21 February 2011
EMA/CHMP/101385/2011

CHMP assessment report pursuant to Article 30 of Directive 2001/83/EC, as amended for Tazocin and associated names

INN: piperacillin-tazobactam

Procedure no: EMEA/H/A-30/1149

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 12 June 2009 the European Commission 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:
Tazocin 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 June, 2009 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Dr Robert James Hemmings (UK) as rapporteur and Dr Bengt Ljungberg (Sweden) as co-rapporteur.

Tazocin medicinal products are registered in the following EU Members States: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, 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 Norway.

2. Scientific discussion during the referral procedure

2.1. Introduction

Tazocin (and associated names) have been included in the list of products for Summary of Product Characteristics (SPC) harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended. Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product (and its associated names), the European Commission notified the CHMP/EMEA Secretariat of an official referral under Article 30 of Directive 2001/83/EC as amended in order to resolve divergences amongst the nationally authorised SPCs and thus to harmonise the SPCs across the EU. Tazocin is approved in all 27 EU member states, as well as in Norway. All existing licenses for Tazocin have been obtained through national approvals. The medicinal products containing piperacillin-tazobactam are presented as 2 g/0.25 g and 4 g/0.5 g powder for solution for injection or infusion in two formulations and are authorised for one or both of these strengths in most of the MS.

Piperacillin sodium is a semi-synthetic ureidopenicillin with broad spectrum anti-bacterial activity, used for the treatment of infections caused by Pseudomonas aeruginosa, and other susceptible bacteria. Its clinical role has been strengthened by the addition of an irreversible β-lactamase-inhibitor (tazobactam), which protects piperacillin against enzymatic degradation from β-lactamase-producing bacteria and therefore expanding the antimicrobial spectrum. Tazobactam is a penicillanic acid sulfone derivative with β-lactamase inhibitory properties similar to those of sulbactam although it is regarded as more potent. It has the potential to enhance the activity of β-lactam antibacterials against β-lactamase-producing bacteria. The combination of piperacillin and tazobactam in a ratio of 8:1 is effective in the treatment of moderate to severe polymicrobial infections including intra-abdominal, skin and soft-tissue and is approved and marketed for the treatment of a number of infections caused by gram-positive and gram-negative aerobic and anaerobic organisms.

The Marketing Authorisation Holder (MAH) took the opportunity to harmonise Module 3 - Quality within the scope of this Article 30 referral procedure and submitted an updated Quality Overall Summary (QOS). The CHMP decided to remove the triple combination (intramuscular administration with lidocaine) from the scope of the Tazocin referral procedure, in line with the official notification which does not address the triple combination.

The MAH was requested to address the main areas of disharmony and in order to allow re-evaluation of the data substantiating a harmonised PI, the MAH was requested to submit a proposed harmonised PI taking into account the latest guidance document, all available information (efficacy and safety data)

substantiating such proposed harmonised PI and updated expert reports justifying the proposal. After the initial assessment, the CHMP was of the opinion that the SPC as proposed by the MAH at the start of this harmonisation procedure under Article 30(2) of Directive 2001/83/EC, as amended, needed further discussion and further supportive data, in particular in support of some of the claimed indications and dose recommendations. A drafting group was convened on two occasions to discuss the relevant issues in this procedure. The discussion followed the structure of the Summary of product Characteristics (SPC).

2.2. Critical Evaluation

Section 4.1 - Therapeutic Indications

Section 4.1 differed considerably between EU MS. The MAH proposed the following harmonised wording:

Tazocin is indicated for the treatment of the following systemic and/or local bacterial infections caused by Gram-positive and Gram-negative aerobic and anaerobic organisms susceptible to piperacillin-tazobactam or piperacillin:

Adults and adolescents > 12 years of age

- Lower respiratory tract infections (community-acquired, hospital-acquired and ventilator-associated pneumonia)
- Urinary tract infections (complicated and uncomplicated)
- Complicated and uncomplicated intra-abdominal infections
- Skin and skin structure infections
- Bacterial infections in neutropenic adults
- Bacterial septicaemia
- Gynaecological infections, including postpartum endometritis and pelvic inflammatory disease (PID)
- Bone and joint infections

Children 2 to 12 years of age

- *Neutropenic children with fever suspected to be due to bacterial infections, in combination with an aminoglycoside*
- *Children with complicated and uncomplicated intra-abdominal infections*

General considerations

Tazocin may be used in the management of patients with polymicrobial infections (sometimes known as mixed infections). Because of its wide spectrum of activity against Gram-positive/Gram-negative aerobic and anaerobic pathogens, it can be used in the management of patients during presumptive therapy before the availability of sensitivity results. As with all anti-infectives, treatment should be adjusted accordingly.

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

The MAH proposed the above-listed indications based upon current guidelines (the *EC guideline on the Summary of Product Characteristics, September 2009* and *CPMP/EWP/558/95 rev 1 - Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections, 2004*). Data to support the proposed harmonised indications were reviewed in depth in the Clinical Expert report. The proposed harmonised indications occur with the highest frequency in the Nationally Approved SPCs. Full details of nationally approved indications were provided by the MAH.

The CHMP provided general comments on Section 4.1, stating that the initial proposals made by the MAH are not in line with current EU guidelines and are not worded appropriately. The Note for Guidance CPMP/EWP/558/95 rev 1, 2004) states that an indication may be granted if the clinical data support a favourable benefit-risk ratio and reflect the range of type and severity of infections that are commonly encountered. Indications have to be infection (site) specific. General statements such as “Lower respiratory tract infections” or “septicaemia” are no longer acceptable. Where an agent may be used in certain patient subpopulations (e.g. immunocompromised patients), it is still required that indications should be as specific as possible based on the available data. Specific indications are discussed below by site of infection. Some of the information added in this section reflects how the

agent may be used in clinical practise but does not belong in a list of indications for use. For all indications, differences in clinical practices and national treatment recommendations will be addressed by the sentence "*Consideration should be given to official guidance on the appropriate use of antibiotics."*

1.1- Lower Respiratory Tract Infections (LRTI)

The MAH provided an overview of the current nationally approved indications. The large majority of MS have approved varying wordings for the respiratory tract infections either as the umbrella term LRTI or a more specific term such as severe nosocomial pneumonia. The MAH proposed the following harmonised indication: *"Lower respiratory tract infections (community-acquired, hospital-acquired and ventilator-associated pneumonia)".*

The CHMP noted that "lower respiratory tract infections" are currently approved in most member states while nosocomial pneumonia is approved in only some member states. The CHMP was of the opinion that the terms "respiratory tract infection" (RTI) and "lower respiratory tract infections" (LRTI) are non-specific and that their precise meaning is open to interpretation. Bacterial LRTIs may include such infections as pneumonia, acute bronchitis, acute exacerbations of chronic obstructive pulmonary disease, pleural empyema, lung abscess, and pulmonary infection associated with cystic fibrosis. Current guidelines require indications to be more specific as it was recognised that different clinical entities summarised under "LRTI" have different etiology and therefore may require different treatment. For example, whether pneumonia was acquired in a hospital setting or not, provides additional clues to the pathogens involved and led to precise definitions of hospital-acquired pneumonia and community-acquired pneumonia. The clinical overview provided by the MAH discusses lower respiratory tract infections *in toto* when referring to the studies submitted originally. However, some of these initial studies and more recent studies performed have selectively included patients with either community acquired pneumonia (CAP) or hospital acquired pneumonia (HAP). The CHMP separated the data and the discussion for CAP and HAP in line with current guidelines. It is considered that other types of specific indications that fall under the umbrella term of lower respiratory tract infections can anyway not be supported by the data.

Original Pivotal Studies

The data submitted in support of the indication treatment of patients with LRTI, as part of the initial European applications, included three open-label, multi-center and non-comparative studies evaluating the safety, tolerance and efficacy study of parenteral piperacillin-tazobactam. The two main registration studies were D68 P13 (treatment of hospitalised patients with lower respiratory tract infections) and D68 P517 (piperacillin-tazobactam in combination with amikacin for the treatment of severe lung infections in patients hospitalised in intensive care units). A third supportive study D68 P512 (the treatment of hospitalised patients with acute lower respiratory tract infections, uncomplicated urinary tract infections, and skin and soft tissue infections) was also provided in the initial registration package.

1.1.1 Community acquired pneumonia (CAP)

Streptococcus pneumoniae accounts for most cases of CAP in all groups of patients, whether treated on an outpatient basis or admitted to the hospital, including the subset admitted to the ICU. In hospitalised patients, *S. pneumoniae* causes between 20 and 60% of all cases of CAP and is also the most important pathogen in terms of mortality. *H. influenzae* and *Moraxella catarrhalis* are more common in elderly patients with chronic obstructive pulmonary disease (COPD) and in smokers, accounting for 3–10% of CAP episodes. Aerobic Gram-negative bacilli such as *Klebsiella* spp., *P. aeruginosa* and *E. coli* are infrequently considered to be causal pathogens of CAP. *S. aureus* CAP occurs mainly as a complication of influenza. The MAH presented a number of studies in support of the CAP indication.

Comparison of piperacillin-tazobactam vs ticarcillin/clavulanate

Shlaes et al; (CAP double blinded study, 1992) conducted a randomised, double-blind, multicenter North American trial (D68 P39) to compare piperacillin-tazobactam 3.375g IV given every 6 hours (i.e. the US-approved regimen) to ticarcillin/clavulanate 3.1g given every 6 hours in 299 hospitalised subjects with community-acquired lower respiratory tract infections (published 1992). A total of 119 (69 piperacillin-tazobactam, 50 ticarcillin/clavulanate) subjects were evaluable for efficacy. The treatment groups were demographically similar. The most common diagnosis was pneumonia which occurred in 83% and 87% of piperacillin-tazobactam- and ticarcillin/clavulanate-treated subjects, respectively. At endpoint, a favorable clinical and bacteriologic response was observed in 84% (58/ 69)

of subjects treated with piperacillin-tazobactam and 64% (32/ 50) of subjects receiving ticarcillin/clavulanate ($p<0.01$ for clinical and $p=0.02$ for bacteriologic response). The most commonly isolated pathogens were *Haemophilus influenzae* (51 isolates) and *Streptococcus pneumoniae* (58 isolates). Gastrointestinal disturbances were the most common adverse events and occurred significantly more frequently in the piperacillin-tazobactam treatment group (31.6%) as compared to the ticarcillin/clavulanate treatment group (20.5%; $p=0.02$). Piperacillin-tazobactam appeared to be more effective than ticarcillin/clavulanate for the treatment of hospitalized subjects with mildly to moderately severe community-acquired pneumonia and bronchitis.

A randomised, open-label clinical trial compared the efficacy and safety of piperacillin-tazobactam and ticarcillin/clavulanate was conducted by Hou Li, and Gao (published 1998) in 124 hospitalized subjects with lower respiratory tract or urinary tract infections. Subjects received piperacillin-tazobactam 4.5g IV given every 8 hours (n=63) or ticarcillin/clavulanate 3.2g given every 8 hours (n=61) for 7 to 14 days. The overall efficacy rates were 90.5% in the piperacillin-tazobactam group and 88.5% in the ticarcillin/clavulanate group. The clinical efficacy rates by type of infection for acute LRTI, were 87.5% and 85.4% for piperacillin-tazobactam and ticarcillin/clavulanate, respectively. A total of 101 pathogens were isolated from the subjects. The overall bacterial eradication rates were 90.2% and 92.0% for the piperacillin-tazobactam and ticarcillin/clavulanate groups, respectively. None of these differences were statistically significant. Adverse events definitely or possibly related to therapy occurred in 7.69% (5/65) of piperacillin-tazobactam subjects and 8.06% (5/62) of ticarcillin/clavulanate subjects.

Comparison of piperacillin-tazobactam vs ceftazidime

One study conducted in Italy used intramuscular (IM) administration in subjects with acute exacerbation of chronic bronchitis (AE-COPD). A comparative open-label multicenter study was carried out in Italy with piperacillin-tazobactam and ceftazidime, both administered IM, in hospitalized and day-hospital patients with AE-COPD. Of the 130 patients (104 males, 26 females, average 64.25 years) enrolled in 8 Pneumology centers, 67 received piperacillin-tazobactam 2.25g IM administered every 12 hours, and 63 patients received ceftazidime 1g IM administered every 12 hours for 5 to15 days. A total of 126 patients were clinically evaluable with a recovery or improvement rate of 98.5% in the piperacillin-tazobactam group and of 90% in the ceftazidime group. One (1) and 6 failures were reported in piperacillin-tazobactam and ceftazidime group, respectively. The most frequently isolated pathogens were *Streptococcus pneumoniae* and *Haemophilus* spp. The eradication rate was 89% in the piperacillin-tazobactam and 84% in the ceftazidime group. No significant adverse events were reported in both groups; 3 patients in the piperacillin-tazobactam and 4 in the ceftazidime group showed clinically not relevant modifications of liver and hepatic functionality.
Study D68 P5 (1988 to 1989) was terminated early by the sponsor after enrolling 26 subjects. This was a study comparing piperacillin-tazobactam and ceftazidime for subjects with hospital acquired LRTI. Piperacillin-tazobactam was dosed at 3.375g IV given every 6 hours. The study was terminated due to suboptimal response in the piperacillin-tazobactam group. The study interim analysis concluded that the clinical and bacteriological responses were higher in the comparator group.

The MAH further discussed the efficacy of piperacillin-tazobactam against the organisms that cause CAP. CAP is likely to be caused by *S. pneumoniae*, which accounts for between 20 and 60% of all cases of CAP and is also the most important pathogen in terms of mortality. *H. influenzae* and *Moraxella catarrhalis* are more common in elderly patients with chronic obstructive pulmonary disease (COPD) and in smokers, accounting for 3–10% of CAP episodes. Aerobic Gram-negative bacilli such as *Klebsiella* spp., *P. aeruginosa* and *E. coli* are infrequently considered to be causal pathogens of CAP. *S. aureus*-associated CAP occurs mainly as a complication of influenza. The MAH also stated that the use of piperacillin-tazobactam is limited to intravenous administration and therefore, in general, is primarily used in the management of hospitalised patients, with pneumonia due to bacteria known to be sensitive to piperacillin-tazobactam that requires intravenous antibiotics. Some of these hospitalised patients may be admitted to hospital with pneumonia (CAP). If the indication is limited to HAP such patients admitted to hospital with CAP, of a severity requiring hospitalisation would not be included in the indication. The MAH also discussed the guidelines of the Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS) and the British Thoracic Society (BTS) as well the view of the British Society for Antimicrobial Therapy (BSAC) Council and the European Respiratory Society (ERS) task force in collaboration with ESCMID (European Society for Clinical Microbiology and Infectious Diseases).

The CHMP noted that the studies submitted in the context of the initial MAA were not discussed or presented in detail by the MAH. The non comparative studies were performed involving patients with respiratory tract infections including lower respiratory tract infections (including pneumonia) and acute

exacerbation of chronic bronchitis (AECB). The CHMP considered that AECB could not be accepted due to the lack of a superiority study. One of the the two randomised trials that compared piperacillin-tazobactam to ticarcillin/clavulanate employed the US dosing regimen and insufficient details were submitted to allow the assessment of the findings. The second study employed the EU dose regimen but the study enrolled a mixed patient population and insufficient details were submitted to support the conclusion that efficacy was demonstrated specifically in the sub-population with CAP.

1.1.2 Hospital acquired pneumonia (HAP)

Hospital-acquired pneumonia (HAP) is a respiratory infection developing more than 48 h after hospital admission. HAP can be divided into early- and late-onset. Early-onset disease occurs within 4–5 days of admission and is more likely to be caused by community-type pathogens than the later-onset infections, which are more often caused by organisms such as Gram-negative aerobic rods and MRSA. In a proportion of patients, HAP is associated with mechanical ventilation, and is commonly known as ventilator-associated pneumonia (VAP). VAP can be divided into early- and late-onset. Early-onset VAP occurs during the first 4 days of mechanical ventilation when the pneumonia is often caused by typical community organisms. Late-onset VAP develops ≥ 5 days after the initiation of mechanical ventilation. The most common pathogens known or suspected to cause HAP are *P. aeruginosa*, *S. aureus* and Enterobacteriaceae (especially *Klebsiella*, *E. coli* and *Enterobacter)*. The MAH presented a number of studies to support this indication.

Piperacillin-tazobactam vs imipenem/cilastatin

A randomised, double-blind, multicenter (Wyeth study 0910A7-303-US/CA, CSR-44881) study was conducted (1997 to 2001) to evaluate the efficacy and safety of piperacillin-tazobactam 4.5g given every 6 hours compared to imipenem/cilastatin 500 mg given every 6 hours for the treatment of nosocomial pneumonia. Subjects in both groups also received tobramycin at least until the identity of the baseline pathogen was determined. A total of 437 subjects were enrolled; of these, 197 subjects could be analyzed for the primary efficacy endpoint, defined as clinical response at the test-of-cure (TOC) visit. Sixty-eight percent (68 %) of the efficacy-evaluable (EE) subjects in the piperacillin-tazobactam group (n=98) and 61% of the EE subjects in the imipenem/cilastatin group (n=99) were considered cured at the TOC visit . Results for non-ventilated subjects were 83% vs 69% for piperacillin-tazobactam and imipenem/cilastatin, respectively. Results for ventilated subjects were 64% vs 58% for piperacillin-tazobactam and imipenem/cilastatin, respectively. Although the cure rates were higher for subjects treated with piperacillin-tazobactam compared with imipenem, the difference was not statistically significant. The coadministration of antibacterial agents other than the study drugs was the primary reason for nonevaluability of subjects. No statistically significant differences were noted between groups in the use of nonstudy antibacterial agents. In both the EE and Intent to Treat (ITT) populations, the microbiological response rates were comparable between groups. The most commonly isolated pathogens from the EE subjects included *Staphylococcus aureus*, *Haemophilus influenzae*, *P. aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Acinetobacter baumannii*. The frequency of reported adverse events was similar in both treatment groups. It was determined that piperacillin-tazobactam 4.5g given every 6 hours plus an aminoglycoside was comparable in efficacy to imipenem/cilastatin 500 mg given every 6 hours plus an aminoglycoside for the treatment of nosocomial pneumonia.

In a randomised double-blind, comparative efficacy and safety study (Jaccard et al (1998) compared the safety and efficacy of piperacillin-tazobactam 4.5g TID and imipenem/cilastatin 500 mg QID in subjects with nosocomial pneumonia or peritonitis, conducted at 3 Swiss hospitals. Among the 154 nosocomial pneumonia subjects, 75 were treated with piperacillin-tazobactam, and 79 were treated with imipenem/cilastatin. In the treatment of nosocomial pneumonia, success was achieved in 83% and 71% of piperacillin-tazobactam and imipenem/cilastatin subjects, respectively (p = 0.09). However, in a subgroup analysis of subjects with nosocomial pneumonia due to *P. aeruginosa* (alone or in combination with other organisms), success was significantly greater in the piperacillin-tazobactam-treated group (90.5% [19/21]) compared to the imipenem/cilastatin-treated group (50% [12/24], p = 0.004). In addition, the investigators found that of the imipenem/cilastatin-treated subjects infected with *P. aeruginosa*, treatment failures were due to the development of resistance while on therapy. Diarrhea was reported more frequently in the piperacillin-tazobactam group as compared to the imipenem/cilastatin group (10/151 vs. 2/162; p = 0.002). The investigators concluded that monotherapy with piperacillin-tazobactam at a dose of 4.5g given every 8 hours for the treatment of nosocomial pneumonia was both safe and effective, with increased efficacy for the treatment of *P. aeruginosa* infections over imipenem/cilastatin.

A randomised, double-blind, multicenter, multinational study Schmitt et al (2006) evaluated the safety and efficacy of piperacillin-tazobactam 4.5g given every 8 hours and imipenem/cilastatin 1 g/1g given every 8 hours in subjects with nosocomial pneumonia. This study was terminated early due to slow enrollment, but 221 subjects were enrolled and randomised (110 subjects in the piperacillin-tazobactam arm and 111 subjects in the imipenem/cilastatin arm). Subjects in both arms received an aminoglycoside if *P. aeruginosa* was present. At the last day of treatment 71.0% of subjects in the piperacillin-tazobactam arm had a clinical response compared to 77.3% in the imipenem/cilastatin arm. At the second follow-up, which occurred 14 days after the end of treatment, 59.8% of subjects in the piperacillin-tazobactam arm were considered to have a positive clinical response compared to 66.4% in the imipenem/cilastatin arm. Adverse events occurred equally in both arms with diarrhea and fever being the most commonly reported in the piperacillin-tazobactam arm and increased alkaline phosphatase, nausea, and vomiting being the most commonly reported events in the imipenem/cilastatin arm.

