g q6h might be considered another reasonable option against *P. aeruginosa*, especially if indicated by the clinical situation (e.g., in a serious infection such as pneumonia). Even in these clinical situations, the benefit-risk ratio should be weighed carefully before the higher dose of 1 g q6h is used. To date, clinical studies investigating the effect of prolonged infusion time with imipenem have not been conducted by the MAH. Thus, the MAH did not propose any additional dosing regimens involving prolonged infusion time. However, a comparison of a 30-minute and 3-hour infusion regimens for imipenem using Monte Carlo simulations was performed by Lee et al. This study demonstrated that prolonged infusions for imipenem may optimize clinical outcomes but noted that a clinical trial in different patient populations would be needed to confirm the modelling results.

The CHMP considered that based on the PK/PD rationale as presently discussed (with $T > MIC$ over 40% or 50%), the most optimal dose would be 1000 mg every six hours (i.e. 1 g q.i.d) for life-threatening conditions, including bacteraemic immunocompromised (incl. neutropenic patients), CF patients and in case of suspected or proven infections with such less susceptible micro-organisms. In conclusion, the CHMP was therefore of the opinion that in light of the present clinical and PK/PD data, a standard dose

of 500 mg every 6 hours or 1g every 8 hours can be accepted, provided that a recommendation is inserted in the SPC stating that for infections suspected or proven to be due to less susceptible organisms (e.g. *P. aeruginosa*) and for very severe infections (e.g. in neutropenic patients with a fever), the 1000 mg q.i.d should be used.

Paediatric patients above 1 year of age

The CHMP did not consider the proposed dose recommendation for children to be adequately justified and requested the MAH to perform a PK/PD analysis with respect to both components of this product in order to further substantiate the proposed dose regimen. The CHMP also requested the MAH to further discuss whether the dose recommendation of 25 mg/kg every 6 hours in children from 3 months to 3 years and 15 mg/kg every 6 hours in children over 3 years is justified for Tienam in all relevant indications in the light of heterogeneity of doses used in the literature.

In the paediatric population, the MAH stated that weight-normalised clearance (CL) does not change with age. Similar to the adult population, the dosing recommendation in paediatric patients should consider the severity of infection and the MIC of the pathogen. An imipenem dose of 15 mg/kg per body weight every 6 or 8 hours is being recommended for treating paediatric patients with infections caused by susceptible pathogens with relatively lower MICs (2 mg/L). A higher imipenem dose regimen, administered at 25 mg/kg per body weight every 6 hours, offers modestly additional pharmacodynamic benefit for treating susceptible organisms with a relatively higher MIC (=4 mg/L). Thus, the higher dose of imipenem is currently being proposed as another option for severe pneumonia (including hospital and ventilator-associated pneumonia) and the proposed indication for broncho-pulmonary infections in cystic fibrosis caused by susceptible *P. aeruginosa* and *Enterococcus* spp. Nonetheless, the benefit-risk ratio of this higher dose must be carefully considered in each individual clinical setting. The CHMP was of the opinion that in light of the present clinical and PK/PD data, for paediatric patients ≥ 1 year of age, a standard dose of 15 or 25 mg/kg/dose administered every 6 hours is recommended. Advice to physicians was provided regarding infections suspected or proven to be due to less susceptible bacterial species (such as *Pseudomonas aeruginosa*) and very severe infections (e.g. in neutropenic patients with a fever), recommending treatment with 25 mg/kg administered every 6 hours.