Piperacillin-tazobactam plus an aminoglycoside vs ceftazidime plus an aminoglycoside

In an open-label, prospective, multicenter, randomised trial in Spain, Alvarez-Lerma et al (2001) evaluated the efficacy and safety of amikacin 15 mg/kg/day combined with either piperacillin-tazobactam 4.5g IV given every 6 hours or ceftazidime 2g IV given every 8 hours for the treatment of nosocomial pneumonia in 124 intensive care subjects requiring mechanical ventilation. There were 109 subjects evaluable for clinical response (piperacillin-tazobactam, n=83; ceftazidime, n=26) and 70 for microbiological response (piperacillin-tazobactam, n=50; ceftazidime, n=20). In the clinically evaluable subjects, cure or improvement occurred in 63.9% of subjects in the piperacillin-tazobactam group and in 61.5% of subjects in the ceftazidime group (p =0.831). The most commonly isolated pathogens included *P. aeruginosa*, followed by methicillin-susceptible *S. aureus* and *H. influenzae*. Eradication or presumed eradication was reported as 68.9% and 65.0% in the piperacillin-tazobactam and ceftazidime groups, respectively (p =0.757). Adverse effects possibly or probably related to study treatment were observed in 23.9% and 13.9% of piperacillin-tazobactam- and ceftazidime-treated subjects, respectively.

Brun-Buisson et al (1998) conducted a randomised multicenter study to compare piperacillin-tazobactam plus amikacin with ceftazidime plus amikacin in the treatment of ventilator-associated pneumonia (VAP). A total of 204 subjects were enrolled and randomised to receive either piperacillin-tazobactam 4.5g IV QID or ceftazidime 1g IV QID both combined with amikacin 7.5 mg/kg twice daily. From the 204 subjects enrolled, 115 subjects were evaluable (piperacillin-tazobactam, n=51; ceftazidime, n=64). Subjects in both treatment groups were similar for duration of mechanical ventilation and disease severity. Among confirmed episodes of VAP, 67% were of late onset (>5 days) and 76% of subjects had previously received antibacterial agents. Confirmed VAP was due to Gram-negative bacteria in 68% of subjects. Thirty-seven percent (37%) of all infections were polymicrobial. *P. aeruginosa* contributed to infection in 32% of episodes. It was determined that the two regimens were similar in clinical and bacteriological cure rates and mortality rates and frequency of adverse events; however, fewer bacteriological failures (resistance, relapse, superinfection or persistence) were seen in the piperacillin-tazobactam-treated versus the ceftazidime-treated group (33% vs 51%, respectively; P =0.05). The investigators concluded that piperacillin-tazobactam with amikacin was safe and effective for empiric treatment of VAP.

Comparison of piperacillin-tazobactam plus an aminoglycoside vs ceftazidime plus an aminoglycoside

In an open-label, multicenter North American trial (1989 to 1992), a total of 300 subjects (D68 P36) with a clinically- or bacteriologically-confirmed diagnosis of hospital-acquired LRTI were randomised to treatment with either piperacillin-tazobactam 3.375g IV given every 4 hours or ceftazidime 2g IV given every 8 hours. In addition, all subjects received tobramycin 5 mg/kg/day (or amikacin 15 mg/kg/day if the isolated organism was not susceptible to tobramycin) until *P. aeruginosa* was excluded as a pathogen. Enrolled subjects had either acute bacterial pneumonia or acute purulent bronchitis; significantly more subjects had pneumonia in the piperacillin-tazobactam arm (87%) as opposed to the ceftazidime arm (72%).

Among evaluable subjects, the rates of clinical cure or improvement at endpoint were 74% (58/78) and 50% (29/58) for the piperacillin-tazobactam- and ceftazidime-treated subjects, respectively (p=0.006). Similar results were observed for bacteriologic response (eradication documented and eradication presumed) at endpoint, with rates of 65% (51/78) for subjects receiving piperacillin-tazobactam and 38% (22/58) for subjects receiving ceftazidime (p=0.003). In the evaluable subjects, *Haemophilus influenzae, Staphylococcus aureus,* and *P. aeruginosa* were the most frequently isolated baseline pathogens. At the endpoint evaluation, 22/22 (100%) and 5/10 (50%) of *H. influenzae*, and 11/16 (69%) and 5/15 (33%) of *S. aureus* isolated at baseline were eradicated in the piperacillin-

tazobactam and ceftazidime treatment arms, respectively. There was a statistically significant difference (p=0.002) in eradication rates for *H. influenzae* in favor of piperacillin-tazobactam at the endpoint evaluation. There were 22 evaluable subjects with *P. aeruginosa* at baseline. At endpoint, 67% (8/12) of subjects treated with piperacillin-tazobactam compared to 60% (6/10) of subjects treated with ceftazidime had a favorable clinical outcome. Bacterial eradication occurred in 67% (8/12) of piperacillin-tazobactam subjects versus 30% (3/10) of ceftazidime subjects. A significantly greater number of deaths occurred in the ceftazidime arm (24 vs. 12; p=0.03). Failure to control infection appeared to be the cause of death in 7/24 deaths in the ceftazidime arm and 1/12 deaths in the piperacillin-tazobactam arm. Study discontinuations due to adverse experiences or laboratory abnormalities occurred in 2.6% (4/155) and 4.8% (7/145) of piperacillin-tazobactam- and ceftazidime-treated subjects, respectively. Piperacillin-tazobactam plus tobramycin was more effective than and as safe as ceftazidime plus tobramycin for the treatment of nosocomial lower respiratory tract infections.

Piperacillin-tazobactam plus amikacin vs clindamycin and aztreonam plus amikacin

Raad et al (2001) conducted a prospective, randomised study to evaluate the use of piperacillin-tazobactam 4.5g IV given every 6 hours versus aztreonam 2g IV given every 8 hours with clindamycin 900 mg IV given every 8 hours (Cl/Az) for the treatment of postoperative nosocomial pneumonia in non-neutropenic cancer subjects. Amikacin 500 mg IV given every 12 hours was added to each study arm until *P. aeruginosa* was ruled out. Demographic characteristics were comparable between the 52 subjects enrolled in the study (30 in the piperacillin-tazobactam group; 22 in the Cl/Az group). Gram-negative organisms were responsible for 21/29 cases (72%) of nosocomial postoperative pneumonia associated with an identified bacterial organism. *Serratia marcescens*, *Enterobacter* species, *P. aeruginosa*, and *K. pneumoniae* were the predominant Gram-negative organisms, while the most common Gram-positive organisms were β-hemolytic streptococci and *S. aureus*. A favorable clinical response associated with a definite or presumed microbiological eradication of the infection occurred in 86% and 83% of the Cl/Az and piperacillin-tazobactam subjects, respectively. Subjects in the Cl/Az group required a mean duration of treatment of 8.1 days; whereas, the piperacillin-tazobactam group required 6.8 days; this difference was not statistically significant. A response rate of 75% in the Cl/Az group and 67% in the piperacillin-tazobactam group was achieved for Gram-negative pneumonia. The crude mortality rate was comparable between the 2 regimens; however, a higher rate of death related to nosocomial pulmonary infection was seen in the piperacillin-tazobactam group (p =0.1). The differences in response rate for Gram-negative pneumonia and rate of death may be explained by a higher frequency of severe pneumonia that resulted in intubation in the piperacillin-tazobactam group compared to the Cl/Az group. In conclusion, efficacy was comparable between the two regimens. However, the study was not powered to detect small differences in responses between the two groups.

Piperacillin-tazobactam vs doripenem

A prospective, randomised, open-label, multicentre study (J&J Registration Study; Rea-Neto, et al) was performed to evaluate the efficacy and safety of doripenem 500 mg every 8 hours compared to piperacillin-tazobactam 4.5g IV given every 6 hours in adult subjects with nosocomial pneumonia. After a minimum of 72 hours of IV therapy, subjects could be switched to oral levofloxacin or an alternative oral antibacterial agent (based on pathogen susceptibility) if four predetermined criteria were met. Vancomycin therapy was permitted if infection with methicillin-resistant *S. aureus* (MRSA) was suspected, and amikacin therapy was recommended in both treatment arms for *P. aeruginosa* infection in at-risk subjects (based on the recommendation for the addition of an aminoglycoside with piperacillin-tazobactam in subjects with known or suspected *P. aeruginosa* infection). Both therapies were to be discontinued if the pathogen was not confirmed by culture results. The primary efficacy analyses of the study were to establish whether doripenem was noninferior to piperacillin-tazobactam in both the clinically evaluable (CE) and clinical modified intent-to-treat (cMITT) populations. Subjects in both groups were treated for a median of 11 days. Clinical cure rates in the CE population were 81.3% (109/134) and 79.8% (95/119) in the doripenem and piperacillin-tazobactam treatment groups, respectively. Results were similar in the cMITT population between groups. Clinical cure rates in various subgroups (gender, age) were generally similar; however, compared to piperacillin-tazobactam cure rates in the doripenem arm were higher in subjects with VAP and lower in subjects with APACHE II scores >15. Both groups were small (<30 subjects in both VAP arms and in the piperacillin-tazobactam arm of APACHE II scores >15), limiting statistical analyses. In the microbiologically evaluable population, the clinical cure rates at the test-of-cure visit were 82.1% (69/84) and 78.3% (65/83) in the doripenem and piperacillin-tazobactam arms, respectively. Favourable microbiologic outcome rates against the most commonly isolated pathogens, including *P. aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* were higher with doripenem than with piperacillin-tazobactam, but did not reach statistical significance. Adverse events were reported in approximately 77% of subjects in the overall ITT population. The incidence of drug-related adverse events was approximately 17% and was similar between treatment groups.

Comparison of piperacillin-tazobactam vs levofloxacin (750 mg once daily)
In a multicenter, open-label study of HAP (Sanofi-aventis registration study), levofloxacin 750 mg once daily was compared to piperacillin/ tazobactam 4.5g IV given every 8 hours. Subjects were treated for 10 to 14 days. Overall, 460 subjects were included, and the clinical per protocol population included 256 subjects. The primary endpoint was the clinical cure rate in the clinical per protocol population at the test of cure (TOC) visit 3 to 8 days post therapy. Clinical cure rates at the TOC visit were 80.3% (102/ 127) for Levofloxacin, and 81.4% (105/ 129 for piperacillin/ tazobactam. Bacteriologic outcome in the per-protocol population was a secondary endpoint, and it was 73.7% (42/ 57) in the Levofloxacin group, and 57.7% (41/71) in the piperacillin/ tazobactam group. Adverse events occurred in 18.9% of subjects in the Levofloxacin group, and in 16.6% of subjects in the piperacillin/ tazobactam group. Diarrhea was the most common adverse event in both groups.

The CHMP noted the comparative studies presented which included patients with HAP only, HAP including VAP or VAP only. These studies used a number of different regimens of Tazocin and a variety of comparators, each administered with or without an aminoglycoside in different studies. The CHMP considered that the total evidence suggests that 4.5 g administered either 8 hourly, or preferably 6 hourly, provides satisfactory efficacy in the treatment of patients with HAP and VAP. It is expected that piperacillin-tazobactam would have to be combined with an aminoglycoside or a fluoroquinolone in patients with infections caused by *P. aeruginosa*. Therefore, the CHMP considered that there is sufficient evidence to support the use of piperacillin-tazobactam in the treatment of HAP and VAP. While the higher daily dose is likely preferable there is some evidence that 8-hourly dosing may be sufficient in selected patients. It is proposed that the dose regimen may be left open for prescribers to choose depending on the patient characteristics. A statement should be added to encourage co-administration with an additional antibacterial agent active against *P. aeruginosa* when this is the known or suspected pathogen.

1.1.3 Other Lower respiratory tract infections

No additional data were presented to support other LRTI indications.

Overall discussion on lower respiratory tract infections

The CHMP considered that the MAH provided satisfactory evidence demonstrating the efficacy of piperacillin-tazobactam in the treatment of lower respiratory tract infections, including nosocomial pneumonia and community acquired pneumonia. The indication is also currently approved in the majority of European countries. In several countries, the agent is only approved for nosocomial pneumonia or severe nosocomial pneumonia, i.e. in these countries the drug is not considered appropriate for the treatment of CAP. The CHMP considered Tazocin to be a very valuable agent due to its broad antibacterial activity including many Gram-positive and Gram-negative pathogens, including anaerobes as well as several multi-drug resistant organisms common in nosocomial infections such as *P. aeruginosa,* which is a ground for not using it in less severe infections, where more appropriate alternatives are available. As the agent is parenterally administered, it is mainly used in severely ill patients and the CHMP considered that piperacillin-tazobactam should be reserved for cases of CAP that require hospitalisation. In conclusion, since the safety profile of Tazocin is considered relatively favourable and at least comparable to that of the carbapenems, also in terms of driving antimicrobial resistance, the CHMP considere*d that f*ollowing discussions within the CHMP drafting group, taking into account the extensive clinical experience and despite the limited data, Tazocin was considered to cover most of the organisms responsible for causing severe CAP. Based on the assessment of the total data on CAP and HAP (including VAP) and taking into consideration the discussions with the CHMP drafting group, the CHMP adopted the following harmonised indication:

"Severe pneumonia including hospital-acquired and ventilator-associated pneumonia"

1.2 Urinary tract infections

The majority of uUTIs in women are caused by facultative faecal flora, predominantly *E. coli* which is isolated in >80% of cases followed by *Staphylococcus saprophyticus* in 5 to 10% of cases. Uncomplicated UTIs are usually treated with oral antibacterial agents; however acute pyelonephritis is also treated with parental antibacterial agents. A complicated urinary tract infection (cUTI) is an infection associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease that interferes with host defence mechanisms, which increase the risks of acquiring infection or of failing therapy. Complicated UTIs are also frequently

associated with the presence of a urinary catheter. A broad range of bacteria can cause a cUTI. The bacterial spectrum is much larger than in uUTIs and bacteria are more likely to be resistant to antibacterial agents. Enterobacteriaceae are the predominant pathogens, with *E.coli* being the most common pathogen. However, *P. aeruginosa* and Gram-positive cocci (e.g. staphylococci and enterococci) may also play an important role, depending on the underlying conditions. The MAH presented the current nationally approved indications and proposed the following harmonized indication: *"Urinary tract infections (complicated and uncomplicated)".*

The MAH described the two key studies in the initial expert report filed with the original Tazocin data package. Study D68 P514 was a multi-centre, open-label, non-comparative, safety, tolerance, and efficacy study of parenteral piperacillin-tazobactam in the treatment of hospitalized patients with complicated urinary tract infection (cUTI) and study D68 P512 was a phase III, open-label, non-comparative, multi-centre, safety, tolerance and efficacy study of parenteral piperacillin-tazobactam in the treatment of hospitalized patients with acute LRTIs, uncomplicated urinary tract infections (uUTIs), and skin and soft tissue infections. The conclusions of the clinical expert were that a very high success rate was to be expected depending on such factors as patient selection and certain aspects of clinical patient management and the data presented, when taken in consideration with the data on piperacillin as a single agent, strongly suggest that piperacillin-tazobactam is as efficacious as any broad spectrum parenteral agent in the management of cUTI. The MAH also presented additional clinical data.

Piperacillin-tazobactam vs. imipenem/cilastatin

Naber et al randomised 337 patients with cUTIs or acute pyelonephritis in a double-blind, multicentre, multinational study. Patients were treated with piperacillin-tazobactam 2.5 g given every 8 hours (n = 166) or imipenem/cilastatin 0.5 g given every 8 hours (n = 171). The majority of infections were classified as complicated urinary tract infections (86.7 % and 89.5%, respectively). Demographic characteristics were similar between groups and a high degree of homogeneity was noted between groups with regard to pre-treatment conditions. There were 327 evaluable patients (161 piperacillin-tazobactam, 166 imipenem/cilastatin). In the intent-to-treat (ITT) analysis, clinical success rates at early follow-up (5-9 days after treatment) were 83% (122/147) in the piperacillin-tazobactam group and 79.9% (123/154) in the imipenem/cilastatin group. The difference between groups was not statistically significant. Bacteriologic response rates were 57.8% (piperacillin-tazobactam) and 48.6% (imipenem/cilastatin). Lower microbiological response rates were attributed to the strict handling of missing data, which yielded higher assumed failure rates and to a significant incidence of secondary organisms. Gastrointestinal symptoms were the most commonly reported adverse events in both treatment groups. No significant differences in adverse events between the two groups were noted. This trial demonstrated equivalent bacterial and clinical efficacy between piperacillin-tazobactam and imipenem/cilastatin for the treatment of complicated urinary tract infections and acute pyelonephritis.

Piperacillin-tazobactam vs. ceftazidime

A Wyeth-sponsored phase 3, double-blind, randomised, comparative, safety, tolerance and efficacy study of parenteral piperacillin-tazobactam versus ceftazidime for the treatment of hospitalized patients with cUTIs was conducted in 10 centers in the US, and 1 center in Canada from November 1988 through December 1990 in 272 patients (D68 P8). Patients received either piperacillin-tazobactam at 3.375 grams given every 8 hours, or ceftazidime 500 mg given every 8 hours. Piperacillin-tazobactam was received by 135 patients, and 137 patients received ceftazidime. Clinical efficacy was compared at early follow-up, late follow-up, and endpoint. The favorable clinical response (cure and improved) of evaluable patients was similar in both treatment arms. They were 89% and 84% at early follow-up, 85% and 86% at late follow-up, and 80% and 75% at endpoint for piperacillin-tazobactam and the comparator respectively. The favorable bacteriological responses (eradication documented) were 54% and 71% at early follow-up, 70% and 61% at late follow-up, and 48% and 55% at endpoint. The safety evaluation revealed 6 (4.4%) of 135 piperacillin-tazobactam and 4 (3.0%) of 137 ceftazidime patients died. One ceftazidime death was considered remotely drug related. All other deaths were considered definitely not drug related. Four (3%) of the 135 piperacillin-tazobactam patients and 3 (2%) of the ceftazidime patients did not complete the study because of adverse experiences or abnormal laboratory findings considered possibly drug related in each case. The overall conclusion was that efficacy and safety were comparable in the two arms.

Noncomparative Studies

Sifuentes-Osornio and colleagues evaluated 79 adult patients with cUTIs who received piperacillin-tazobactam 4.5 g three times daily for a minimum of 5 days. Sixty-one (61) patients were clinically and bacteriologically evaluable and were treated for a mean of 9.1 days (range 5 to 15 days). The most common isolates collected before initiation of therapy were *E. coli, Enterococcus* species, *Klebsiella pneumoniae, P. mirabilis, P. aeruginosa* and *Enterobacter* spp. A favorable clinical response

was seen in 79.7% of patients; bacterial eradication was seen in 79.6% of treated patients. Six of the persistent infections were due to *E. coli* and one was due to *K. pneumoniae*. Superinfections occurred in 5 patients and were due to *K. pneumoniae* (2), *E. coli* (2), and *Candida* spp. (1). The investigators concluded that piperacillin-tazobactam was an effective and safe alternative for the treatment of complicated and non-complicated nosocomial and community-acquired urinary tract infections produced by a wide range of Gram-negative or Gram-positive microorganisms, but that further comparative trials were needed before recommending the use of piperacillin-tazobactam monotherapy for the treatment of urinary tract infections caused by *P. aeruginosa*.

Other MAH Studies

A multicenter study was carried out in Italy in patients treated with piperacillin-tazobactam 2g/0.25g given every 12 hours administered IM. Seventy (70) patients, hospitalized and in day-hospital, with mild urinary tract infections were enrolled in 3 centers (31 males, 39 females, average age = 66.7 years). Treatment duration was 5 to 12 days (average 5.89 days). All 70 patients were clinically evaluable and recovery was obtained in 97.2% of cases. Fourty-one (41) patients were microbiologically evaluable. The most frequent isolated pathogens were *E. coli* (68%), followed by *Proteus* spp. and *Proteus vulgaris* (21%). Eradication at the end of treatment was 100%. Table 41 shows eradication rate at the end of treatment by pathogens. Treatment was well tolerated: no adverse event was reported. Only some mild modifications of the laboratory values (haemochrome and hepatic functionality) were recorded, however, these did not require treatment suspension.

The CHMP noted that most member states list UTI as an indication and that in some SPCs the indication is limited to complicated UTIs. Based on the numerous clinical studies, the pharmacokinetic properties of Tazocin and its antibacterial spectrum, the efficacy of the drug is established in this indication, but the CHMP also noted that uncomplicated UTI is a very common infection and according to international guidance documents, there are several recommended treatment options, generally not including Tazocin. As already stated, piperacillin-tazobactam should be preserved for situations where a broad-spectrum agent really is required, i.e. not for the treatment of non-severe infections. The CHMP therefore considered that Tazocin is not appropriate for the routine treatment of uncomplicated urinary tract infections. Instead, the more restricted indication in complicated UTI and pyelonephritis was proposed, in line with other recently harmonised products and piperacillin-tazobactam generics as well as in compliance with clinical practice. The optimal dose is not clear from the data presented but, taking into account the pharmacokinetics of the two components of Tazocin, a dose of 2.25 g every 8 h may be sufficient. Following discussions with the CHMP drafting group and based on the total available data, the CHMP decided to restrict the indication and adopted the following indication:

"Complicated urinary tract infections (including pyelonephritis)"

1.3 Gastrointestinal, Biliary and Abdominal Infections

Generally there are two major types of intra-abdominal infections: uncomplicated and complicated. In uncomplicated intra-abdominal infection, the infectious process only involves a single organ and no anatomical disruption is present. Patients with such infections can usually be managed with surgical resection alone and antimicrobial perioperative prophylaxis. In complicated intra-abdominal infections, the infectious process proceeds beyond the organ that is the source of the infection, and causes either localised or diffuse peritonitis. cIAI is generally polymicrobial in nature and the pathogens involved will depend on the origin of the abdominal site of infection but include a wide variety of Gram-positive and Gram–negative aerobes and anaerobes, including *P. aeruginosa, E. coli* other Enterobacteriaceae, *Bacteroides spp.* and various Gram-positive cocci. The MAH presented the current nationally approved indications and proposed the following harmonised indication: "*Complicated and uncomplicated intra-abdominal infections".*

The MAH described the three key studies included in the initial expert report filed with the original Tazocin data package: D68 P521: a randomised, open-label, comparative, multi-center, safety, tolerance and efficacy study of piperacillin-tazobactam versus imipenem/cilastatin in patients with IAIs, D68 P505: a randomised, open-label, comparative, multi-center, safety, tolerance and efficacy study of parenteral piperacillin-tazobactam versus imipenem/cilastatin in the treatment of hospitalized patients with IAIs and D68 P515: an open-label, non-comparative, multi-center, safety, tolerance and efficacy study of parenteral piperacillin-tazobactam in the treatment of hospitalized patients with IAIs.

Additional clinical trials reviewed below include use of Tazocin within a dose range of 4.5 g given every 8 hours and 3.375 g given every 6 hours. Also reported is data at 4.5 g given every 6 hours in severe generalized peritonitis. The dose range in the studies reflects, in part, the variations in protocols and

disease severity evaluated, and evolution of the indication and protocols over the period of time since Tazocin was first approved in Europe for the treatment of cIAI.

Piperacillin-tazobactam has been evaluated for the treatment of cIAIs in numerous comparative and non-comparative clinical trials including appendicitis complicated by rupture, peritonitis, acute cholecystitis, acute cholangitis, intra-abdominal abscesses, and diverticulitis. Comparators have included imipenem/cilastatin, moxifloxacin, ertapenem, combination therapy such as metronidazole with ciprofloxacin, clindamycin and gentamicin, cefotaxime or cefuroxime; and triple therapy with metronidazole, gentamicin, and ampicillin or amoxicillin. The use of piperacillin-tazobactam with and without an aminoglycoside for the treatment of severe peritonitis also has been studied. Several clinical trials are summarized below.

Piperacillin-tazobactam 4.5 g 8-hourly vs imipenem/cilastatin 1 g 8-hourly

In a phase-3 Wyeth study 0910A6-302-US (GMR-33073 US), the safety and efficacy of piperacillin-tazobactam 4.5g given every 8 hours was compared to imipenem/cilastatin 1g every 8 hours in a multicenter (US), randomised, double-blind registration trial. Four hundred and twenty-two (422) subjects with IAIs including appendicitis, perforations of the stomach, small bowel, or large bowel, complicated cholecystitis and cholangitis and diverticulitis, were randomised 1:1 to receive study medication for up to 14 days. A total of 261 and 219 subjects were evaluable for clinical and bacterial efficacy, respectively. The 2 treatment groups were similar with respect to most baseline variables; however, the mean baseline Acute Physiologic and Chronic Health Evaluation (APACHE) II score of subjects in the piperacillin-tazobactam treatment group was significantly higher than that in the imipenem/cilastatin group (6.2 vs 5.3, respectively).

At the early follow-up visits (1 to 27 days post-treatment), the clinical cure rates were 74% and 78% for the piperacillin-tazobactam and imipenem/cilastatin groups, respectively. At the TOC visit (≥ 28 days after treatment), the cure rate was 72% in the piperacillin-tazobactam group as compared to 73% of subjects who received imipenem/cilastatin (p=0.889). The bacterial eradication rates at the early follow-up visit were 70% for the piperacillin-tazobactam-treated subjects and 77% for the imipenem/cilastatin-treated subjects. At the TOC visit, the rates were 67% and 74% among the evaluable subjects in the piperacillin-tazobactam and imipenem/cilastatin groups, respectively (p=0.282). The most common adverse events (reported by > 10% of subjects) were diarrhoea, nausea, and vomiting. The incidence of specific adverse events was similar between the two groups, with the exception of lung edema, which was reported in 4% (8/211) of piperacillin-tazobactam-treated subjects and <1% (1/211) of imipenem/cilastatin-treated subjects. Monotherapy with piperacillin-tazobactam 4.5g given every 8 hours was shown to be as effective as imipenem/cilastatin 1g/1g given every 8 hours for the treatment of intra-abdominal infections, with a similar safety profile.

Niinkoski, et al conducted a multicentre study comparing piperacillin-tazobactam 4.5 g given every 8 hours with imipenem/cilastatin 1 g given every 8 hours for the treatment of patients hospitalized with a clinically- or bacteriologically-confirmed diagnosis of IAI. The study was conducted at 5 sites and 86 patients were evaluated (47 piperacillin-tazobactam, and 39 imipenem/cilastatin). A favorable clinical response in the clinically evaluable population was 87% for piperacillin-tazobactam and 77% for imipenem/cilastatin. The bacteriologic eradication rate among the bacteriologically evaluable patients was 100% for piperacillin-tazobactam and 89% for imipenem/cilastatin. The eradication rate of pathogens isolated from subjects evaluable by biologic factors was 100% from the piperacillin-tazobactam group, and 96% from the imipenem/cilastatin group. In the piperacillin-tazobactam group, the incidence and type of adverse reactions were similar to piperacillin alone. The authors concluded piperacillin-tazobactam was safe and efficacious in patients hospitalized with intra-abdominal infections.

Piperacillin-tazobactam vs ertapenem

Solomkin et al performed a double-blind, multinational, randomised trial comparing ertapenem 1g given once daily with piperacillin-tazobactam 3.375 g given every 6 hours for complicated intra-abdominal infections requiring operative or percutaneous intervention. The primary analysis was performed on the microbiologically evaluable population. A total of 193 subjects in the piperacillin-tazobactam group and 203 subjects in the ertapenem group were determined to be microbiologically evaluable. Polymicrobial infections were present in the majority of subjects (84.6%); the most frequently isolated organisms were *E. coli*, *B. fragilis* and other *Bacteroides* spp, and *Clostridium* spp.

Favorable clinical and microbiological responses were demonstrated in 176 of 203 (86.7%) subjects treated with ertapenem compared to 157 of the 193 (81.3%) subjects treated with piperacillin-tazobactam. Ertapenem provides limited coverage against *P. aeruginosa* and enterococci; as expected, susceptibility rates for *P. aeruginosa* and enterococci were lower for ertapenem than for piperacillin-

tazobactam, as were clinical response rates for *P. aeruginosa* [19/26 (73.1%) and 23/26 (88.5%), respectively]. Both agents were generally well-tolerated and reported adverse events were similar between groups. Two subjects in the ertapenem group developed *Clostridium difficile*-associated diarrhoea, compared to no reported cases in the piperacillin-tazobactam group; however, no subjects discontinued treatment due to diarrhoea. A total of 31 deaths were reported: 20 in the ertapenem group versus 11 in the piperacillin-tazobactam group. The deaths occurred in subjects with significant co-morbidities and/or severe baseline infections and none of the deaths were attributed to either drug by the investigators. In this study, the efficacy of ertapenem was equivalent to piperacillin-tazobactam for the treatment of complicated intra-abdominal infections.

A similar study comparing ertapenem 1g given once daily to piperacillin-tazobactam 3.375 g given every 6 hours in 494 subjects with cIAIs was conducted by Namias et al. Subjects were stratified according to the severity of disease (APACHE II score $\leq$10 or >10). The primary efficacy analysis was performed on the microbiologically evaluable population at two weeks after discontinuation of intravenous antibacterial agent therapy, adjusted for APACHE score and site of infection. Two-hundred and thirty-one (231) subjects were microbiologically evaluable and favourable overall microbiological responses were demonstrated in 101 of 123 subjects (82.2%) in the ertapenem group and 88 of 107 (82.5%) in the piperacillin-tazobactam group. Statistically similar cure rates were observed with ertapenem arm (82.1%; n=122) and piperacillin/ tazobactam (81.7%; n=107). Both study drugs were generally well tolerated.

Piperacillin-tazobactam vs moxifloxacin

Malangoni et al conducted a prospective, double-blind multicenter trial of adult subjects with complicated intra-abdominal infections. The investigators compared sequential intravenous/oral (IV/PO) regimens of moxifloxacin 400 mg IV followed by 400 mg given orally every 24 hours versus piperacillin-tazobactam 3.375g given every 6 hours followed by amoxicillin/clavulanate 800mg/114mg given orally every 12 hours. Subjects were switched from IV to PO therapy at the discretion of the investigator. A total of 656 subjects (379 in the efficacy-valid population) were entered in the study over a period of 2.5 years. At the TOC visit, 78% of subjects in the piperacillin-tazobactam-amoxicillin/clavulanate arm (n=196) and 80% in the moxifloxacin arm (N=183) were considered clinical cures. Clinical cures by diagnosis were comparable for most of the infection types. For subjects with hospital-acquired infections, moxifloxacin provided a significantly higher cure rate (82%, 22/27) than piperacillin-tazobactam (55%, 17/31, p=0.05). Clinical cure rates for subjects with community-acquired infections were similar in both treatment arms (80% vs. 82%). The MAH provided the bacteriologic response rates in both treatment arms for the most frequently isolated pathogens. A significant limitation of this study was the choice of oral use of amoxicillin/clavulanate in the piperacillin-tazobactam arm. The incidence of adverse events was similar for the two treatment arms. The most frequently reported adverse events in both arms of the trial were nausea, constipation, hypokalemia, abdominal pain, insomnia, anemia, and diarrhoea.

Piperacillin-tazobactam vs cefuroxime + metronidazole

Ohlin et al conducted a multicentre, randomised, open-label trial to assess the efficacy of piperacillin-tazobactam 4.5g given every 8 hours compared to cefuroxime 1.5g given every 8 hours + metronidazole 1.5g given every 24 hours for the treatment of intra-abdominal infections. A total of 205 subjects were evaluable for follow-up: 105 subjects in the piperacillin-tazobactam group and 100 in the cefuroxime-metronidazole group. The most common intra-abdominal infections treated in this study were appendicitis complicated by rupture or abscess, peritonitis, and diverticulitis. *E. coli* and *B. fragilis* were the predominant pathogens isolated. Distribution of pathogens did not differ significantly between groups. At early follow-up, 97% (102/105) of subjects in the piperacillin-tazobactam group and 94% (94/100) of subjects in the cefuroxime-metronidazole group had responded to therapy. At late follow-up (4-6 weeks after treatment), 88% (92/105) and 83% (83/100) of the piperacillin-tazobactam and cefuroxime-metronidazole groups, respectively, had remained free of infection. Reported adverse events, primarily affecting the gastrointestinal tract, were similar between groups. Both regimens were considered to be safe and effective for the treatment of IAIs.

Piperacillin-tazobactam vs piperacillin-tazobactam + amikacin

Dupont et al conducted a multicentre, prospective, randomised, open-label trial to compare the efficacy and safety of piperacillin-tazobactam alone or combined with amikacin for the treatment of severe generalized peritonitis. Piperacillin-tazobactam was administered at a dosage of 4.5 g given every 6 hours. The amikacin dosage used was 7.5 mg/kg twice daily as a 30-minute infusion. A total of 204 subjects were included in the analyses; 99 in the monotherapy group (MT) and 105 in the combination therapy (CT) group. Demographic characteristics were similar for each treatment group. Pathogens isolated from the peritoneal fluid did not differ between the 2 groups. The failure rate after

the 30-day post-treatment follow-up period (56% MT; 52% CT), the time to failure (11.3 ± 10.7 days MT; 11.5 ± 8.3 days CT), and the duration of treatment for cured subjects (9 ± 3.8 days MT; 9.3 ± 2.7 days CT) were similar in each treatment group. No difference was observed in adverse events between the two regimens.

The CHMP noted that all involved member states included the indication intra-abdominal infections, although the exact wording differed. The CHMP revised the MAH proposal to bring it in line with the current guidelines and considered that the available evidence sufficiently supports the use of Tazocin 4.5 g 8 hourly for this indication. Following discussions with the CHMP drafting group and based on the total available data, the CHMP decided to restrict the indication and adopted the following indication:

"Complicated intra-abdominal infections"

1.4 Skin and Soft Tissue Infections

Skin and soft tissue infections (SSTIs) are frequently encountered in clinical practice. SSTIs can be acute, recurrent and chronic, and occur in the community, as well as being health care-associated. SSTIs may range from 'simple uncomplicated' superficial infections, such as erysipelas, folliculitis, cellulitis, abscesses, furuncles and wound infections, to deeper 'complicated' infections, such as necrotising fasciitis, myositis, surgical site infections and gas gangrene. An SSTI is considered complicated when it involves deeper skin structures, such as fascia or muscle layers, requires significant surgical interventions or arises in the presence of significant co morbidities, such as in the presence of diabetes mellitus or HIV infections. In general, *S. aureus* including MRSA, and streptococci, are by far the most common causes of uncomplicated and complicated SSTIs. Polymicrobial infections with Gram-negative and anaerobic organisms are typically seen in complicated infections. The MAH presented the current nationally authorised indications and proposed the following harmonised indication: "*Skin and skin structure infections".*

The two key studies described in the initial expert report filed with the original Tazocin data package were study D68 P516: a multi-centre, open-label, non-comparative, safety, tolerance, and efficacy study of parenteral piperacillin-tazobactam in the treatment of hospitalized patients with skin and skin structure infections (SSSIs) and study D68 P512: a phase 3, open-label, noncomparative, multi-centre, safety, tolerance, and efficacy study of parenteral piperacillin-tazobactam in the treatment of hospitalized patients with acute LRTI, uUTI, and SSSIs. The conclusions of the clinical expert were that although the total number of bacteriologically evaluable patients was not high, the results suggest that piperacillin-tazobactam was efficacious in the treatment of SSSIs and it was not possible to say with certainty whether a lower dose is indicated in less severe infections, however, it would be reasonable to conclude that 2 g/250 mg would 'probably' be satisfactory in mild to moderate infections.

Discussion of Additional Clinical Data

Piperacillin-tazobactam vs. ticarcillin/clavulanate

Tan et al conducted a randomised, double-blind, comparative clinical trial involving 251 hospitalized subjects with SSSIs (study D68 P9, circa 1991) in 20 centres throughout the US and Canada. This study was used to support approval for the original indication for piperacillin-tazobactam for complicated SSSIs (cSSSIs) in the US, as well as the original indication for DFI in the US. Piperacillin-tazobactam 3.375 g IV given every 6 hours and ticarcillin/clavulanate 3.1 g IV given every 6 hours were administered to 153 and 98 subjects, respectively. Therapy was instituted for a minimum of 5 days and for at least 48 hours after resolution of signs and symptoms. Treatment groups were demographically similar. Types of infections were classified as cellulitis with drainage, cutaneous abscess, diabetic or ischemic foot infection, and infected wounds or ulcers with drainage. Infections were community-acquired in 85% and 91% of piperacillin-tazobactam- and ticarcillin/clavulanate-treated subjects, respectively. Most subjects (96%) in each group had infection graded as moderate or severe, with cellulitis being the most common diagnosis. Evaluability rates were 44% (67/153) and 45% (44/98) for piperacillin-tazobactam and ticarcillin/clavulanate, respectively. Monomicrobial infections were seen in 42% (28/67) and 27% (12/44) of evaluable subjects treated with piperacillin-tazobactam and ticarcillin/clavulanate, respectively. *S. aureus* was the most frequently isolated pathogen in this study. Analysis of evaluable subjects showed that 76% (51/67) of the subjects treated with piperacillin-tazobactam had a favorable (cured/improved) clinical response versus 77% (34/44) of those treated with ticarcillin/clavulanate (*P*=NS). Among evaluable subjects, bacterial eradication of *S. aureus* as a single pathogen occurred in 75% (12/16) of piperacillin-tazobactam- and 50% (3/6) of ticarcillin/clavulanate-treated subjects. Polymicrobial infections with *S. aureus* were eradicated in 68%

(17/25) and 80% (17/20) of subjects treated with piperacillin-tazobactam and ticarcillin/clavulanate, respectively. Adverse events involving the gastrointestinal tract were the most frequently reported, with 11% of subjects in each treatment group reporting such events. Diarrhoea was the most common drug related adverse event, with an incidence of 4.1% in the ticarcillin/clavulanate group and 6.5% in the piperacillin-tazobactam group. Piperacillin-tazobactam was as effective and safe as ticarcillin/clavulanate for the treatment of subjects with complicated skin and skin structure infections.

Piperacillin-tazobactam vs. clinafloxacin

In a randomised, multicenter, investigator-blind clinical trial, Siami et al evaluated piperacillin-tazobactam 3.375 g IV given every 6 hours (plus vancomycin if MRSA or enterococci were suspected) versus clinafloxacin 200 mg IV given every 12 hours for the treatment of severe SSTIs. After a minimum of 3 days of IV therapy, subjects could be switched to oral therapy (oral clinafloxacin for the clinafloxacin group; amoxicillin/clavulanate for the piperacillin-tazobactam group). A total of 213 and 196 subjects were randomised to receive clinafloxacin and piperacillin-tazobactam, respectively. Other than more subjects ≥ 65 years of age in the piperacillin-tazobactam group, demographic characteristics and baseline diagnoses were similar in the 2 groups. The predominant types of infections were cellulitis, wound infections, and diabetic foot infections. The most frequently isolated baseline pathogens were *S. aureus* (n = 139, 25 of the isolates were methicillin-resistant), *Enterococcus faecalis* (n=37), and *P. aeruginosa* (n=34). The percentage of baseline isolates resistant to clinafloxacin, piperacillin-tazobactam, and amoxicillin/clavulanate were 1.8%, 6.2%, and 20.5%, respectively. Organisms which showed resistance to clinafloxacin were MRSA and *E. faecalis*, while isolates of MRSA, *Enterobacter cloacae*, and *P. aeruginosa* showed resistance to piperacillin-tazobactam. Overall, 55% of infections were polymicrobial. At the TOC visit (6-14 days after therapy), there were 279 subjects (clinafloxacin 144; piperacillin-tazobactam 135) who were clinically evaluable and 204 subjects (clinafloxacin 108; piperacillin-tazobactam 96) who were microbiologically evaluable. Clinical cure rates at the test of cure visit were 68.8% and 65.2% in the clinafloxacin and piperacillin-tazobactam groups, respectively. Microbiologic eradication rates in the clinafloxacin-treated group (61.5%) and piperacillin-tazobactam-treated group (57.2%) were equivalent. Drug-associated adverse events were reported in 39% and 30% of subjects in the clinafloxacin and piperacillin-tazobactam groups, respectively. The most common drug-associated adverse events were phototoxicity (11%) in the clinafloxacin group and nausea (5.3%) and diarrhea (8.9%) in the piperacillin-tazobactam group. There were 21 subjects in the clinafloxacin group and 8 subjects in the piperacillin-tazobactam group who discontinued therapy due to a treatment-related adverse event (P=.032). Piperacillin-tazobactam (with vancomycin if MRSA or methicillin-resistant enterococci are suspected) was as effective as clinafloxacin for the treatment of severe SSTIs.