Elderly population

The CHMP noted that the serum half life of imipenem is around 60 min in healthy volunteers. According to the proposed SPC section 5.2, the mean plasma half life of imipenem was 91 ± 7 min in healthy elderly volunteers. The MAH was therefore requested to provide data to justify that no dose adjustment is necessary for the elderly population, considering the possibility for overdose which may lead to seizures. The MAH provided data from pharmacokinetic studies showing a reduction in plasma clearance of imipenem in healthy elderly (65-75 years) subjects. Plasma levels of imipenem were increased by approximately 50% and the plasma half-life (1.5 hr) was slightly longer as compared to healthy young volunteers (1.0 hr). These changes were attributed to the slightly decreased kidney function which is characteristic of this age group. In fact, the pharmacokinetic parameter values in elderly subjects most closely resemble those in patients with mild renal impairment. In comparison to healthy volunteers, total imipenem plasma AUC increased by a factor of 1.7 in patients with mild renal impairment, by a factor of 2.8 in patients with moderate impairment, and by a factor of 3.6 in patients requiring haemodialysis. Based on information derived from these studies, the MAH considered that no dose adjustment was required in elderly patients, except in cases of moderate to severe renal impairment. The CHMP agreed that no dose adjustment is required for the elderly patients with normal renal function, as indicated in the SPC.

Paediatric patients with renal impairment

Considering the lack of data and the potential serious side effects for paediatric patients with impaired renal function, the CHMP proposed to include a statement on this issue. The MAH acknowledged that there is insufficient data to recommend dosing but considered that according to the SPC guideline, the Contraindications section should only mention situations where the medicinal product must not be given for safety reasons. These situations should be unambiguously, comprehensively and clearly outlined. The MAH therefore proposed to mention renal impairment under sections 4.2 and 4.4. The CHMP acknowledged that it may not be appropriate to list children with renal impairment and CNS-affection under contraindications and agreed to the following harmonised statement: "*Clinical data are insufficient to recommend dosing for paediatric patients with renal impairment (serum creatinine > 2 mg/dl). See section 4.4.*"

Doses \geq 4 gm/day

The CHMP requested the MAH to carry out a relevant safety analysis across dose levels to confirm that the reason for not recommending the higher dose of 1 g q6h in several indications was not driven by safety aspects. The MAH carefully reviewed both the clinical trial data and the literature to look for any safety findings identified with the 1 g q6h dose (4 g/day). The Merck clinical trial data contained a single report (PN5006, submitted as part of the original WMA) which summarises results from a subset of 140 patients who received 3 g/day or 4 g/day of imipenem prior to licensure. In this non-comparative study report, all 140 patients were included in the safety evaluation. The data confirmed that no notable differences in safety were observed between the lower dose (3 g/day) and the higher dose (4 g/day) groups. Clinical adverse experiences were reported for 48% (29/60) in the 3 g/day group, and 29% (23/80) in the 4 g/day group. Overall, 18% (11/60) in the 3 g/day group and 4% (3/80) in the 4 g/day group had adverse experiences that were considered probably or definitely drug related. Additionally, 32 laboratory adverse experiences from 18/60 patients (30%) in the 3 g/day group and 50 laboratory adverse experiences from 24/80 patients (30%) in the 4 g/day group were reported. Of these, 8 laboratory adverse experiences in 4 patients in the 3 g/day group were considered probably or definitely drug related. In comparison, 4 laboratory adverse experiences in 2 patients in the 4 g/day group were considered probably or definitely drug related. The detailed literature review for each of the proposed indications also evaluated the daily dose of imipenem used. This review did not identify any safety concerns with the 1 g q6h dose from the literature, albeit the number of identified reports using the 1 g q6h dose were limited and there was no robust comparative data for this dose relative to lower imipenem doses. In summary, the MAH could not identify, neither in the Merck clinical trial data nor in the previous literature reviews any special safety concerns with the 1 g q6h dose.