Piperacillin-tazobactam IV-amoxicillin/clavulanate PO vs. sequential IV/PO moxifloxacin

Giordano et al conducted a prospective, double-blind multicentre trial of adult subjects with complicated skin and skin structure infections, including DFIs. The investigators compared moxifloxacin 400 mg IV daily followed by 400 mg orally (PO) daily verses 3.375 g piperacillin-tazobactam given every 6 hours followed by 800 mg of amoxicillin/clavulanate given every 12 hours orally, subjects were switched from IV to PO therapy at the discretion of the investigator. A total of 617 (317 in the efficacy-valid population) subjects were enrolled and randomised in the study over a period of two and a half years. Infections included: abscess, cellulitis, diabetic foot infections, infected ischemic ulcers, and surgical wound infections. The average length of IV therapy was 6 days in both treatment arms. At the TOC visit 82% (153/187) of subjects in the piperacillin-tazobactam-amoxicillin/clavulanate arm and 79% (143/180) in the moxifloxacin IV/PO arm were considered clinical cures. Clinical cures by diagnosis were comparable for most of the infection types including: cellulitis, diabetic foot infections, infected ischemic ulcers, and surgical wound infections. There was a statistically significant difference in the clinical cure rates of abscesses (93% [52/56] for piperacillin-tazobactam-amoxicillin/clavulanate arm verses 79% [42/53] for moxifloxacin therapy [P = 0.04]). The most frequently isolated Gram-positive pathogens and clinical cure rates for piperacillin-tazobactam-amoxicillin/clavulanate vs. moxifloxacin IV/PO respectively, were *S. aureus* (80% [47/59] vs. 78% [50/64]), *S. agalactiae* (76% [19/25] vs. 54% [7/13]), *S. pyogenes* (67% [8/12] vs. 72%[13/18]), *E. faecalis* (75% [9/12] vs. 67% [12/18]). The most frequently isolated and clinically cured Gram-negative pathogens included: *E. coli* (92% [11/12] vs. 88%[7/8]), *K. pneumoniae* (57% [4/7] vs. 83% [5/6]), and *Proteus mirabilis* (83% [5/6] vs. 60% [3/5]). For the anaerobes *Peptostreptococcus* spp. (92% [11/12] vs. 60% [6/10]), *Bacteroides* spp. (90% [9/10] vs. 100% [9/9]), and *Prevotella* spp. (82% [9/11] and 64% [9/14]) were the most frequently isolated pathogens. The most frequently reported adverse events in both arms of the trial were diarrhoea and nausea. The most common serious adverse events included cellulitis (3 subjects in the moxifloxacin group vs. 6 subjects in the piperacillin-tazobactam group), osteomyelitis (3 vs. 6) and localized infection (4 vs. 2).

Piperacillin-tazobactam vs. ertapenem

Graham et al conducted a prospective, randomised, double-blind trial to compare the efficacy of ertapenem 1g daily versus piperacillin-tazobactam 3.375 g given every 6 hours for the treatment of complicated skin and skin-structure infections.(This was the first of two studies comparing Ertapenem to Tazocin for the indication for skin infection – below is the more recent SIDESTEP trial Ertapenem used to gain the indication for DFIs). A total of 540 subjects were randomised (piperacillin-tazobactam 266; ertapenem 274), of which 174 in the piperacillin-tazobactam group and 185 in the ertapenem group were considered clinically evaluable. Baseline demographic and disease characteristics were similar between the treatment groups. In the clinically evaluable subjects, the mean (± SD) duration of therapy was 9.8 ± 3.3 days for the piperacillin-tazobactam group and 9.1 ± 3.1 days for the ertapenem group. Skin or soft-tissue abscesses and lower-extremity infections associated with diabetes were the most common diagnoses. S. aureus was the most frequently isolated pathogen and was present in 40.8% and 37.8% of the clinically evaluable subjects in the piperacillin-tazobactam and ertapenem groups, respectively. Among the clinically evaluable subjects at the test-of-cure assessment (10-21 days after the completion of therapy), the response rates were equivalent with 84.4% of piperacillin-tazobactam- and 82.4% of ertapenem-treated subjects considered cured. Bacterial eradication rates among evaluable subjects at test of cure were 83.4% and 82.6% for the piperacillin-tazobactam and ertapenem groups, respectively. Local infusion-related complications, diarrhoea, nausea, and mild to moderate transient elevations of liver transaminase levels were the most common drug-related adverse events for both drugs. Piperacillin-tazobactam was as effective as ertapenem for the treatment of skin and skin structure infections with a similar safety and tolerability profile.

Clinical Data on piperacillin-tazobactam use in Diabetic Foot Infections

Piperacillin vs ampicillin/sulbactam

Harkless et al (CSR-0910X-100468 GMA DFI) conducted a prospective, randomised, multicentre, open-label trial comparing the safety and efficacy of piperacillin-tazobactam to ampicillin/sulbactam for the treatment of DFIs. Patients were randomised to receive either piperacillin-tazobactam 4.5 g given every 8 hours or ampicillin/sulbactam 3 g given every 6 hours. Vancomycin 1 g given every 12 hours could be added to both treatment groups if MRSA was cultured as part of a polymicrobial infection. Patients were required to have at least one full- or partial-thickness infected ulcer at or below the ankle. The subjects were also required to have purulent drainage and 2 of the following criteria: erythema, local edema, fluctuance, induration, increased local warmth, or fever. 314 subjects were enrolled in the trial at 67 sites in the United States. One hundred eighty-five subjects completed the trial and were clinically evaluable (CE). The mean duration of therapy was 8 days in the piperacillin-tazobactam group and 8.5 days in the ampicillin/sulbactam group. Demographics were similar in both treatment arms. The clinical cure rates in the CE population at the TOC, the primary efficacy endpoint, were similar between the 2 groups: 81.3% in the piperacillin-tazobactam group and 83.1% in the ampicillin/sulbactam (P = 0.124). Patients in the modified all-treated (MAT) population (n=289) with monomicrobial infections had a 71.2% clinical success rate with piperacillin-tazobactam versus 60.5% in those treated with ampicillin/sulbactam. In subjects with polymicrobial infections in the MAT population, piperacillin-tazobactam-treated subjects had a 66.7% clinical success rate while ampicillin/sulbactam-treated subjects had a 60.6% success rate. The most commonly isolated pathogens included *S. aureus*, *Streptococcus agalactiae*, *E faecalis*, and *P. aeruginosa*. Drug-related adverse events for both arms of the study were comparable in frequency and severity (primarily mild-to-moderate). There was a difference in incidence of gastrointestinal events between the 2 groups (11.6% for piperacillin-tazobactam vs 5% for ampicillin/sulbactam, P = 0.041).

Piperacillin-tazobactam vs ertapenem

Lipsky et al conducted a multicentre, double-blind, randomised, controlled trial to evaluate the safety and efficacy of ertapenem and piperacillin-tazobactam for the treatment of moderate to severe diabetic foot infections. Patients were randomised to receive ertapenem 1 g daily (followed by a saline placebo every 6 hours for 3 additional doses) or piperacillin-tazobactam 3.375 g given every 6 hours. Vancomycin could be added to either arm of the trial for suspected or proven antibacterial agent-resistant *Enterococcus* spp. or MRSA. After at least 5 days of intravenous therapy, subjects could be switched to oral therapy of amoxicillin/clavulanic acid 875/125 mg given every 12 hours, for up to 28 days of total therapy. There were no significant demographic differences in the patient population. A total of 586 subjects were randomised into the study (295 subjects in the ertapenem arm and 291 in the piperacillin-tazobactam arm), of which 445 were clinically evaluable. The clinical response rates at the discontinuation of intravenous therapy were 92% in the piperacillin-tazobactam arm and 94% in the ertapenem arm. There was no statistical difference in the clinical cure rates between treatment arms at the 10-day follow-up visit: 83% for piperacillin-tazobactam and 87% for ertapenem. No

significant difference was found between the treatment groups with regard to the bacteria isolated and the clinical response to therapy. The MAH provided the most frequently isolated pathogens and the microbiologic response. No significant differences in drug-related adverse events were noted between the treatment groups; diarrhoea, nausea, and headache were the most commonly reported events.

The MAH also submitted further data in support of the indication diabetic foot infection (DFI) The study supporting the original application was study D68 P516, a non-comparative, open-label, multicentre, safety and efficacy trial on parenteral piperacillin / tazobactam in the treatment of hospitalised patients with skin and skin structure infections. A total of 136 patients with a clinically or bacteriologically confirmed SSTI were enrolled and received piperacillin / tazobactam 4 g/0.5 g IV q8h for a minimum of 5 days. This study contained a patient subset of ischaemic / diabetic foot infections. The MAH provided the full study report of this study and summarised the available clinical data on piperacillin-tazobactam for the treatment of DFI. DFI has previously been regarded as a subset of SSTI, although severe DFI complicated by osteomyelitis relates also to the area of bone and joint infections. However, as foot infections in diabetic patients may be associated with conditions such as peripheral vascular disease and neuropathy, DFI is now widely considered to be a unique indication. DFI may require prolonged treatment with broad-spectrum antibiotics proven effective in this indication. The MAH also stated that distribution and tissue penetration of piperacillin / tazobactam into the interstitial space fluid of inflamed soft tissues in patients with DFI has been shown in an open-label study by means of in-vivo microdialysis (Legat et al., 2005). The penetration of piperacillin / tazobactam into bone is important for the effective treatment of DFI. In conclusion, the MAH considered that the clinical as well as microbiological outcomes in the DFI trial subsets support the use of piperacillin-tazobactam in the treatment of DFI. Finally, the MAH was of the opinion that the therapeutic value of piperacillin / tazobactam in clinical practice is further illustrated by guidelines and treatment recommendations for DFI management, in particular in moderate to severe cases (Edmonds 2009, Lipsky et al. 2004, Lipsky et al. 2007).

The CHMP was of the opinion that the safety and efficacy of Tazocin in the treatment of skin and soft tissue infections is well justified by numerous clinical studies, treatment guidelines from scientific societies and experience from clinical practice. The MAH has provided a number of clinical studies which included patients with DFI or patients with DFI as a subset of SSTIs, which show that piperacillin-tazobactam is efficacious in the treatment of moderate to severe DFI, though clinical cure rates ranged from about 40% to 80%. Studies with low response rates generally had patients with osteomyelitis in addition to DFI. Therefore the CHMP considered it acceptable to include DFI in the indication complicated SSTIs. However, the wording proposed by the MAH was not in line with the common European terminology. Following discussions with the CHMP drafting group and based on the total available data, the CHMP therefore decided to reword and restrict the indication and adopted the following indication:

"Complicated skin and soft tissue infections (including diabetic foot infections)"

1.5 Infections in Neutropenic Patients

Febrile neutropenia is defined by a single oral temperature measurement of at least 38.3°C, or a temperature of ≥38.0°C for ≥1h, often with other signs of infection, in a patient with a neutrophil count of <500cells/mm3, or a count of <1000 cells/mm3 with a predicted decrease to <500 cells/mm3. Febrile neutropenia can develop in any form of neutropenia but is generally recognised as a complication of antineoplastic chemotherapy for solid tumours and haematological malignancies. Fever is actually caused by infection in 50% of cases and at least one-fifth of patients with neutrophil counts of <100 cells/mm3 have bacteraemia. Most bacterial infections in neutropenic patients are caused by endogenous skin, oral or intestinal flora. Historically, most of the bacterial septicaemia in this patient population was due to Gram-negative organisms. While certain Gram-negative bacilli, specifically *P. aeruginosa, E. coli* and *Klebsiella* species still remain prominent causes of infection, Gram-positive bacteria now account for approximately 60-70% of microbiologically confirmed infections. Generally, there are three IV antibacterial agent regimens for the treatment of febrile neutropenia: monotherapy usually with β-lactams, two drug therapy without a glycopeptide (vancomycin) and monotherapy or two drug therapy with vancomycin. Broad spectrum antibacterial agents are usually initiated to cover Gram-negative and Gram-positive bacteria. The MAH presented the current nationally approved indications and proposed the following harmonised indication: "*Bacterial infections in neutropenic adults"*

According to the clinical expert report the one key study described in the initial expert report filed with the original Tazocin data package was study D68 P523: an open-label, non-comparative, multi-centre,

safety, tolerance and efficacy study of parenteral piperacillin-tazobactam plus aminoglycoside in the treatment of hospitalized patients with neutropenia and bacterial infections**.** Although the study report was not provided by the MAH according to the expert report, the conclusions of the clinical expert at the time was critical of the lack of a comparator group in the study and concluded that there is nothing from the study to suggest that piperacillin-tazobactam will be less efficacious than other β-lactam/aminoglycoside combinations, however, there is also nothing beyond theoretical arguments to establish the superiority of piperacillin-tazobactam compared to other such combinations. The use of piperacillin-tazobactam has been reported in adult and paediatric populations for the treatment of febrile neutropenia with and without an aminoglycoside in a number of studies. Comparators have included combination therapy of ceftazidime, cefepime, meropenem, and ceftriaxone with an aminoglycoside and monotherapy with ceftazidime, meropenem, imipenem/cilastatin, and cefepime. Several of the large-scale clinical trials are summarized below.

Piperacillin-tazobactam Monotherapy

Piperacillin/taobactam vs cefepime

In a randomised, open-label, multicentre (US, Canada, and Australia) study by *Bow et al* evaluated the use of piperacillin-tazobactam or cefepime as empirical treatment of febrile neutropenia in subjects undergoing treatment for leukaemia or hematopoietic stem cell transplantation. 528 subjects were included; 265 subjects received piperacillin-tazobactam 4.5g given every 6hours and 263 subjects received cefepime 2g given every 8 hours. Treatment success, defined as defervescence at 72 hours without treatment modification, was achieved in 57.7% of subjects on piperacillin-tazobactam and in 48.3% of subjects on cefepime (P=0.036). Success rates at the end of treatment were 39.6% and 31.6% (P=0.064) and for the test-of-cure visit (at least 7 days post-treatment), 26.8% and 20.5% (P=0.11), respectively. Prolonged severe neutropenia was more common among piperacillin-tazobactam recipients, while more cefepime recipients discontinued therapy, primarily due to adverse events. The investigators concluded that the study met its primary objective of demonstrating the non-inferiority and safety of piperacillin-tazobactam monotherapy, compared with cefepime, for the empirical treatment of febrile neutropenia in subjects with cancer.

Piperacillin/taobactam with or without addition of amikacin

A double-blind, placebo-controlled, randomised trial was conducted by *Del Favero et al* to compare piperacillin-tazobactam 4.5g given every 8 hours with or without amikacin 7.5 mg/kg BID for the empiric treatment of adults with neutropenic fever. A total of 733 subjects were considered evaluable for efficacy; 364 in the monotherapy group and 369 in the combination therapy group. Most of the subjects had acute leukaemia with profound and persistent neutropenia. Demographic characteristics did not differ significantly between the 2 groups. Overall success, defined as resolution of fever and clinical signs of infection and eradication of infecting organisms without a change in the initial regimen, was similar: 49% and 53% in the monotherapy and combination therapy groups, respectively. Response rates were comparable for subjects having clinically documented infections (53% and 43%, respectively) and fever of unknown origin (63% and 70%, respectively). The occurrence of bacteraemia was documented in 140 subjects on monotherapy and 137 subjects on combination therapy. Response rates were similar for the monotherapy and combination therapy groups, respectively, in the following types of bacteraemias: Gram-positive (27%, 32%), coagulase-negative staphylococci (17%, 18%), streptococcal and enterococcal (60%, 71%), Gram-negative (36%, 34%), and *P. aeruginosa* (14%, 12%). Factors that may have contributed to poor response rates in Gram-negative bacteraemia include low susceptibility rates (50% and 43% susceptible to piperacillin-tazobactam and amikacin, respectively) and high prevalence of *P. aeruginosa*, and lower daily dosage of piperacillin-tazobactam (given every 8 hours vs given every 6 hours). In addition, the double-blind design of the study may have prompted clinicians to modify initial treatment for cases of documented Gram-negative bacteraemia, thus contributing to the low response rate for these infections. It was concluded that piperacillin-tazobactam monotherapy was as effective as piperacillin-tazobactam plus amikacin for the treatment of febrile neutropenia in oncology subjects.

Piperacillin/taobactam with or without addition of vancomycin

In a double-blind, prospective, randomised trial, *Cometta et al* (an European Organization for Research and Treatment of Cancer (EORTC) study) evaluated whether the addition of vancomycin reduced the time to defervescence in neutropenic subjects (both adult and children) with persistent fever 48-60 hours after the initiation of empiric piperacillin-tazobactam therapy. Persistent fever was defined as an oral or axillary temperature of >38.5°C once, or >38°C twice in the previous 12 hours. Patients were excluded from randomization if one of the following conditions was present at initial enrolment: microbiologically documented Gram-negative bacterial infection; documented infection due to piperacillin-tazobactam resistant Gram-positive bacteria; documented viral, fungal, or mixed infections,

clinically documented catheter-related infections; or a documented lung infiltrate. A total of 165 subjects were randomised, after 48-60 hours of empiric piperacillin-tazobactam monotherapy, to receive either vancomycin therapy (n=86) or placebo (n=79), in addition to piperacillin-tazobactam therapy. Demographic characteristics were similar between groups, including underlying disease, duration of neutropenia, and documentation of infection. Fevers of unknown origin accounted for the majority of febrile episodes. Clinically documented infections were reported in 14 and 13 subjects in the vancomycin and placebo groups, respectively. Most cases of bacteraemia were caused by viridans streptococci susceptible to piperacillin-tazobactam and vancomycin. Resolution of fever was observed in 95% (82/86) and 92% (73/79) of subjects in the vancomycin and placebo groups, respectively (P = 0.52). The most frequent modification to therapy was the addition of open-label vancomycin or teicoplanin after the administration of vancomycin or placebo was stopped. Amphotericin B was added to the therapeutic regimen at a similar rate in both groups. The difference between the median time to defervescence after the addition of vancomycin or placebo was not statistically significant (3.5 days and 4.3 days, respectively). The occurrence of adverse events and overall mortality rates were similar between groups. Due to a reduction in the expected sample size, the power of the trial was reduced from 85% to 78%. However, the results of this study suggest that the empirical addition of vancomycin therapy to the treatment regimen of persistently febrile subjects on piperacillin-tazobactam is not justified.

The non-comparative trial evaluating the use of piperacillin-tazobactam monotherapy in subjects with febrile neutropenia, from which the above-described patient population was derived, has also been published (an EORTC study). A total of 763 subjects, including the 165 subjects randomised to receive either vancomycin or placebo, were included in the intention-to–treat (ITT) analysis. Success was defined as resolution of fever and clinical signs of infection for four consecutive days, with no relapse within 1 week of discontinuation of antimicrobial therapy, and when isolated, eradication of the infecting bacteria without treatment modification. Of the 763 subjects, 388 (51%) were treated successfully. The per-protocol (PP) analysis was conducted with 609 subjects, after excluding subjects for the following reasons: treatment modification without adequate reason (n=84); addition of an aminoglycoside within the first 60 hours (n=23); therapy for an inadequate period (n=16); fever unrelated to infection (n=7); and other conditions (n=24). In this group, the response rate was 62% (377/609), with documented clinical deterioration (n=119) as the most common reason for treatment failure. The response rate for subjects with bacteraemia was 34% and 47% in the ITT and PP analyses, respectively. The lowest response rates for subjects with bacteraemia were noted with *E. coli* and *P. aeruginosa*, although this was not due to in vitro resistance.

Combination Therapy

Piperacillin/taobactam plus amikacin vs ceftazidime plus amikacin

A prospective, randomised, controlled trial evaluated the efficacy of piperacillin-tazobactam with amikacin versus ceftazidime plus amikacin in 858 febrile episodes involving 696 granulocytopenic cancer subjects (also from EORTC). Of the evaluable febrile episodes studied, 342 episodes were treated with piperacillin-tazobactam 4.5g in adults (or piperacillin 80 mg/tazobactam 10 mg/kg in children ≤50kg) given every 6 hours plus a single daily dose of amikacin 20 mg/kg/day; and 364 episodes were treated with ceftazidime 2g (35 mg/kg in children) given every 8 hours plus amikacin 20 mg/kg/day. There was no significant difference in the overall occurrence of adverse events between treatment regimens. This study suggests that piperacillin-tazobactam plus amikacin may be more effective than ceftazidime plus amikacin for the empiric treatment of fever and bacteraemia in granulocytopenic cancer subjects.

Another multicentre trial compared piperacillin-tazobactam plus amikacin to ceftazidime plus amikacin in 222 febrile adult subjects with severe granulopenia after chemotherapy. A total of 188 evaluable subjects received piperacillin-tazobactam 4.5g given every 8 hours (n=94) or ceftazidime 1g given every 8 hours (n=94). Each group also received amikacin 7.5 mg/kg given every 12 hours. Vancomycin was added in subjects with persistent fever or septic syndrome on day 3. Amphotericin B therapy was instituted at day 5 or later if fever persisted in subjects treated with 3 antibiotics. Compared to the ceftazidime/amikacin regimen, the piperacillin-tazobactam/amikacin therapy demonstrated better control of initial fever (60.6% vs. 44.7%, P = 0.028), decreased frequency of super-infection (23% vs. 41%, P<0.008), fewer febrile days (6.8 days vs. 9.1 days, P=0.02), a greater likelihood to control the entire neutropenic episode without a change of antibiotic (16% vs. 6.4%, P=0.04) and a lower likelihood of the addition of vancomycin to existing therapy (77% vs. 90%, P=0.01). Tolerance was similar in the two treatment groups with no significant differences in toxicity.

Piperacillin-tazobactam plus tobramycin vs ceftazidime plus tobramycin

Marie et al conducted another study, with the additional objective of reducing empiric vancomycin use. Adult neutropenic subjects, who experienced a total of 247 febrile episodes, were randomised to receive ceftazidime 1g TID plus tobramycin 1.5 mg/kg BID or piperacillin-tazobactam 4 g/0.5g TID plus tobramycin 1.5 mg/kg BID. Vancomycin was added to the ceftazidime regimen in cases of persistent fever (longer than 72 hours) and only to the piperacillin-tazobactam regimen in the presence of a bacteriologically documented infection resistance. Apyrexia at 72 hours was achieved more frequently with piperacillin-tazobactam than with ceftazidime (54.4% vs. 37.6%, *P*=0.008); however, the time to apyrexia (3.6 days vs. 4.2 days) and the total number of days with fever (6 days vs. 7 days) did not differ significantly between the groups. Major infectious events occurred in 2.6% of the piperacillin-tazobactam-treated subjects versus 11.3% of the ceftazidime-treated subjects (*P*=0.02). The addition of vancomycin occurred in 54.4% of piperacillin-tazobactam-treated subjects and 77.4% of ceftazidime-treated subjects; only 40% of the piperacillin-tazobactam subjects received vancomycin according to protocol. Complete success, defined as persistent apyrexia without a change of antibiotic, was achieved in 21.9% of piperacillin-tazobactam subjects and 11.3% of ceftazidime subjects (*P*=0.02).

Piperacillin-tazobactam vs cefepime

Sanz et al evaluated the use of amikacin 20 mg/kg/d (maximum: 1.5g/d) along with either piperacillin-tazobactam 4.5g given every 6 hours or cefepime 2g given every 8 hours in 867 febrile episodes, during an open, randomised, multicentre trial. Demographic characteristics of the subjects, as well as underlying disease and infection, were comparable in both groups. In subjects with a microbiologically documented infection (MDI), success was achieved in 39% and 40% of the subjects in the piperacillin-tazobactam and cefepime groups, respectively. Success was seen in 33% of piperacillin-tazobactam and 38% of cefepime-treated subjects who had a MDI and bacteraemia. Patients with a clinically documented infection were successfully treated in 54% of subjects receiving piperacillin-tazobactam plus amikacin and 47% of subjects receiving cefepime plus amikacin. No statistically significant difference in efficacy between the two groups was found. The empiric regimen of amikacin with either piperacillin-tazobactam or cefepime was equally effective and safe in the initial management of febrile neutropenic subjects.

Piperacillin-tazobactam plus amikacin vs cefttriaxone plus amikacin

Rossini et al compared the safety and efficacy of ceftriaxone plus amikacin against piperacillin-tazobactam plus amikacin for the treatment of subjects with haematological neoplasia and severe neutropenia. Patients who met the eligibility criteria were randomly assigned to receive either ceftriaxone at a dose of 30 mg/kg/day (max of 2g per day) or piperacillin-tazobactam 200 mg/kg/day (in 4 divided doses). Both groups received amikacin 20 mg/kg/day. The patient population was well balanced between the 2 treatment groups in regard to age, sex, length of hospital stay, duration/intensity of granulocytopenia or type of intravenous line access. There were a total of 243 evaluable episodes of febrile neutropenia from 224 subjects. Success, defined as complete resolution of fever and with clinical signs of eradication of the infecting organism, was achieved in 50.8% of the episodes treated with ceftriaxone vs. 52.9% of the episodes treated with piperacillin-tazobactam. These success rates were lower than other previous studies and the authors attributed this to an increased prevalence of MRSA. There was no statistical difference between treatment groups in time to defervescence, duration of therapy, the number of subjects who were afebrile at 72 hours or in the time to clinical failure. The only significant difference in regard to the safety of these two regimens was the incidence of further infection (17.2% in the ceftriaxone group vs. 9.9% in the piperacillin-tazobactam group, *P*=0.06).

The CHMP considered the safety and efficacy of piperacillin-tazobactam as single therapy or in combination with an aminoglycoside in the management of patients with febrile neutropenia to be supported by the available clinical documentation and noted that the most reliable evidence of efficacy comes from the studies in which Tazocin was administered at 4.5 g every 6 h in conjunction with an aminoglycoside. The option of concomitant aminoglycoside administration should be guided by local practice and official guidance documents and is considered covered by the sentence *Consideration should be given to official guidance on appropriate use of antibacterial agents.* With different definitions of clinical success and variable rates of documented bacteraemia, the CHMP proposed that the indication should be worded to reflect the utility of Tazocin in the overall management of neutropenic patients who have fever that is thought to be due to a bacterial infection. The routine dose should be 4.5 g 6 hourly and it should be co-administration with an additional antibacterial agent with anti-pseudomonal activity should be recommended unless the pathogen is known. Following

discussions with the CHMP drafting group and based on the total available data, the CHMP decided to reword the indication and adopted the following indication:

"Tazocin may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection"

1.6 Septicaemia, bacteraemia

The MAH presented the current nationally approved indications and proposed the following harmonised indication: "*Bacterial septicaemia"*. Following the initial assessment, the CHMP did not accept the indication and the MAH was invited to further justify this indication. The MAH referred to the 2004 guideline "Notes for guidance on evaluation of medicinal products indicated for treatment of bacterial infections" (CPMP/EWP/558/95 rev 1), interpreting it as stating that primary septicaemia i.e. a septicaemia with no defined focus of infection is not specifically excluded and that the decision not to include septicaemia as a specific indication is based on the need to prevent antibiotics being used for septicaemia, when the indication being sought was for a single site infection, e.g. skin and soft tissue infection. If under such circumstances, the MAA included too few cases of septicaemia related to complicated skin and soft tissue infections, to assess whether a specific antibiotic is effective, it would not be appropriate to include septicaemia as an indication. In these circumstances, only one site of infection would have been adequately studied and the septicaemic complications of such a specific infection would have been inadequately studied. If the number of septicaemia cases has been low enough to be of concern, or if the pharmacokinetic characteristics of the drug may not secure sufficient concentrations in blood, this will then be mentioned in other parts of the labelling, usually in the section 'Special warnings and precautions for use'. However, in the case of an intravenous broad-spectrum antibiotic such as piperacillin-tazobactam that has been studied in multiple infections and in patients with septicaemias following various focal infections or even primary septicaemias with no focal infection, this approach does not seem appropriate or to reflect current medical practice.

Currently the 2004 guideline is under review and the indications section in particular is being reviewed, with specific reference to treatment of bacteraemia. The "Concept paper on the need for revision of the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 1)" states (EMEA/CHMP/EWP/ 435635/2008): *"Some of indications to be discussed include (but may not be limited to) treatment of bacteraemia, treatment of patients suspected to have bacterial infections on the basis of persistent fever during a period of neutropenia, catheter-related infections and eradication of carriage."*

The implication, from the guidelines is that in principle, indications have to be site-specific and infective pathogens in the blood and vascular system has not been considered to be a site of infection. This approach is appropriate when there is a known site of infection such as pneumonia or a urinary tract infection and the complications of such an infection lead to blood borne pathogens. However, the EMEA "Guideline on clinical investigation of medicinal products for the treatment of sepsis" states (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 who demonstrate all findings suggestive of sepsis, a source of infection cannot be confirmed."*

In the case of a blood borne infection due to an infected indwelling intravenous catheter (the source of infection), which is subsequently removed leaving pathogenic bacteria in the blood that require treatment to prevent "seeding" of other organs, or in patients where no focus of infection can be determined, there appears to be no approved treatment. Therefore, it would seem appropriate that a primary bacteraemia is an exception to the principle proposed in the guideline. It is unclear how, for the numerous patients with a clinical diagnosis of sepsis, bacterial pathogens isolated from the blood, but with no clear focal site of infection should be treated. The rationale for defining infection by site appears to be based on the need, following administration, for an antibiotic to penetrate to the site of infection. This is appropriate when drugs are not administered directly to the site of infection and have to be absorbed and distributed to the site of infection. However, when antibiotics are delivered directly to the site of infection, such as inhaled antibiotics for treating lung infections, bladder instillation for bladder/urinary tract infections or intraventricular administered antibiotics to treat meningitis, it is apparent that the antibiotic will reach the site of infection. Piperacillin-tazobactam is administered intravenously and therefore is administered to the primary "site" of infection, namely the blood, although other anatomical sites may also be infected and possibly require additional antibiotics.

The literature widely supports the diagnosis of a condition of bacterial septicaemia, bacteraemia, sepsis or septicaemia. A review of the current guidelines does raise the point that up to 33% of cases are due

to primary bacteraemia, i.e. no source of infection is identifiable but bacteria are detected in the blood. The primary source of the infection may become apparent only after treatment has started. In a study by Kumar et al. (2006) a total of 2,731 cases of septic shock were assessed. A total of 120 (4.4%) of these were classified as primary blood stream infection defined as bacteraemia without an identifiable source. The National Health Service in the UK estimate that in England and Wales there are 31,000 cases of severe sepsis every year, of these between 30% and 50% will die. If it is assumed that, some 30% of these patients have an unknown focus of infection that would be 9,300 patients a year that have an infection but no "site" to treat other than the bacteria circulating in the blood. Extrapolating these figures across Europe would result in some 300,000 cases of septic shock and 90,000 cases with no diagnosed focal infection.

Initiation of antimicrobial treatment is of vital importance in saving the lives of patients with sepsis as described by Dellinger and colleagues on the International Surviving Sepsis Campaign Guidelines Committee (Dellinger et al., 2008). In particular, they recommend obtaining the appropriate cultures before starting antibiotics, beginning intravenous antibiotics as early as possible, using a broad-spectrum of agents (one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source) and reassessing the antimicrobial regimen daily. Hence, it can be seen that this international group of experts consider that the initiation of therapy in a timely manner is more important that identifying the site of infection. Failure to initiate therapy results in a higher mortality rate particularly for those patients with septic shock. Follow up on the implementation of the guidelines on surviving sepsis has indicated that in hospitals where the guidelines were followed the mortality rate has dropped significantly ($p \leq 0.008$) (Levy et al., 2010).

It has been estimated that delay in initiating appropriate antibiotic therapy to patients with septic shock (severe septicaemia with associated hypotension) results in the survival rate decreasing by an average of 7.6% per hour over the first 6 hours of the delay (Kumar et al., 2006). The survival rate for patients treated in the first hour was 79.9% and therefore a delay of 4 hours in initiating therapy will result in a reduced survival rate of approximately 58%. Clearly, it is of vital importance to initiate broad-spectrum, high-dose antibiotics as soon after the diagnosis of septic shock as possible. If antibiotics are only indicated for site-specific indications and the blood is not considered to be a site, then there is a risk that delay in initiating treatment will occur while samples are taken from multiple sites trying to identify the site of infection. This process will be contra to the recommendations of the International Surviving Sepsis Campaign Guidelines Committee and could be potentially life threatening to patients with known pathogens in their blood and no focal site identified. The most common focal sites of infection that lead to septicaemia are the lungs (hospital-acquired pneumonia), urinary tract infection (complicated), intra-abdominal infections (complicated) and skin and soft tissue infections (complicated). All of these indications appear to be approvable across the European Economic Area (EEA) for piperacillin-tazobactam and therefore, even with no focal site proven, the probability is that one of these sites will be the focus of infection. Therefore, initiating empirical early treatment with an effective broad-spectrum antibiotic is appropriate for the management of the 30% of patients with septicaemia and no focal site identified. Piperacillin-tazobactam is a broad-spectrum antibiotic active against Gram-positive and Gram-negative pathogens, including both aerobes and anaerobes.

The MAH noted that the main issue is the validity of the indication. Currently, 21 of the EEA member states have some form of indication for bacterial septicaemia and only six member states do not include such an approval for piperacillin-tazobactam. Removal of the indication will reduce the number of drugs available for use in treating severely ill patients in 21 member states and potentially delay essential therapy while a site of infection is sought, which does not reflect current medical practice. Such delay in initiating therapy will potentially jeopardise the lives of several thousand patients in the EU who have primary septicaemia or septic shock. From a medical point of view, the principle of the guideline does not appear to be in line with medical needs or current medical practice. As discussed elsewhere in this response document, piperacillin-tazobactam has been associated with a lower incidence of *C. difficile* infection and a lower incidence of emergence of resistance of certain infections (MRSA, VRE, and gram negatives including ESBLs) when used in place of certain other broad-spectrum antibiotics. Thus, empirical use in the indication primary bacterial septicaemia or septic shock may be a valuable and important option. The MAH acknowledged that bacterial septicaemia may be a very broad indication and therefore proposed to qualify this to specify primary bacterial septicaemia or septic shock in line with current medical practice. In conclusion, the MAH proposed the following harmonised indication: *"Patients with primary bacterial septicaemia or septic shock demonstrated or suspected to be due to susceptible bacteria"*

While the CHMP acknowledged that several studies have demonstrated the safety and efficacy of Tazocin in the management of patients with septicaemia, and that the use of broad-spectrum agents such as piperacillin-tazobactam is widely used in clinical practice in these situations, the CHMP could not accept the terms "sepsis" or "*septicaemia* as stand alone indications according to current EU guiedlines. The NfG on "Evaluation of Medicinal Products indicated for the Treatment of bacterial Infections" (CPMP/EWP/558/95 rev 1, 2004) states that indications should be site-specific and septicaemia is generally a complication (secondary condition) to the primary site infection. In the indicated primary conditions, Tazocin has been demonstrated to be effective with or without bacteraemic complications. Accordingly, in the light of previous recommendations from experts and to be consistent with recent EU assessments, "septicaemia" was not considered acceptable as a stand-alone indication. The CHMP discussed this topic exhaustively and considered that a possible indication for use of Tazocin in the management of patients with a suspected or proven bacteraemia in association with clinical signs and symptoms of systemic infection may be acceptable, provided that the MAH provided appropriate data. The MAH was requested to summarise the evidence that might support a possible indication.

Original Studies In Different Indications

The MAH conducted a prospective meta-analysis in patients with clinically or bacteriologically documented concomitant infections, in support of the use of Tazocin in bacteraemia / septicaemia. Patients with positive blood cultures were pooled for further analysis from a total of nine clinical pivotal studies, comprising the following types of infectious diseases: IAI, SSTI, lower respiratory tract infections (LRTI), and UTI as well as infections in neutropenic patients. Of the 1,110 patients treated with piperacillin / tazobactam in these trials, bacteraemia / septicaemia was documented in a total of 142 patients. Patients were also treated with an aminoglycoside, and the data were presented for patients undergoing treatment with piperacillin-tazobactam only ('monotherapy') and for patients undergoing treatment with piperacillin-tazobactam combined with an aminoglycoside ('combination therapy'). There were a total of 94 patients on monotherapy and 48 patients on combination therapy. The MAH stated that the distribution of demographic characteristics was homogeneous. Approximately 50% of the patients were considered clinically evaluable, both in the group treated with monotherapy and the one using the combination, while only 34% and 48%, respectively, were bacteriologically evaluable. The most frequent reasons for clinical non-evaluability were inadequate dosage and the use of other antibiotics before and during the study. The low percentage of bacteriological evaluability was due, in particular, to the lack of a follow-up blood culture after treatment.

Clinical Response:
The percentages of favourable clinical responses among clinically evaluable patients were 86% (n=42/49) in bacteriaemic patients treated with monotherapy and 50% (n=12/24) in those patients treated with combination therapy. In the combination therapy treatment group, the favourable response in 50% of patients is in line with published data. Only 4 of the failures had a positive blood culture at end point, 3 with persistence and 1 with a super-infection.

Bacteriological Response:
Considering the bacteriological response, piperacillin-tazobactam proved to be highly effective, eradicating 93.4% of the pathogens isolated in patients undergoing repeated follow-up cultures. In particular, 97% of the isolated microorganisms were eradicated in the group treated with monotherapy, while 88% of the microorganisms in the group treated with piperacillin / tazobactam and an aminoglycoside were eradicated. In the first group of patients, the predominant pathogen was *E. coli*, isolated in 12 patients and eradicated in 100% of the cases. The group treated with combination therapy consisted in large part of neutropenic patients and in this group, *S. epidermidis* was the most frequently isolated pathogen (n=9), confirming the importance of this microorganism in bacteraemia in this patient category (n=39). The frequent discovery of *S. epidermidis* is probably related to the use of central venous catheters and the use of ciprofloxacin for intestinal decontamination. Of the 9 strains of *S. epidermidis* isolated in the study in question, 7 (77%) were eradicated.

The CHMP noted that based on the submitted data, it can be seen that the total number of patients with bacteraemia across all studies in different indications was quite small, n=142. Out of these only 73 were clinically evaluable and 55 bacteriologically evaluable. Bacteraemia was documented in 33% of patients with febrile neutropenia (FN), in 19% of patients with pneumonia hospitalized in intensive care, in 18% of patients with cUTI, and in 16% of patients with IAI. It is presumed that the definitions of cured, favourable response and failures are the same as in the original studies. The results show that in this small dataset, piperacillin-tazobactam shows good efficacy when used as monotherapy (about

85% in clinically evaluable and over 90% in bacterialogically evaluable) and combination therapy (50% in clinically evaluable and over 80% in bacterialogically evaluable).

Other Studies

The MAH mentioned that no specific analysis for bacteraemic patients potentially reported in the various trials in FN, CAP, HAP, IAI, SSTI, and cUTI has been carried out. However the MAH contends, that historically all of these indications have a significant incidence of associated secondary bacteraemia / septicaemia. Therefore piperacillin-tazobactam is effective in those specified and localised infections which are likely associated with secondary bacteraemia / septicaemia or which are likely associated with primary bacteraemia / bacterial septicaemia of an unidentified origin. Although an updated subgroup analysis across all indications was not available, the MAH provided a review of some of the larger piperacillin-tazobactam clinical studies, in particular in FN patients, which were largely discussed in the previous sections of this report. In addition, the *Del Favero, et al GIMEMA study* included 277 bacteraemic patients (140 on piperacillin-tazobactam alone, and 137 on piperacillin-tazobactam with amikacin); the *Viscoli, et al EORTC study* included 218 patients with bacteraemia on piperacillin-tazobactam (763 patients received piperacillin-tazobactam alone, and on day three, 165 of these patients with persistent fever were given vancomycin or placebo); the *Marie, et al* study that comparing piperacillin-tazobactam plus tobramycin to ceftazidime plus tobramycin included 27 bacteraemic patients on piperacillin-tazobactam; the *Bow, et al* study in which patients received monotherapy with piperacillin-tazobactam or with cefepime included 51 bacteraemic patients on piperacillin-tazobactam; the *Hurler, et al* study in which patients received either piperacillin-tazobactam or ceftazidime included 51 bacteraemic patients on piperacillin-tazobactam; finally, the *Vedat, et al* study in which patients received piperacillin-tazobactam or cefepime for FN included 19 bacteraemic paediatric patients on piperacillin-tazobactam. In these studies combined, almost 2000 patients were treated with piperacillin-tazobactam (some more than once for recurrent episodes of fever), and over 500 had bacteraemia. In those studies in which there was a comparator, piperacillin-tazobactam was at least non-inferior to the comparator. Many of these patients were treated with piperacillin-tazobactam monotherapy as well.