To evaluate postmarketing adverse events reported in temporal association with patients who received higher doses of imipenem/cilastatin, the MAH conducted a cumulative (28-Jun-1984 to 14-Oct-2010) search of the Worldwide Adverse Experience System (WAES) database to identify reports submitted by healthcare providers involving total daily doses of \geq 4 gm/day. A total of 55 relevant reports were identified, 52 of these contained a dose of 4 gm/day and 3 contained a dose of 6 g/day. Fifty one reports provided patient age: 48 were in adults (\geq 18 years) and 1 report each contained an age of 17 years, 12 years, and 9 years. The 55 reports (43 serious) contained 148 adverse events (84 serious). Of these 148 events, 74 (44 serious, 30 non-serious) were identified in the proposed EU SPC for imipenem/cilastatin and 74 (40 serious, 34 non-serious) were not. Of the most frequently reported serious adverse events the top 3 were present in the proposed EU SPC: convulsion (n=11), renal failure (n=4), overdose (n=3). Comparison of the most frequently reported serious adverse events for reports containing imipenem/cilastatin doses of \geq 4 gm/day with those containing doses of $<$ 4 gm/day during the same cumulative period did not identify meaningful differences. Similar to the higher dose group, convulsion, renal failure and agranulocytosis were 3 of the 5 most frequently identified serious adverse events for the reports containing a dose of $<$ 4 gm/day. To further investigate adverse events reported with higher doses of imipenem/cilastatin, the 3 reports of patients $<$ 18 years of age were reviewed along with the 3 reports containing doses of $>$ 4 gm/day. No new safety concerns were identified in these reports. For patients less than 18 years of age, the recommended paediatric dose of imipenem/cilastatin listed in the proposed EU SPC is 15 – 25 mg/kg every 6 hours based on type and severity of infection. Of the 3 paediatric reports, the first involved a 9 year old who received imipenem/cilastatin 28mg/kg every 6 hours and experienced blepharoptosis and eyelid ptosis which resolved after the dose was reduced. The second involved a 12 year old with seminoma and malignant neoplasm who received 20mg/kg every 6 hours and experienced vomiting, worsening malignant neoplasm and seminoma. The final report was in a 17 year old with non-Hodgkin lymphoma and bone marrow transplant failure who received 1,000 mg every 6 hours who experienced purpura, bone marrow depression and skin rash. Of the 3 reports containing a dose of $>$ 4g/day, each reported a dose of 6 gm/day. Of those reports, 1 contained the terms thrombocytopenia, blood creatinine increased, blood urea increased, renal failure and overdose which are all present in the SPC. The remaining 2 reports were from the same reporter and contained the terms optic atrophy, amaurosis in both reports with the term pupil fixed in one report and tunnel vision in the other. Both of these reports were confounded by omeprazole use which has been reported to cause ocular toxicity, including optic atrophy.

In summary, the adverse event identified in the 55 postmarketing reports containing a dose of \geq 4 gm/day are consistent with events documented from postmarketing reports with lower doses of imipenem/cilastatin. This analysis, as well as the review of the literature and clinical trial data, did not reveal new safety issues with the use of imipenem/cilastatin doses of \geq 4 gm/day. The MAH therefore concluded that making the 1 g q6h dose available for more indications is acceptable, as the possibility remains that relatively less susceptible organisms with higher MICs (such as *Pseudomonas aeruginosa*)

may be encountered across all the proposed indications. The MAH agreed to propose the additional 1 g q6h dose for the indications, as suggested by the CHMP.

The CHMP considered that the MAH clarified satisfactorily that no new safety issues or increased ADRs were observed with the use of imipenem/cilastatin doses of ≥ 4 gm/day as compared to doses of <4 gm/day, based on the review of clinical trial data in the original WMA, PMS data and the literature. The CHMP considered the issue to be resolved.

The CHMP also deleted the low doses of 250 mg every 6 hours as mild infections should not be treated with imipenem/cilastatin and removed the dose recommendations for indications which were not considered approvable. In conclusion, the CHMP adopted a harmonised wording for section 4.2, including the following dose recommendations:

"Adults and adolescents

For patients with normal renal function (creatinine clearance of >70 ml/min/1.73 m²), the recommended dose regimens are:

*500 mg every 6 hours OR
1000 mg every 8 hours OR every 6 hours*

It is recommended that infections suspected or proven to be due to less susceptible bacterial species (such as Pseudomonas aeruginosa) and very severe infections (e.g. in neutropenic patients with a fever) should be treated with 1000 mg administered every 6 hours.

The maximum total daily dose should not exceed 4000 mg/day.

Elderly population

No dose adjustment is required for the elderly patients with normal renal function (see section 5.2).

Paediatric population ≥ 1 year of age

For paediatric patients ≥ 1 year of age, the recommended dose is 15 or 25 mg/kg/dose administered every 6 hours.