Guidelines

Piperacillin-tazobactam studies in monotherapy and dual therapy for the indication febrile neutropenia are discussed in the IDSA 2002 Guidelines for the use of Antimicrobial Agents in Neutropenic subjects with Cancer. The use of piperacillin alone is also discussed in those guidelines, as well as in the IDSA 1997 guidelines. Guidelines of the Infectious Disease Working Party (AGIHO) of the German Society of Haematology and Oncology (DGHO) were published in 2003 and list piperacillin-tazobactam as a monotherapy option for initial empiric therapy for standard risk patients with fever in neutropenia following high dose therapy (chemo-/radiotherapy) and autologous haematopoietic stem cell transplantation. The guideline describes a piperacillin-tazobactam dose of 4.5 g given every 8 hours.

The CHMP noted that the supporting evidence is mainly derived from studies in febrile neutropenia. Only about a quarter of patients across different trials had “bacteraemia”. It was noted that piperacillin-tazobactam had similar efficacy as the comparator used in the studies. Some of the studies mentioned above were sponsored by the MAH and therefore it appears that these have already been considered in the first section where the pooled analysis is discussed.

In conclusion, based on the data provided by the MAH, the CHMP noted that all cases of “bacteraemia” were in patients with one or more of the other indications i.e. RTI, UTI, SSTI, IAI and FN. The pooled analysis included patients with positive blood cultures however none of the studies had prospectively defined these patients and therefore it is very likely that most of these patients would not satisfy the criteria for sepsis. Taking into account the view of the CHMP drafting group that the data was very limited for this indication and acknowledging the difficulties of conducting retrospective analysis, the CHMP was of the opinion that piperacillin-tazobactam has broad-spectrum antibacterial activity and is therefore be a suitable option for the treatment of bacteraemia. The CHMP adopted the following harmonised indication:

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

1.7 Gynaecological Infections including postpartum endometritis and pelvic inflammatory disease

Acute pelvic infections in women include several diagnoses that may be categorized as infections related to delivery and those which occur after gynaecological surgery. Risk factors for acute pelvic infection are delivery by Caesarean section, hysterectomy or incomplete abortion. Although these procedures are often preceded or followed (for Caesarean section) by antimicrobial prophylaxis, the rate of infection may be as high as 20%. Acute pelvic infections are usually polymicrobial. The major causal pathogens are those that comprise the normal vaginal flora, namely *Streptococcus agalactiae*, *Escherichia coli*, peptostreptococci, *Prevotella spp., Bacteroides spp*. and *Gardnerella vaginalis*. Antimicrobial regimens for the treatment of acute pelvic infection must therefore provide coverage against a broad spectrum of aerobic and anaerobic bacteria. The MAH presented the current nationally approved indications and proposed the following harmonised indication: "G*ynaecological infections, including postpartum endometritis and pelvic inflammatory disease (PID)".*

The one key study described in the initial expert report filed with the original Tazocin data package was study D68 P522: an open-label, non-comparative, multi-center, safety, tolerance and efficacy study of parenteral piperacillin-tazobactam in the treatment of hospitalized patients with gynaecological infections.

Piperacillin-tazobactam vs clindamycin plus gentamicin
A randomised, multicentre, open-label, comparative safety, tolerance and efficacy study of piperacillin-tazobactam versus clindamycin plus gentamicin in the treatment of hospitalized subjects with gynaecological infections was conducted in 299 female subjects between 15 and 73 years of age in 12 centres in the United States and 2 centres in Canada from 1989 through 1991 (Protocol D68 P28). A 2:1 randomization resulted in 196 subjects receiving piperacillin-tazobactam 3.375 grams given every 6 hours, and 103 subjects receiving clindamycin 900 mg given every 8 hours plus gentamicin 2.5-5.0 mg/kg/day, divided and given every 8 hours (or every 12 hours for mild to moderate renal dysfunction). Bacteriologically-confirmed gynaecological infections were present in 205 of the 299 subjects (69%); 114 (38%) of subjects met evaluability criteria (86 piperacillin-tazobactam subjects and 28 comparator subjects). Clinical efficacy was performed at early, late, and end-point follow-up visits. Favourable clinical responses (cured and improved) were similar in both treatment arms. They were 83% and 83% at early follow-up, 87% and 92% at late follow-up, and 78% and 82% at end-point for piperacillin-tazobactam and the comparator respectively. The favourable bacteriological responses (eradication documented and eradication presumed) were also similar in both treatment arms. They were 79% and 74% at early follow-up, 84% and 91% at late follow-up, and 77% and 79% at end-point for piperacillin-tazobactam and the comparator respectively. 12 evaluable subjects treated with piperacillin-tazobactam had these organisms as baseline pathogens. The 12 isolated organisms were either *E. coli,* or *S. aureus.* At early follow-up, 75% (6/8) R/S piperacillin-tazobactam-treated subjects demonstrated eradication (3 documented, and 4 presumed), while 2 subjects had persistence. At late follow-up, 88% (7/8) R/S piperacillin-tazobactam-treated subjects demonstrated eradication (2 documented, and 5 presumed), while one patient had persistence. At end-point, 83% (10/12) R/S piperacillin-tazobactam-treated subjects demonstrated eradication (3 documented, and 7 presumed) while 2 subjects with persistence were reported. There were no deaths in the study for piperacillin-tazobactam or the comparator. Five (3%) of 196 piperacillin-tazobactam-treated and 2 (2%) of 103 comparator-treated subjects did not complete the study due to adverse events or abnormal laboratory findings. The study conclusions were that piperacillin-tazobactam was as efficacious and safe as the comparator for the treatment of hospitalized subjects with gynaecological infections.

The CHMP noted that the initial applications for Tazocin included preliminary data in support of piperacillin-tazobactam for use in treating patients with gynaecological infections, including an open-label, non-comparative, multi-centre, safety, tolerance and efficacy study of parenteral piperacillin-tazobactam in the treatment of hospitalized patients with gynaecological infections. However, no new data was submitted to support the indication except a small study in about 50 patients comparing pip-tazo vs ampicillin plus gentamicin in patients with post-cesarean endometritis. The CHMP concluded, in line with the position of the CHMP drafting group, that the data for this broad indication was too limited to support the indication or any qualified version of this indication. The indication was therefore deleted by the CHMP.

1.8. Bone and Joint Infections

Gram-positive organisms, particularly staphylococci and streptococci, are responsible for the majority of bone and joint infections. However, anaerobes are also implicated in causing osteomyelitis secondary to diabetic foot infections and septic arthritis. Gram-negative organisms are also responsible for some bone and joint infections. Enterobacteriaceae and *P. aeruginosa* are commonly found in

nosocomial bone and joint infections. The most important parameters in selecting an antimicrobial agent for treatment of bone infection are its spectrum of activity and whether it penetrates bone. The MAH presented the current nationally approved indications and proposed the following harmonised indications: "*Bone and joint infections".*

There was a single study noted in the initial expert report filed with the original Tazocin data, study D68 P519: a multi-centre, open-label, non-comparative, safety, tolerance and efficacy study of parenteral piperacillin-tazobactam for the treatment of hospitalized patients with bone and joint infections.

Discussion of Additional Clinical Data

D68 P519 evaluated the efficacy of piperacillin-tazobactam 4.5 g given every 8 hours in 50 subjects with osteomyelitis or acute septic arthritis in a multicentre, open-label, clinical trial. Patients with septic arthritis received at least 7 full days of therapy. Patients with osteomyelitis received at least 14 full days of therapy. Patients were enrolled at three sites in 2 countries (Germany and South Africa). Thirty seven (37) patients were enrolled from 1 site in Germany, and 43 patients in total were enrolled in Germany. Of the 50 patients enrolled, 50 completed a full course of therapy, 29 (58%) of the patients were considered clinically evaluable and 21 were bacteriologically evaluable. Treatment continued for a mean duration of 14 days in subjects with osteomyelitis (21 subjects had acute infections and 22 had chronic infections) and for 8.4 days in those with septic arthritis (n = 7).

Regarding the clinical response at end-point for all patients, 40/50 patients had a valid response, and 36/40 (90%) had a response of cured or improved, with 4/40 (10%) had a response of relapse. The end-point bacterial eradication rate in all patients with a valid response was 94% (30/32). One patient had persistence, and one had a new infection. Evaluation of the pathogen response revealed that at end-point, 56/85 pathogens (66%) isolated at baseline had a valid response. Of these, 55/56 (98%) were eradicated, and one *S. aureus* was persistent. Among the clinically evaluable population at end-point, 26/29 (90%) had a response of cure or improvement, and 3 patients had a response of relapse. The end-point cure/ favourable response rate in the bacteriologically evaluable population was 95% (20/21), with one patient that had a response of relapse. There were no deaths in the study, and the incidence and type of adverse events were similar to those seen with piperacillin alone. The most frequently isolated pathogen was *Staphylococcus aureus*. Approximately 50% of bone infections were polymicrobial, with many anaerobes isolated. Treatment was successful in all subjects with septic arthritis. Four weeks after the end of antibacterial agent treatment, clinical cure or improvement was achieved in 95% (39 of 41) of subjects with osteomyelitis. The authors concluded that piperacillin-tazobactam was effective for patients hospitalized for bone and joint infections

Bone/Synovial Tissue Penetration

Incavo et al investigated the penetration characteristics of a single dose of piperacillin-tazobactam 3.375 g into cortical and cancellous bone tissues from 10 subjects undergoing elective total hip replacement. The findings from the study were that the levels of piperacillin (8.5 to 43.3 mcg/g) and tazobactam (1.28 to 4.52 mcg/g) found in the bone tissue after a single dose of piperacillin-tazobactam were "…sufficient to assure antibacterial activity of piperacillin and the β-lactamase inhibitory activity of tazobactam…" The concentration ratios of piperacillin-tazobactam (1 hour after initiation of the 30-minute intravenous infusion) were 9.4 ± 1.8 in cancellous bone tissue and 8.0 ± 2.2 in cortical bone tissue, which were close to the 8:1 ratio of drugs administered. The mean ratios of drug concentrations in bone vs. plasma were similar for both cancellous and cortical tissue, 23% and 18%, respectively, for piperacillin and 26% and 22%, respectively, for tazobactam.

Boselli and colleagues conducted a single-dose, open-label study with 12 subjects undergoing elective total hip replacement to quantify piperacillin-tazobactam's bone tissue penetration. Concentrations of piperacillin and tazobactam in plasma, cancellous tissue, and cortical tissue were determined at approximately 1.5 hours after the initiation of a single 4.5 g infusion of piperacillin-tazobactam. Mean concentrations of piperacillin and tazobactam were as follows: 68.5 ± 4.4 mcg/mL and 7.8 ± 0.5 mcg/mL in plasma; 15.1 ± 2.0 mcg/g and 2.0 ± 0.3 mcg/g in cortical tissue; and 18.9 ± 2.3 mcg/g and 2.0 ± 0.3 mcg/g in cancellous tissue. The mean bone/plasma ratios for piperacillin in cortical and cancellous tissues were 0.2 and 0.3, respectively. In both cortical and cancellous tissues, tazobactam exhibited a mean bone/plasma ratio of 0.3. The mean piperacillin-tazobactam concentration ratio was 7.8:1 in cortical bone tissue and 9.3:1 in cancellous bone tissue.

The penetration of piperacillin-tazobactam into synovial tissue also was evaluated in a single-dose, open-label study. A total of 6 subjects undergoing total hip replacement surgery received piperacillin-tazobactam 4.5 g as a single intravenous infusion prior to surgery. The mean plasma concentration of

drug at the time of bone removal was 69.9 ± 4.9 mcg/mL and 7.7 ± 0.3 mcg/mL for piperacillin and tazobactam, respectively (mean 1.5 h after the initiation of infusion). In synovial tissue, piperacillin concentrations ranged from 33.6 to 39.5 mcg/g (mean 37.1 ± 2.1) and tazobactam concentrations ranged from 2.1 to 3.1 mcg/g (mean 2.8 ± 0.4). Mean ratios of piperacillin and tazobactam concentrations in synovial tissue / plasma were 0.53 ± 0 and 0.36 ± 0, respectively. The mean piperacillin-tazobactam concentration ratio was 9.1 ± 0.8 in plasma and 13.5 ± 2 in synovial tissue. The MIC_{50} values of piperacillin-tazobactam and corresponding inhibitory quotients for frequently encountered pathogens in bone infections were calculated. The findings from this study showed that levels of piperacillin and tazobactam, after a single dose of 4 g and 500 mg, respectively, are adequate against most microorganisms encountered in joint infections, with the exception of oxacillin-resistant S. aureus and Enterobacter spp. However, it should be noted that uninfected synovial tissue samples were used in this study, therefore concentrations of piperacillin and/or tazobactam achieved in infected tissue may differ. In addition, MIC values used to calculate the inhibitory quotients were taken from data found in the published literature, rather than from microbiologic assays of isolated organisms.

The CHMP noted that the indication bone and joint infections was approved in about half of the EU member states; however the data provided in support of the indication was very limited. No new data was submitted and the single study supporting the initial European application for Tazocin for the indication bone- and joint infections was an open-labelled non-comparative study. Results from three single-dose, open label studies to characterize the tissue penetration of piperacillin-tazobactam were provided, suggesting that piperacillin and tazobactam concentrations in both bone and synovial tissue are sufficient to treat the majority of infections caused by susceptible organisms but these data alone could not justify the indication claimed. The CHMP concluded, in line with the CHMP drafting group position, that neither the broad indication of bone and joint infections nor the septic arthritis were acceptable due to lack of data. The CHMP therefore deleted the indication.

1.9. Neonates and children

The MAH provided a summary of the available data supporting paediatric indications and stated that piperacillin-tazobactam has been widely used to treat paediatric infections since 1989. It is approved for use in children in more than 20 countries for the treatment of intra-abdominal infections (IAI) and febrile neutropenia (FN). The MAH presented the current nationally approved indications and proposed the following harmonised indication:

"*Children 2 to 12 years of age:*
- Neutropenic children with fever suspected to be due to bacterial infections, in combination with an aminoglycoside
- Children with complicated and uncomplicated intra-abdominal infections

Discussion of use in Children
The initial European indication for piperacillin-tazobactam across the EU was for IAI in paediatrics based on a primary study conducted by MAH. This was supplemented with 6 additional studies from the literature which provide valuable efficacy data and safety information on paediatric subjects with IAIs. For treatment of paediatric subjects with FN, an EORTC study was used to obtain approval. This was supplemented further with 5 studies from the literature, which provide valuable efficacy data and safety information on paediatric subjects with FN.

Intra-abdominal Infections
The one key study noted in the initial expert report filed with the original Tazocin paediatric data package was study 0910A8-304-EU: A multicentre, open-label, randomised comparison of the safety and efficacy of piperacillin-tazobactam (100/12.5 mg/kg) and cefotaxime (50 mg/kg) plus metronidazole (7.5 mg/kg) administered intravenously every eight hours to hospitalized paediatric patients for the treatment of severe intra-abdominal infection. The conclusions of the clinical expert were that this was a well-performed and well-reported study with a sufficient number of enrolled patients. The 2 groups were well matched and no difference was seen in exclusion of the patients from the EE population.

The two key supporting safety/efficacy studies noted in the initial expert report filed with the original Tazocin paediatric data package were studies D68 P544: a non-comparative, multicentre, safety, tolerance, and efficacy study of parenteral piperacillin-tazobactam (80/10 mg/kg every 8 hours) in the treatment of hospitalized paediatric patients aged 2 months to 6 years with intra-abdominal infections and D68 P543: a prospective, multicentre, open-label, randomised comparison of the safety, tolerance, and efficacy of parenteral piperacillin-tazobactam versus cefotaxime plus metronidazole in the

treatment of hospitalized paediatric patients with intra-abdominal infections. The conclusions of the clinical expert were that the first study was of non-comparative design which does not allow for a firm conclusion while in the second study the combination cefotaxime plus metronidazole was significantly better than piperacillin-tazobactam in the EE but not in the ITT population. A total of seven studies were included in the safety analysis; further discussion of those studies is available in the expert's report. Pharmacokinetic and clinical efficacy studies have evaluated the paediatric use of piperacillin-tazobactam. Several of these studies are summarized below.

Discussion of Additional Clinical Data
In a prospective non-comparative evaluation, Fishman et al described 138 children (age range 1.4 to 19.6 years) with perforated appendicitis who received 10 days of piperacillin-tazobactam as part of treatment that included surgery and drain placement. (Dose used not mentioned). The study, which took place over a 43-month period, included up to 5 days of piperacillin-tazobactam treatment (administered when possible on an outpatient basis). An outcome analysis compared these children to 373 historic controls who received ampicillin, gentamicin, and clindamycin (dose not specified) at the same institution over an 11-year period. The protocol, which included immediate surgery, drain placement, and primary wound closure, was unchanged. The complications reported did not differ significantly from the subjects treated on the original protocol of ampicillin plus gentamicin plus clindamycin. In fact, piperacillin-tazobactam subjects had similar types and numbers of complications, with intra-abdominal abscess (3.3%), cecal fistula (1.3%), phlegmon (2%), and wound infection (2.7%). No deaths were reported. Although adequate comparison is difficult, secondary to the use of an historical control group, the authors concluded piperacillin-tazobactam therapy effectively treated postoperative perforated appendicitis with few infectious complications, including subjects who received a portion of their therapy on an outpatient basis.

A prospective, randomised study in Greece by Maltezou et al compared piperacillin-tazobactam with cefotaxime plus metronidazole in 70 children, aged 0 to 14 years, with IAI. Thirty five (35) children received piperacillin-tazobactam (100 mg/kg piperacillin/12.5 mg/kg tazobactam every 8 hours). Piperacillin-tazobactam was as effective, well tolerated, and safe as the comparator.

A phase III, non-comparative, multi-centre, safety, tolerance, and efficacy study of parenteral piperacillin-tazobactam in the treatment of hospitalized paediatric subjects with intra-abdominal infections was initiated in 1992, and terminated prior to completion in 1993 (Protocol LED D68 P67, GMR 37391). Enrolment was stopped at the time due to reassessment of company strategy. Efficacy and pharmacokinetic analyses were not performed. However, safety data were included in the report. A total of 82 hospitalized subjects (age range 2 months to 12 years) were enrolled in the study, and received piperacillin-tazobactam (80mg/10mg/kg) every 8 hours. Duration of therapy was at least 3 days. Safety results revealed no deaths or serious adverse events. One patient was withdrawn due to a rash probably related to study drug according to the investigator. A total of 41 (50%) subjects experienced at least one adverse event. These included diarrhoea in 17.1%, rash in 8.5%, stool changes in 8.5%, vomiting in 3.7%, and pruritus in 3.7%. All adverse events were considered mild or moderate in severity. It was concluded that piperacillin-tazobactam was well tolerated in paediatric subjects with intra-abdominal infections. The Wyeth study report for this study is included in this submission.

Febrile Neutropenia
Tazocin has been studied in paediatric FN in multiple trials in EU, both non-comparative and comparative in design. A summary of comparators and paediatric dosing regimens that were used in the included paediatric clinical studies was provided.

A prospective, non-comparative, open-label study of paediatric cancer subjects with FN in Germany evaluated 239 episodes of fever in 105 children (7 of the original 112 subjects were excluded for protocol violations). Children aged 12 and older received piperacillin-tazobactam (80 mg/kg and 10 mg/kg given every 8 hours) with gentamicin, while younger children received piperacillin and sulbactam in combination with gentamicin. Other antibacterial agents and antifungals were added sequentially if needed per the protocol. Efficacy rates were similar to those reported in earlier studies with third-generation cephalosporins and carbapenems. However, it is difficult to draw adequate comparisons to these studies. Side effects were seen in 21 of 234 febrile episodes. They included vomiting, 2 cases of *C. difficile* diarrhoea, 3 subjects with rashes, and hypokalemia in 13 of 21 subjects who received amphotericin.

Le Guyader et al published an observational non-comparative trial in France in which 148 neutropenic episodes in 104 children (mean age 7 years) were treated with piperacillin-tazobactam (100 mg/12.5

mg/kg) given every 8 hours, along with netilmicin. When indicated, a glycopeptide and antifungals were added. No deaths occurred; 1 child had a rash that resolved after piperacillin-tazobactam was discontinued. The authors concluded that piperacillin-tazobactam was efficacious and well tolerated.

In a non-comparative trial in Germany published in 1998, Nurnberger et al assessed the tolerability of piperacillin-tazobactam (80 mg/10 mg/kg given every 8 hours) in 19 children (aged 2 to 18 years, with 7 children under age 12) who developed fever during aplasia after high-dose radio or chemotherapy and autologous stem cell transplantation (HD-SCT) for primary multifocal or relapsed solid tumours. No severe side effects and no relevant laboratory abnormalities secondary to piperacillin-tazobactam were seen. Most children did have a mild reversible glultamyltransferase (GGT) elevation, and although piperacillin-tazobactam cannot be excluded as a cause, this was felt to be secondary to cytoreductive therapy.