It is recommended that infections suspected or proven to be due to less susceptible bacterial species (such as Pseudomonas aeruginosa) and very severe infections (e.g. in neutropenic patients with a fever) should be treated with 25 mg/kg administered every 6 hours.

Paediatric population <1 year of age

Clinical data are insufficient to recommend dosing for children less than 1 year of age."

Section 4.3 - Contraindications

The CHMP noted the MAH proposal for this section and adopted the following harmonised wording for section 4.4.

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

Section 4.4 - Special warnings and precautions for use

The CHMP noted the MAH proposal for this section and added an introductory statement on considering the appropriateness of carbapenem treatment, in line with statements introduced for other carbapenems. A statement requesting close monitoring of hepatic function due to the risk of hepatic toxicity was inserted, in line with other carbapenems, together with a statement on the need for close monitoring of liver function in patients with liver disease. The section was also supplemented with a warning on the antibacterial activity spectrum and eventual need for concomitant therapy. A sentence on documented positive Coombs tests was also added. As it has been established that concomitant use of carbapenems and valproic acid leads to decreases in valproic acid levels to below the therapeutic range, a statement that the use of imipenem with valproic acid is not recommended was inserted. The CHMP added a statement concerning the limited susceptibility of specific pathogens and the concomitant use of an appropriate anti-MRSA agent or of an aminoglycoside:

"The antibacterial spectrum of imipenem/cilastatin should be taken into account especially in life-threatening conditions before embarking on any empiric treatment. Furthermore, due to the limited susceptibility of specific pathogens associated with e.g. bacterial skin and soft-tissue infections, to imipenem/cilastatin, caution should be exercised. The use of imipenem/cilastatin is not suitable for treatment of these types of infections unless the pathogen is already documented and known to be susceptible or there is a very high suspicion that the most likely pathogen(s) would be suitable for treatment. Concomitant use of an appropriate anti-MRSA agent may be indicated when MRSA infections are suspected or proven to be involved in the approved indications. Concomitant use of an aminoglycoside may be indicated when Pseudomonas aeruginosa infections are suspected or proven to be involved in the approved indications (see section 4.1)."

In conclusion, the CHMP adopted a harmonised wording for section 4.4.

Section 4.5 - Interaction with other medicinal products and other forms of interaction

The CHMP noted the MAH proposal for this section. Regarding interaction with valproic acid, a text in line with that agreed for ertapenem was adopted, stating that the concomitant use of carbapenems and valproic acid leads to decreases in valproic acid levels to below the therapeutic range. As such, the use of imipenem with valproic acid is not recommended (as stated in section 4.4). Regarding oral anticoagulants, the CHMP noted that there is currently no data specific to co-administration of warfarin and imipenem/cilastatin justifying the inclusion of a class label wording. Instead, a statement warning that increased anti-coagulant effects have been reported in patients concomitantly receiving antibacterial agents was inserted, also recommending that the INR (international normalised ratio) should be monitored frequently. Finally, a statement on the interaction with probenecid (previously located in section 5.2) was inserted. In conclusion, the CHMP adopted a harmonised wording for section 4.5.

Section 4.6 – Fertility, Pregnancy and Lactation

The CHMP noted the MAH proposal for this section and considered the suggested wording for use during pregnancy to be acceptable, with the addition of the sentence: "The potential risk for humans is unknown." regarding breast-feeding, the proposal was amended to reflect the fact the benefit of using Tienam must be weighed against the consideration that small quantities of imipenem/cilastatin are excreted in the mother's milk. A section on fertility was added, in line with the current version of the Notice to Applicants guidance document. In conclusion, the CHMP adopted the following harmonised wording for section 4.6:

Pregnancy:

There are no adequate and well-controlled studies for the use of imipenem/cilastatin in pregnant women. Studies in pregnant monkeys have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Tienam should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation:

Imipenem and cilastatin are excreted into the mother's milk in small quantities. Little absorption of either compound occurs following oral administration. Therefore it is unlikely that the suckling infant will be exposed to significant quantities. If the use of Tienam is deemed necessary, the benefit of breast feeding for the child should be weighed against the possible risk for the child.

Fertility

There are no data available regarding potential effects of imipenem/cilastatin treatment on male or female fertility."

Section 4.7 - Effects on ability to drive and use machines

The CHMP noted and agreed with the MAH proposal for this section. In conclusion, the CHMP adopted the following harmonised wording for section 4.7:

"No studies on the effects on the ability to drive and use machines have been performed. However, there are some side effects associated with this product that may affect some patients' ability to drive or operate machinery (see section 4.8)."

Section 4.8 - Undesirable effects

The CHMP noted the MAH proposal for this section and requested a revision of the table of adverse reactions. A number of adverse reactions were introduced, the frequencies were revised and the adverse reactions were reordered. The MAH searched their post marketing safety database again and performed frequency estimations. Using the calculated reporting rates for each of the adverse experiences listed in Section 4.8 followed by the conversion to an estimated frequency rate as indicated above, the frequency of reports for each adverse event identified from the post-marketing environment was estimated to be very rare. Obtaining accurate and complete supporting data for adverse events reported during past clinical studies is problematic. The clinical study database for imipenem/cilastatin does not conform to conventional coding (as many of the studies were performed at least 20 to 30 years ago) and classification methods and cannot accurately be queried to verify the frequency of adverse events included in Section 4.8. The CHMP endorsed the MAH proposal to maintain the highest frequency as currently listed and to use the highest frequency reported in a clinical. However, as data are insufficient to make a proper estimation of the frequency, the frequency 'unknown, cannot be estimated from the available data' and therefore has to be maintained. An introductory summary of the safety profile was also inserted at the beginning of section 4.8 together with a paediatric sub-section at the end of section 4.8, according to the current SPC guideline. In conclusion, the CHMP adopted a harmonised wording for section 4.8.

Section 4.9 - Overdose

The CHMP noted the MAH proposal for this section and revised it to include symptoms. In conclusion, the CHMP adopted the following harmonised wording for section 4.9:

"Symptoms of overdose that can occur are consistent with the adverse reaction profile; these may include seizures, confusion, tremors, nausea, vomiting, hypotension, bradycardia. No specific information is available on treatment of overdose with Tienam. Imipenem-cilastatin sodium is haemodialyzable. However, usefulness of this procedure in the overdose setting is unknown. "

SECTION 5 - PHARMACOLOGICAL PROPERTIES

Section 5.1 - Pharmacodynamic properties

The CHMP noted the MAH proposal for this section but implemented a number of revisions. In particular, the table of EUCAST breakpoints and the table of susceptible species were revised, including the insertion of a number of footnotes. The EUCAST information was aligned with the current EUCAST recommendations. In conclusion, the CHMP adopted a harmonised wording for section 5.1

Section 5.2 - Pharmacokinetic properties

The CHMP noted the MAH proposal for this section and requested additional relevant information on renal insufficiency, hepatic insufficiency and elderly patients, relevant data. The interaction with probenecid was moved to section 4.5 Interaction.

Renal insufficiency

Regarding renal insufficiency, the MAH submitted the results from study 513, as requested by the CHMP and grouped the results in accordance with the current guideline. The CHMP noted that normal renal function is now defined as GFR (ml/min/1.73m²) >80. Mild, moderate and severe renal impairment are defined as GFR (ml/min/1.73m²) 50-80, 30-<50 and <30, respectively. Using the renal impairment grouping provided in study #513, the normal, mild and moderate groups had 6 patients each while the severe renal impairment group consisted of 5 subjects. With the classification based on CHMP/EWP/225/02, the number of patients in each group has changed for mild, moderate and severe to 3, 3 and 11 patients, respectively. As a result, the differences in AUC between the groups changed, and have been included in the text, which is agreed. As dosing is based upon renal function and not specified as renal function status, the dose recommendations are still applicable.