Neonates
In South Africa in 1998, Pillay et al administered piperacillin-tazobactam (Dose used not mentioned) plus amikacin to 13 of 33 neonates with *Klebsiella pneumoniae* infections. This small retrospective analysis also included 17 of the 33 subjects who received imipenem/cilastatin (I/C); 2 other subjects received cefotaxime, and 1 received ciprofloxin. Dose regimens were not specified. The neonates had a mean gestational age of 32 weeks. All-cause mortality was 35.3% in the piperacillin-tazobactam plus amikacin group, and 46.2% in the I/C group. These differences were not considered significant, and the duration of antimicrobial therapy and total hospital stay were also similar.

Very Low Birth Weight Infants, And Premature Infants
Berger et al conducted an open-label, non-comparative study of piperacillin-tazobactam in very low birth weight infants, defined in the study as those having a birth weight ≤ 1500 g. This safety evaluation enrolled 27 preterm infants, with 17 (63%) having suspected necrotizing enterocolitis (NEC), 3 (11%) having other IAIs, 4 (15%) having nosocomial sepsis with Gram-negative rods, and another 3 (11%) having a nosocomial infection that did not respond to empiric therapy. The subjects were all initially treated with vancomycin plus an aminoglycoside. In the event of clinical failure, defined as a lack of response to empiric therapy in the first 48 hours, subjects were given piperacillin-tazobactam 80/10 mg/kg IV given every 8 hours for a minimum of 3 days, in addition to the vancomycin and aminoglycoside combination. The only exception to this was when the growth of Gram-negative rods was observed in the blood culture, in which case the vancomycin was discontinued. Clinical evaluation revealed cure or improvement in 17 (63%) subjects. There were no study drug-related adverse events, and the authors concluded that piperacillin-tazobactam was safe and well tolerated in preterm infants with bacterial infections, particularly those involving the gastrointestinal tract.

Miscellaneous Clinical Studies in Children
Reichardt et al in 1999, described leukocytopenia, thrombocytopenia and fever related to piperacillin-tazobactam treatment in a retrospective analysis of 38 children (median age 14 years) with cystic fibrosis. These children received 100 antibacterial agent treatment courses (including piperacillin-tazobactam) for a mean duration of 12.5 days. Patients received between 191 and 672 mg PT per kg daily (mean 288 ± 91 mg/kg/day). Of the subjects receiving piperacillin-tazobactam (84%), 6 subjects (18.75% of piperacillin-tazobactam-treated subjects, 10.3% of piperacillin-tazobactam treatment courses) developed fever, malaise, and headache during treatment without signs of acute infection. One patient developed definite thrombocytopenia and neutropenia; 2 others developed milder decreases in leukocyte and platelet counts. Events were time-and dose-dependent, occurring between days 11 and 15 of treatment. After piperacillin-tazobactam discontinuation, fever subsided within 24 hours and blood cell counts normalized. The authors concluded that the fevers and blood count changes were secondary to piperacillin-tazobactam therapy.

A phase 3, non-comparative, multi-centre, safety, tolerance, and efficacy study of parenteral piperacillin-tazobactam in the treatment of hospitalized paediatric subjects with skin and skin structure infections was initiated by Lederle in 1992, and terminated prior to completion in 1993. Enrolment was stopped at the time due to reassessment of company strategy. Efficacy and pharmacokinetic analyses were not performed. However, safety data were included in the report. A total of 103 hospitalized subjects (age range 2 months to 12 years) were enrolled in the study, and received piperacillin-tazobactam (80mg/10mg/kg) every 8 hours. Treatment duration was to be at least 3 days (9 doses) up to clinical improvement, followed by protocol specified oral antibacterial agent therapy not to exceed 7 days. Safety results revealed that one patient died of respiratory failure not related to study drug, and two withdrew for safety reasons; one had thrombocytopenia with septic shock not related to study drug; the other had a rash probably secondary to amoxicillin. Twenty-one (21) of 103 (20.4%) of subjects treated with piperacillin-tazobactam, and 21 of 93 (22.6%) of subjects treated with another

antibacterial agent experienced at least one adverse event. It was concluded that piperacillin-tazobactam was well tolerated in paediatric subjects with skin and skin structure infections.

In conclusion, the MAH provided an overview of the available clinical data and the key studies which demonstrate the efficacy, safety, and clinical pharmacokinetics of piperacillin-tazobactam in paediatric patients with IAI and concluded that the available clinical trials demonstrate that piperacillin / tazobactam at the doses applied is efficacious and safe in children treated for IAI. This is further supported by its wide use in medical practice for more than a decade. Based on the pivotal studies in paediatric patients with IAI, complemented by pharmacokinetic (PK) simulations (see below), the recommended dose is 100 mg/12.5 mg per kg of body weight q8h, not exceeding 4 g piperacillin / 0.5 g tazobactam per dose. Regarding febrile neutropenia, the MAH state that a considerable number of clinical studies have been conducted and concluded that piperacillin-tazobactam appears to be safe and efficacious in the treatment of neutropenic children with fever suspected to be due to bacterial infections, in combination with an aminoglycoside, at the doses applied. Based on clinical evidence in paediatric patients and adults, complemented by PK simulations, the recommended dose is 80 mg / 10 mg per kg body weight q6h, not exceeding 4 g piperacillin / 0.5 g tazobactam per dose, administered by slow intravenous infusion. The MAH was not aware of further studies and no additional experience is available in children below 2 years of age. Hence, the MAH abstained from recommending the use of piperacillin-tazobactam in these paediatric subsets.

The CHMP considered that the relevance of efficacy data obtained in adults for the paediatric population for systemically acting drugs depends on a number of factors such as the aetiology and course of the disease, as well as the mechanism of action of the drug in adult and paediatric patients. As the data from adults was considered relevant, the pharmacokinetic information can be used to extrapolate efficacy to the paediatric population. If similar exposure in adult and paediatric patients can be assumed to produce similar efficacy, pharmacokinetic data alone can be used to extrapolate efficacy. For antibacterial agents this should be the case where the same spectrum of bacteria can be expected to cause a specific type of infection in children and adults. Where the expected bacteria differ, PK/PD data may be useful in supporting a proposed indication. As clinical data in children are very sparse and will mainly have to be derived by extrapolation from the adult population, the acceptance of indications in this population will be influenced by the indications accepted for the adult population.

In view of the submitted data and the clinical experience of the safety and efficacy of piperacillin-tazobactam in neutropenic and non-neutropenic children, the CHMP considered the inclusion of the paediatric indications to be justified. There is vast clinical experience in treating neutropenic adults as well as children > 2 years with fever suspected to be due to bacterial infections, often in combination with an aminoglycoside. The safety of piperacillin-tazobactam is well documented in immunocompetent patients. Comparison with data from neutropenic subjects does not reveal any new safety risk. There seems to be no additional hazard in children. The CHMP acknowledged that piperacillin-tazobactam acts synergistically with aminoglycosides against certain strains of *Pseudomonas aeruginosa*. Combined therapy has been successful, especially in patients with impaired host defences. The statement "*Consideration should be given to official guidance on the appropriate use of antibacterial agents."* addresses the recommendation to combine piperacillin-tazobactam with an aminoglycoside.

Clinical data from comparative studies in adults and children, pharmacokinetic data for children as well as wide clinical experience in the treatment of severe IAIs in children aged > 2 years, support the safety and efficacy of piperacillin-tazobactam in the treatment of intra-abdominal infections in paediatric patients. This indication is currently approved in most member states, with some variation of the specific wording. The most common causes of IAI in children are complications of appendicitis, gangrene or perforation of appendix, peritonitis or abscess formation. The CHMP revised the wording of the indication to reflect the study population in the pivotal study and current practice and brought it in line with the indication in adults. In conclusion, the CHMP adopted the following harmonised indications:

"Children 2 to 12 years of age

- Complicated intra-abdominal infections

Tazocin may be used in the management of neutropenic children with fever suspected to be due to a bacterial infection"

Section 4.2 Posology and method of administration

a) Method of administration

All countries have approval for intravenous injection and intravenous infusion and there are only minor divergences throughout the national SPCs. Only 2 member states have different administration times listed in comparison to the other countries. The MAH argued that while slow intravenous push is permitted, intravenous infusion over 30 minutes takes advantage of the improved understanding of the relationship between efficacy of a dose and the concentration of piperacillin-tazobactam. The relationship between concentration and effect of antibacterial agent treatment was not well understood during the original development of piperacillin-tazobactam. Dosing was empiric and doses shown to be effective in small studies were carried forward into larger studies without necessarily understanding why the dose and dosing regimens that were selected worked better than the others that had been tried. It has been shown for piperacillin-tazobactam that the time during which the free (unbound) drug concentration in blood exceeds the MIC of the organism (T > MIC) is the best predictor of outcomes, and that a T>MIC for more than 40 to 50% of the dosing interval is generally considered effective. Infections caused by bacteria with higher MIC values will require more frequent dosing, while more sensitive bacteria may be adequately treated with less frequent dosing. The MAH presented a detailed overview of the nationally approved information on the method of administration and proposed a harmonised wording for Section 4.2 for both the dual and triple combination presentation.

The CHMP removed all extraneous information from section 4.2 in accordance with the most recent CHMP guidance on the SPC and adopted the following wording:

"Tazocin 2 g / 0.25 g or 4g / 0.5g is administered by intravenous infusion (over 30 minutes)."

b) Adult and Adolescent Patients (> 12 years of age)

A detailed overview of the divergences in the dose recommendation for adult and adolescent patients was presented by the MAH. The dosage depends on the severity, location of the infection and the indication. The majority of member states recommend '4 g piperacillin/0.5 g tazobactam given every 6 to 8 hours' intravenously. For certain indications a more frequent dosage administration is recommended. For example, 11 member states recommend a dose for the treatment of pneumonia and/or bacterial infections in neutropenic patients. In the majority of these countries a dosage interval of 'every 6 hours' is recommended. Similarly, more frequent administration is recommended for LRTI (HAP and VAP) in many member states. The MAH proposed the following harmonised wording for the "Adult and adolescent patients (over 12 years of age)" subsection:

Adult and adolescent patients (over 12 years of age)
Infections
The dose of Tazocin depends on the severity and localisation of the infection and expected pathogens. Neutropenic patients with signs of infection (e.g., fever) should receive immediate presumptive antibiotic therapy before laboratory results are available.

For lower respiratory tract infections (community-acquired pneumonia), urinary tract infections (complicated and uncomplicated), intra-abdominal infections, skin and skin structure infections, gynaecologic infections, bone and joint infections and bacterial septicaemia the usual dosage is 4 g / 0.5 g Tazocin (4 g piperacillin / 0.5 g tazobactam) given every 8 hours.

For lower respiratory tract infections (hospital-acquired and ventilator-associated pneumonia and Bacterial infections in neutropenic patients the usual dosage is 4 g / 0.5 g (4 g piperacillin / 0.5 g tazobactam) administered every 6 hours.

The MAH provided a Clinical Expert Analysis, and referred to numerous studies both by the MAH and by other clinical investigators which used a 4.5 g dose of Tazocin. These studies routinely concluded that the use of Tazocin at this dose, given every 8 hours, is both safe and effective and leads to good patient outcomes. For patients with more severe infections, a dose of 4.5 g Tazocin given every 6 hours has also shown to be effective. The MAH further stated that the individualisation of dosing needs to be balanced with convenience and ease of administration in order to efficiently deliver health care and minimise the potential of errors. Calculation of the dose to administer to children offers an additional opportunity for errors in calculations and product wastage. Children weighing 40 kg or more will receive the adult dose of 4/0.5 g. The 50th percentile values for weight for 12 year old girls and boys in the United States are 42 and 40 kg, respectively, and the 50th percentile for weight for children in the United Kingdom is also approximately 40 kg. The 3rd and 5th percentiles for children aged 12 years are approximately 30 kg and so there may be concern that administration of the adult dose of 4/0.5 g would be too much medication and cause toxicity. It is helpful to consider the weight of adults

participating in clinical trials and their response to treatment. In three randomized clinical trials in adults with complicated intra abdominal infections being treated with 4/0.5 g IV, the smallest adults were 42, 36 and 45 kg respectively. There appeared to be no weight-related toxicity in the analysis of safety for these studies. The MAH concluded that the ease of administration and the decreased likelihood of dosing error offered by a flat dosing for children more than 12 years outweigh the modest potential risk of reduced tolerability. When treating children who are particularly small, physicians may choose to extend dosing using the paediatric dosing guidelines provided in the SPC.

The CHMP agreed with the proposed dosing but implemented a tabular presentation of the doses according to each individual approved indication.

c) Elderly with Normal Renal Function / Adults and adolescent patients (over 12 years of age)

The MAH identified no major divergences in the dose recommendation for elderly patients with normal renal function. In the majority of countries it is explicitly mentioned that no dose adjustment is needed in this population except in the case of renal insufficiency where the dose needs to be adjusted. Nine out of 28 countries do not give a dose recommendation. Only one member state recommended the dosage recommendation for renal impairment in general for elderly patients. The MAH presented the current nationally approved wordings and proposed not to include a dose recommendation for elderly patients as results from clinical studies show that no dose adjustment is needed for elderly patients (> 65 years). Dose adjustments are recommended in patients with renal insufficiency and in the absence of a renally-compromised elderly patient, the MAH did not consider a dose reduction to be warranted.

The CHMP agreed with the MAH position that a dose reduction for elderly patients in the absence of renal insufficiency in the categories noted below is not warranted. However the CHMP requested the insertion of an appropriate sentence under the heading 'Elderly patients' as per the SPC guideline.

d) Renal impairment / Adults and adolescent patients (over 12 years of age)

The nationally approved dose recommendation for patients with renal impairment varies. The MAH stated that 50 to 60% of piperacillin and tazobactam of an administered dose is eliminated by renal excretion and biliary excretion is less than 2% of the dose. The mean clearance values for piperacillin and tazobactam are 15 and 12 to 15 l/hr respectively. The corresponding half-lives are 0.8 to 0.9 for both compounds. In the presence of renal impairment, decreased clearance and increased half-lives would therefore be expected. In a study of 8 subjects with moderate renal impairment, creatinine clearance of 20 to 38 ml/min, and 8 subjects with normal renal function, those with moderate renal impairment were observed to have piperacillin clearance that was 52% and tazobactam clearance that was 60% that of those with normal renal function. The dosage adjustments recommended are predicted to provide concentration-time profiles similar to patients with normal renal function. Haemodialysis procedures removed 31 and 39% of the administered doses of piperacillin and tazobactam after single doses of 3/0.375 g administered over 30 minutes. It had been shown previously that 46% of the administered dose of piperacillin when administered alone was removed by dialysis procedures, and so the wider range of 30 to 50% was retained in the SPC, and a dose of piperacillin-tazobactam representing 50% of the usual dose, 2/0.25 g, suggested for the supplemental dose after dialysis. The MAH presented the variations in the wording for the use in patients with renal impairment and proposed the following harmonised wording for the subsection 'Adult and adolescent patients (over 12 years of age), Renal Impairment':

The intravenous dosage should be adjusted to the degree of actual renal impairment as follows (each patient must be monitored closely for signs of drug toxicity; drug dose and interval should be adjusted accordingly):

Creatinine clearance *(ml/min)*	***Tazocin (recommended dosage)***
> 40	*No dosage adjustment necessary*
20-40	*Maximum dosage suggested: 4 g / 0.5 g every 8 hours*
< 20	*Maximum dosage suggested: 4 g / 0.5 g every 12 hours*

For patients on haemodialysis, one additional dose of piperacillin-tazobactam 2 g / 0.25g should be administered following each dialysis period, because haemodialysis removes 30%-50% of piperacillin in 4 hours.

The CHMP considered the justifications provided by the MAH for the proposed wording to be acceptable; however PK/PD data was requested to support the wordings.

e) Use in Patients with Hepatic Impairment / Adults and adolescent patients (over 12 years of age)

The MAH identified no major variations in the dose recommendation for adult and adolescent patients (over 12 years of age) with hepatic impairment. In the majority of member states it is explicitly mentioned that no dose adjustment is needed in this population. Eight member states do not give a dose recommendation. The MAH presented the current nationally approved wordings and proposed the following harmonised wording for the hepatic impairment subsection:

Hepatic impairment
No dose adjustment is necessary (see section 5.2).

A single dose study of 17 cirrhotic subjects and 6 normal subjects showed that piperacillin clearance was significantly reduced by 29% compared with normal subjects. Non-renal clearance was reduced by 53% while renal clearance was increased by 7%, which was not significant. Although prolonged by 25%, there was no statistically significant difference in t½ values observed in the cirrhotic subjects compared with the normal subjects. Similar differences were observed when comparing tazobactam concentrations between the two groups. However, because the predicted accumulation index assuming dosing every 4 hours was similar between the two groups, no dosing adjustment was considered necessary for every 4 hour or less frequent dosing.

The CHMP considered the justification provided by the MAH for the proposed wording to be acceptable.

f) Children Aged 2-12 Years With Normal Renal Function

The MAH stated that the treatment of children with IAIs is approved in most member states and provided a detailed overview of the various nationally approved wordings. There were no divergences in the dose recommendation for children with IAIs.

The MAH stated that the treatment of children with FN is approved in four member states, that fifteen do not include a dose recommendation for this population, while the rest (14 out of 29) present a dose recommendation for the use in children between 2 to 12 years in paediatric neutropenia. The MAH presented an overview of the nationally approved wordings. In addition, general information for the treatment of paediatric patients weighing more than 40 kg and with normal renal function is presented in the majority of the member states. Several pharmacokinetic studies on piperacillin-tazobactam have been conducted in children aged 2 to 12 years and concentration time data analyzed by several authors. In children aged 2 to 5 months, piperacillin $AUC_{0-\omega}$ is approximately 40% higher than in children aged 6 months to 12 years. The elimination half lives are longer in both groups of children compared with older children and adults. Weight normalized volume of distribution is independent of age. After 2 years of age, piperacillin clearance primarily depends upon weight; dosing at 100/12.5 mg/kg should achieve exposures similar to adults receiving 4/0.5 g. Simulation has shown that 100/12.5 mg/kg will provide similar concentration-time exposure in children as 4/0.5 g in adults. It is recommended that children with febrile neutropenia receive more frequent dosing (q6h instead of q8h) in order to take advantage of the understanding that time above MIC has been shown to be predictive of clinical response. Dosing more frequently would be expected to be associated with an increased time above MIC and clinical success in this critical infection. The MAH proposed the following harmonised wording:

Infections

The following table summarises the treatment frequency and the dose per body weight for paediatric patients 2-12 years of age by indication or condition:

Dose per weight and treatment frequency	*Indication / condition*
80 mg Piperacillin / 10 mg Tazobactam per kg body weight / every 6 hours	*Neutropenic children with fever suspected to be due to bacterial infections**
100 mg Piperacillin / 12.5 mg Tazobactam per kg body weight / every 8 hours	*Complicated intra-abdominal infections**

** Not to exceed the maximum 4 g / 0.5 g per dose over 30 minutes.*

g) Use in Children between 2 and 12 years of age with renal impairment

The MAH stated that all but one member state included a dose recommendation for the treatment of paediatric patients with renal insufficiency. In most member states, the wording of the dose recommendation is similar. Eight member states have different wording and a few recommend slightly different dosages for this population. The MAH stated that no data are available to describe the pharmacokinetics of piperacillin-tazobactam in children with renal impairment. A study by Wilson et al investigated the pharmacokinetics of piperacillin alone in 15 children, including 3 with impaired renal function. As in adults, piperacillin clearance was highly correlated (r^2 = 0.67) with creatinine clearance and the MAH suggested a dosing equation resulting in the recommendation of 35 mg/kg every 6 to 8 hours depending upon the indication for patients in complete renal failure. A more practical suggestion for dosing was also developed, suggesting no change in dosing until estimated creatinine clearance decrease to 50 ml/min, at which time, dosing is reduced to 70/8.75 mg/kg every 8 hours with a supplemental dose of 40/5 mg/kg to be administered after dialysis treatments to compensate for the drug removed. Simulations have shown that this dosing provides concentration time profiles similar to children with normal renal function. No piperacillin-tazobactam concentration time data are available in children on haemodialysis, and so a dosing recommendation corresponding to what is suggested based upon data from studies in adults is suggested. The MAH presented an overview of the current nationally authorised wordings and proposed the following harmonised wording for the subsection "Use in children ages 2-12 years, Renal impairment":

"Renal impairment
The intravenous dosage should be adjusted to the degree of actual renal impairment as follows (each patient must be monitored closely for signs of drug toxicity; drug dose and interval should be adjusted accordingly):

Creatinine clearance (ml/min)	Tazocin (recommended dosage)
> 50	No adjustment needed.
≤ 50	70 mg piperacillin / 8.75 mg tazobactam/kg every 8 hours, by slow intravenous infusion.