Hepatic insufficiency

The CHMP noted the MAH statement that no clinical studies were performed in subjects with hepatic insufficiency. However, due to the limited degree of hepatic metabolism (imipenem and cilastatin are excreted almost completely intact in urine) hepatic impairment is not expected to significantly affect the pharmacokinetics and no dose adjustment is therefore recommended for patients with impaired hepatic function.

Paediatric patients

The CHMP could not agree with the wording proposed by the MAH for paediatric patients, as the results of the provided overview on pharmacokinetics in paediatric patients should be better reflected. The CHMP instead adopted a revised wording.

Elderly

The pharmacokinetics in elderly is supported by a specific study (study 665), in which 13 elderly, aged between 66 – 86 years, received doses of 500/500 mg imipenem/cilastatin. GFR ranged from 31 – 84 ml/min. The CHMP agreed with the inclusion of data on the elderly obtained from study 665.

The MAH agreed to provide the full comprehensive (interim) report of the ongoing SMART study (Merck-sponsored Study to Monitor Antimicrobial Resistance Trends, started in 2002) and the MAH's own PK/PD data analysis with underlying PK analysis (including population kinetics), together with the methodological assays used for the generation of the PK data in tested patients and healthy volunteers (in total 54 subjects).

In conclusion, the CHMP adopted a harmonised wording for section 5.2.

Section 5.3 - Preclinical safety data

The CHMP noted the MAH proposal for this section and requested the removal of the information about the LD50, as it was not considered clinically relevant. The section regarding reproductive toxicity was also streamlined and mentions of the intramuscular administration were deleted. In conclusion, the CHMP adopted a harmonised wording for section 5.3.

SECTION 6 – PHARMACEUTICAL PARTICULARS

The CHMP inserted a number of statements made in Section 6 – Pharmaceutical particulars, in particular with regards to the reconstitution and storage recommendations.

Section 6.3 – Shelf life and section 6.6 – Special precautions for disposal and other handling

The MAH discussed a number of quality issues, including a justification for the use of the current HPLC method. Concerns were raised regarding the lack of stability of the reconstituted solution. The MAH and the CHMP therefore extensively discussed the stability of the reconstituted solution and the reconstitution recommendations, based on the common knowledge that carbapenems are unstable in solution. Indeed, a mass imbalance for imipenem and its degradation products was identified as the degradants are further degraded to substances that are either not detected or underestimated by the analytical method. However, it appears there are degradation products above the qualification limit and therefore, the reconstitution solutions should be restricted in such a way that degradation is avoided as much as possible. A warning was therefore added to state that diluted solutions should be used immediately and that the interval between beginning of reconstitution and the end of intravenous infusion should not exceed two hours. In addition, special attention was given to the appropriate infusion solution. In-use studies have shown that for a dilution in 5% glucose-solution the decrease in assay after 2 hours is much higher compared to 0.9% sodium chloride solution, which is the preferred solution, along with water for injection. The use of 5% glucose was restricted to exceptional circumstances where 0.9% sodium chloride cannot be used for clinical reasons while all other solvents were deleted from the list of compatible solutions since the compatibility and stability of imipenem/cilastatin in these solutions is not adequate. All mentions of storage under refrigerated conditions were removed.

2.3. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Recommendation

In conclusion, the CHMP recommended the revision and harmonisation of the Product Information for Tienam and adopted the following harmonised indications:

Tienam is indicated for the treatment of the following infections in adults and children 1 year of age and above (see sections 4.4 and 5.1):

- *complicated intra-abdominal infections*
- *severe pneumonia including hospital and ventilator-associated pneumonia*
- *intra- and post-partum infections*
- *complicated urinary tract infections*
- *complicated skin and soft-tissue infections*

Tienam may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

2.5. Conclusions

The basis for this referral procedure was a harmonisation of the SPC, labelling and package leaflet. The CHMP having considered:

- the rapporteur and co-rapporteur assessment reports,
- scientific discussion within the Committee,

the CHMP was of the opinion that the benefit/risk ratio of Tienam and associated names is considered to be favourable. The CHMP adopted a positive opinion recommending the harmonisation of the SPC, labelling and package leaflet as set out in Annex III of the CHMP opinion for Tienam and associated names (see Annex I).