For children on haemodialysis, one additional dose of 40 mg piperacillin / 5 mg tazobactam /kg should be administered following each dialysis period."

h) Use in children aged below 2 years

The MAH stated that the treatment of children below the age of 2 years is not approved in any member state and that 16 out of 28 countries do not recommend use in children below 2 years of age. The MAH presented the wording of the current national SPCs and stated that only limited pharmacokinetic data are available for piperacillin alone or piperacillin-tazobactam in children less than the age of 2 years. The MAH was not aware of further studies and no additional experience is available in children below 2 years of age and was therefore unable to recommend a Tazocin dose for use in these patients. The MAH proposed the following harmonised wording:

"Use in children aged below 2 years

The safety and efficacy of Tazocin in children 0- 2 years of age has not been established.

No data from controlled clinical studies are available."

The CHMP considered the justification provided by the MAH for the proposed wording to be acceptable.

i) Treatment Duration (Children and Adults)

The MAH stated that a majority of member states include a statement recommending treatment duration for children between 2 and 12 years, while the rest do not have a recommendation for this population in the SPC. There are only minor divergences in the SPC wording on treatment duration. 23 member states included the same or similar wording on treatment duration. The MAH stated that the duration of therapy should be adjusted according to patient factors (underlying and concurrent illnesses), and the type and severity of the particular infection, at the discretion of the treating

physician. Piperacillin/ tazobactam demonstrated safety and efficacy in numerous clinical studies with a duration of therapy generally between five and 14 days. It is also generally prudent to continue therapy for 48 hours beyond resolution of clinical signs and symptoms of infection. There are a few notable exceptions, such as osteomyelitis, that may require more prolonged treatment. In order to propose a duration of treatment for HAP, the MAH also provided an overview of HAP and its management, the treatment experiences with piperacillin-tazobactam in clinical trials, and treatment guidelines. Based on this evidence, the MAH proposed that the treatment duration for HAP should be at least 8 days and until a resolution of clinical features of infection is evident and also that a longer treatment duration may be required if *P. aeruginosa* or *S. aureus* is the etiologic pathogen. The MAH noted that the current general recommendation for the treatment of HAP is to keep the treatment rather short as compared to 'traditional' more prolonged treatments. The proposal to treat for at least 8 days was deemed to sufficiently reflect current recommendations and also to be in line with the clinical study outcomes on piperacillin-tazobactam with an average treatment duration of around 10 to 11 days. The MAH presented the current nationally agreed wordings and proposed a harmonised wording for the 'Treatment duration' subsection.

The CHMP was of the opinion that advice to continue dosing until at least 48 h after resolution of fever or symptoms is inappropriate. Similarly, basing duration on "bacteriological progress" is unhelpful and rarely applicable. Instead, the CHMP recommended that no minimum is set (since patients may be switched to some suitable oral follow-on therapy) and inserted a statement stating that the duration should depend on the infection being treated, informing of the possibility of switching to a suitable oral follow-on treatment and stating that therapy should not usually continue beyond a maximum of 14 days. The information on treatment duration was also grouped for all categories of patients under a separate subheading as the information is the same. The CHMP adopted the following harmonised wording:

"Treatment duration

The usual duration of treatment for most indications is in the range of 5-14 days. However, the duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress."

j) Co-administration with other antibacterial agents

The MAH stated that all member states include varying information on co-administration with other antibacterial agents and provided a detailed overview of the nationally approved wording. The MAH proposed the following wording for the subsection 'Co-administration with other antibacterial agents', in line with the company Core Data Sheet, version 15.0 dated 4 June 2009.

The CHMP did not consider the MAH proposal to be acceptable and removed the statement on the lack of need to add an agent. There should be a cross reference to 4.2 from the affected indications in 4.1. Information on the in-vitro interaction should be in section 6.

In conclusion, the CHMP adopted a harmonised wording for Section 4.2.

Section 4.3 - Contraindications

The MAH noted that only two member states had a statement that "Children below 2 years of age must be excluded from therapy until further experience is available." The information on hypersensitivity to the active substances or any of the other ingredients and class specific hypersensitivity to b β-lactams and β-lactamase inhibitors was included in all national SPCs. The MAH proposed a harmonised wording in line with the current MAH Core Data Sheet (CDS) where the contraindications are "hypersensitivity to piperacillin, tazobactam, or any other ingredients, as well as hypersensitivity to any β-lactams or β-lactamase inhibitors." Each of the local labels discusses these same contraindications. Since the CDS language accurately reflects the language of these local labels, it was proposed for use in the harmonised SPC. The recommendation that children below 2 years of age should be excluded from therapy until further experience is available, present in two nationally approved SPCs, was moved to Section 4.2.

The CHMP did not agree with the MAH proposal and instead adopted the following harmonised wording:

"Hypersensitivity to the active substances, any other penicillin-antibacterial agent or to any of the excipients.

History of acute severe allergic reaction to any other beta-lactam active substances (e.g. cephalosporin, monobactam or carbapenem).”

Section 4.4 - Special Warnings and Precaution for Use

The MAH listed the warnings and precautions present in all 28 countries and provided an overview of all additional warnings and precautions approved in only a few member states. The MAH submitted a proposal for a harmonised Section 4.4 in line with its Core Data Sheet, version 15.0 dated 4 June 2009.

The CHMP largely agreed with the MAH proposal but enforced some additions. In particular, there needs to be a caution regarding use in patients without severe hypersensitivity reaction to non-penicillin β-lactams but who may have had non-severe reactions. The MAH should discuss the potential risk of these types of reactions to other classes of β-lactam agents occurring in response to Tazocin treatment. The warning on pseudomembranous colitis should also be supplemented in the end with *“Tazocin should be discontinued.”* In addition, the MAH was requested to add statements regarding the emergence of resistant organisms. The MAH agreed with the CHMP proposals and inserted precautionary language to state the risk of hypersensitivity reactions in patients with previous reactions to penicillins, other β-lactam agents (e.g., cephalosporins, monobactam, or carbapenem), and other allergens. The CHMP agreed with the revised proposal and adopted the following harmonised wording for Section 4.4.

“The selection of piperacillin-tazobactam to treat an individual patient should take into account the appropriateness of using a broad-spectrum semi-synthetic penicillin based on factors such as the severity of the infection and the prevalence of resistance to other suitable antibacterial agents.

Before initiating therapy with Tazocin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, other beta-lactam agents (e.g. cephalosporin, monobactam or carbapenem) and other allergens. Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid [including shock]) reactions have been reported in patients receiving therapy with penicillins, including piperacillin / tazobactam. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens. Serious hypersensitivity reactions require the discontinuation of the antibiotic, and may require administration of epinephrine and other emergency measures.

Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. In these cases Tazocin should be discontinued.

Therapy with Tazocin may result in the emergence of resistant organisms, which might cause super-infections.

Bleeding manifestations have occurred in some patients receiving beta-lactam antibiotics. These reactions sometimes have been associated with abnormalities of coagulation tests, such as clotting time, platelet aggregation and prothrombin time, and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

Leucopenia and neutropenia may occur, especially during prolonged therapy; therefore, periodic assessment of haematopoietic function should be performed.

As with treatment with other penicillins, neurological complications in the form of convulsions may occur when high doses are administered, especially in patients with impaired renal function.

Each vial of Tazocin 2 g / 0.25 g contains 5.58 mmol (128 mg) of sodium and Tazocin 4 g / 0.5 g contains 11.16 mmol (256 mg) of sodium. This should be taken into consideration for patients who are on a controlled sodium diet.

Hypokalaemia may occur in patients with low potassium reserves or those receiving concomitant medications that may lower potassium levels; periodic electrolyte determinations may be advisable in such patients.”

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

The MAH stated that the piperacillin-tazobactam SPC listed the following interactions: non-depolarizing muscle relaxants, oral anticoagulants, methotrexate, probenecid, aminoglycosides, and vancomycin. The MAH provided an overview of the divergences between the nationally approved wordings for Section 4.5 of the SPC and presented a proposed harmonised Section 4.5 in line with the MAH Core Data Sheet, version 15.0 dated 4 June 2009.

The CHMP largely agreed with the MAH proposal. However, the MAH was requested to comment on what, if any, specific interaction studies have been carried out with piperacillin-tazobactam. As necessary section 4.5 should include a statement about the lack of specific interaction studies. The MAH should confirm that a comprehensive literature search was performed to identify other possible interactions. The MAH should also confirm that post marketing pharmacovigilance data have been studied to identify further drug interactions. The CHMP also requested specific headings to be inserted for each interaction. In addition, the paragraph regarding interaction with tobramycin should be further developed and a statement that the metabolism of tobramycin in patients with normal renal function and severe renal dysfunction is different should be inserted, which implies that the dosing of both agents may need to be adjusted accordingly. A similar warning regarding penicillins/cephalosporins is present in the SPC for tobramycin. A reference to Section 6.2 and Section 6.6 regarding the administration of piperacillin-tazobactam with aminoglycosides was also inserted.

The MAH agreed with the CHMP comments and stated that the support for the current wording comes from several sources including the approved piperacillin label, studies performed during piperacillin-tazobactam development and from publications by other investigators besides the MAH. The MAH discussed the available data supporting each of the drug interactions currently described in the proposed harmonised SPC, carried out a literature and discussed post-marketing pharmacovigilance reports. No specific drug interaction studies were performed to study the interaction with non-depolarizing muscle relaxants, with heparin or oral anticoagulants nor with methotrexate. The MAH listed and discussed the studies carried out dring the development program for piperacillin-tazobactam: drug-drug interaction studies were conducted in healthy volunteers between piperacillin and tazobactam, between piperacillin-tazobactam and probenecid, and with tobramycin and vancomycin. A second interaction study with tobramycin was performed shortly after approval of piperacillin-tazobactam in the USA. The MAH reviewed the literature available, discussing publications by Hansen et al (2010), Wise et al, Strenkoski et al, Landersdorfer (2008), Hitt (1997), Zarychanski et al (2006) and Wong (2009) and stated that all reports of drug interaction in the PSUR are routinely reviewed. No new safety information has been added to the RSI based on these reviews. The MAH considered the available information on the interaction studies to justify the proposed harmonised wording in the SPC. The CHMP agreed and adopted a harmonised wording for Section 4.5.

Section 4.6 – Fertility, pregnancy and lactation

The MAH stated that the contents of the section '4.6 Pregnancy and lactation' were the same in all countries although the wording used was slightly different. The MAH presented a proposed wording in line with the MAH Core Data Sheet, version 15.0 dated 4 June 2009.

The CHMP considered the justification provided by the MAH for the proposed wording to be acceptable, however, it was noted that published studies conducted with the combination of piperacillin-tazobactam, via intraperitoneal and intravenous route of administration, have shown developmental toxicity. The CHMP requested the MAH to mention the conclusions of these studies in a succinct manner under section 4.6, with cross-reference to a summary of the relevant data under section 5.3 of the SPC. The MAH agreed to the proposed wording and the CHMP therefore adopted the following harmonised wording for Section 4.6:

"Pregnancy

There are no or a limited amount of data from the use of Tazocin in pregnant women.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic (see section 5.3).

Piperacillin and tazobactam cross the placenta. Piperacillin-tazobactam should only be used during pregnancy if clearly indicated, i.e. only if the expected benefit outweighs the possible risks to the pregnant woman and foetus.

Breast-feeding

Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Women who are breast-feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

Fertility

A fertility study in rats showed no effect on fertility and mating after intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam (see section 5.3)."

Section 4.7 - Effects on ability to drive and use machines

The MAH stated that the wording of Section '4.7 was similar ('not relevant / not known') in all countries with exception on five member states and proposed the wording "Not relevant." For this section, in line with the MAH Core Data Sheet, version 15.0 dated 4 June 2009. In conclusion, the CHMP adopted the following harmonised wording for Section 4.7:

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

Section 4.8 - Undesirable effects

The MAH noted no major differences in the nationally approved SPCs for Section 4.8. Several member states used outdated wording of the Systemic Organ Classes (SOC) and the ADRs were in some cases listed with different frequencies. Several member states also listed information on other systemic adverse reactions observed in clinical studies following administration of piperacillin-tazobactam without causal connections. The MAH provided an overview of the divergences in the nationally approved wordings and proposed a harmonised wording for this section, updated in accordance with the current MedDRA terminology. In addition, the adverse drug reactions (ADRs) were presented in order of decreasing seriousness within each frequency group. The section 4.8 is in all countries consistent with the company Core Data Sheet, version 15.0 dated 4 June 2009. The information on other systemic adverse reactions which have been observed in clinical studies following administration of piperacillin-tazobactam and for which a causal connection could not be established were deleted.

The CHMP considered that the justifications provided by the MAH for the proposed wording were acceptable. The MAH was requested to discuss and clarify the insertion of the following ADRs in the applicable SOCs: dizziness, hallucinations, diarrhoea haemorrhagic, dry mouth, hyperhidrosis, eczema, muscular weakness, myalgia, oedema, asthenia and fatigue, which appear to be missing.
The MAH agreed to include three terms (Candidal superinfection, Maculopapular rash, and Exanthema) without further assessment and conducted cumulative safety reviews for the remaining terms (Muscle weakness, Hallucination, Convulsion, Dry mouth, Erythema, Increased sweating, Eczema, Tiredness, Myalgia, and Edema). Based on these reviews, the MAH agreed to include the term Myalgia as proposed by the CHMP. However, for the remaining proposed terms, a reasonable suspicion of causality could not be established based on the lack of meaningful reports. The MAH therefore proposed to exclude these terms from the ADR table. The CHMP agreed to the MAH proposal and adopted a harmonised wording for Section 4.8.

Section 4.9 - Overdose

The MAH noted and provided an overview of the differences between the currently approved wording of Section 4.9 and proposed a harmonised wording in line with the MAH Core Data Sheet, version 15.0 dated 4 June 2009.

The CHMP considered the MAH justification to be acceptable but added a sentence on discontinuation of treatment in case of overdose and the absence of an antidote. In conclusion, the CHMP adopted the following harmonised wording for Section 4.9:

"Symptoms
There have been post-marketing reports of overdose with piperacillin / tazobactam. The majority of those events experienced, including nausea, vomiting, and diarrhoea, have also been reported with the usual recommended dose. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment
In the event of an overdose, piperacillin / tazobactam treatment should be discontinued. No specific antidote is known.

Treatment should be supportive and symptomatic according to the patient's clinical presentation.

Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis (see section 4.4)."

Section 5.1 - Pharmacodynamic properties

The MAH stated that due to different national requirements at the time of approval, differences were introduced in the approved wordings of Section 5.1. All required information e.g. 'Mechanism of action' and 'Mechanism of resistance' is present in all countries, but the statements differ in the depth of elaborations. All member states use the same minimum inhibitory concentration (MIC) based on UK-breakpoints but due to national approvals and different approval times there were minor divergences in the presentation of the data and also the summary/listing of susceptible organism differed slightly. The MAH only provided in vitro data in support of this section and identified the pathogens against which clinical efficacy has been demonstrated in clinical trials. In addition, the MAH internal database searches did not indicate any lack of efficacy reports for any pathogen. The MAH presented an SPC Comparison Table with detailed country-specific information and proposed a harmonised wording.

The CHMP did not accept the MAH proposal and required a complete re-write of the section. Irrespective of current national divergences, it should be written strictly in accordance with current guideline *NfG on evaluation of medicinal products indicated for treatment of bacterial infections CPMP/EWP/558/95 rev 1*) and without excessive listings of species (genera to be used instead of species wherever appropriate). Only the EUCAST MIC breakpoints should be inserted and only species relevant for the approved indication should be listed. The CHMP also deleted *Neisseria gonorrhoeae* from the table in Section 5.1, as the indication "*Gynaecological infections, including postpartum endometritis and pelvic inflammatory disease" was deleted*. The MAH accepted the proposed changes and revised the table of commonly susceptible species. The CHMP agreed to the revised proposal and adopted a harmonised wording for Section 5.1.

Section 5.2 Pharmacokinetic properties

The MAH stated that due to different national requirements at the time of product approval, divergences exist between the approved wordings: while the required information is present in all member states, the statements differ in the depth of elaborations. The MAH proposed a wording in line with the company Core Data Sheet, version 15.0 dated 4 June 2009.

The CHMP noted that no data was submitted in support of PK data for the intramuscular route or the paediatric population. Regarding absorption, the CHMP requested clarifications on whether these data refer to healthy subjects or patients. T_{max} after i.m. and i.v. administration and Css after multiple dosing should be specified. AUC after i.m. and i.v. administration should be reported. In addition, it was not clear from where all the figures mentioned in this section were obtained. Appropriate PK data to support these should be provided. The MAH provided full references for all the figures mentioned in Section 5.2 and revised the relative ratio of piperacillin-tazobactam tissue to plasma ratios to reflect the current practice of using ratios of AUC instead of individual concentrations. This was accepted by the CHMP and a harmonised wording was adopted for Section 5.2.

Section 5.3 Preclinical safety data

The MAH stated that due to different national requirements at the time of product approval, there are differences in the approved wordings of this section. Although the required information is present in all member states, the statements differ in the depth of elaborations. The MAH proposed a harmonised wording, in line with the company Core Data Sheet, version 15.0 dated 4 June 2009.

The CHMP recommended presenting only the preclinical information relevant to the prescriber, in a succinct manner and also requested the MAH to insert a wording reflecting the current state of knowledge about the reproductive toxicity of the product, in line with the text approved for recent EU procedures for generics of piperacillin-tazobactam and including a summary of published data about the reproductive toxicity testing of piperacillin and tazobactam. The MAH agreed and the CHMP adopted the following harmonised wording for Section 5.3:

"Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity. Carcinogenicity studies have not been conducted with piperacillin / tazobactam.

A fertility and general reproduction study in rats using intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam reported a decrease in litter size and an increase in fetuses with ossification delays and variations of ribs, concurrent with maternal toxicity. Fertility of the F1 generation and embryonic development of F2 generation were not impaired.
Teratogenicity studies using intravenous administration of tazobactam or the combination piperacillin / tazobactam in mice and rats resulted in slight reductions in rat fetal weights at maternally toxic doses but did not show teratogenic effects.

Peri/postnatal development was impaired (reduced pup weights, increase in stillbirths, increase in pup mortality) concurrent with maternal toxicity after intraperitoneal administration of tazobactam or the combination piperacillin / tazobactam in the rat."

Section 6 - PHARMACEUTICAL PARTICULARS

Section 6.1 – List of excipients

The MAH noted the variations across the EU due to differing national nomenclature and requirements of how the information is presented in the national SPCs and presented a harmonised wording based on the information in Module 3, section 3.2.P.1 '3.0 Composition'.

The CHMP noted the MAH clarification that only EDTA-containing formulations are currently registered in all the member states. The CHMP adopted a harmonised wording for Section 6.1.

Section 6.2 Incompatibilities

The MAH stated that information on concurrent use with another antibiotic, together with statements that the medicinal product should not be mixed with other drugs in a syringe or infusion bottle and statements that the product should not be used in solutions containing only sodium bicarbonate are present in all member states. However, some information is not present in all member states and the MAH presented an overview of the divergences. Piperacillin and tazobactam for injection (EDTA Formulation) drug product was shown to be compatible for co-administration via a Y-site intravenous tube with amikacin, tobramycin and gentamicin (Module 3, section 3.2.P.2.6). The MAH proposed a harmonized wording based on the results of the compatibility tests provided in the harmonised Module 3.

The CHMP considered the wording for this section to be acceptable and adopted a harmonised wording for Section 6.2.

Section 6.3 Shelf life

The MAH presented the divergences between the nationally approved wordings and submitted stability data to support the 3 year shelf life in the harmonised Module 3, section 3.2.P.8 for all member states. Solution stability studies on samples reconstituted with Sodium Chloride Injection held at 25ºC and tested after 0 and 24 hours and held at 2-8ºC and tested after 7 days, indicated that the reconstituted product remains physically and chemically stable under these time and temperature conditions (Module 3, section 3.2.P.8.3). To give appropriate information to the user for the handling after the dilution or reconstitution of the medicinal product, the wording recommended in the 'CPMP/QWP/159/96 corr - Note For Guidance On Maximum Shelf Life For Sterile Products For Human Use After First Opening Or Following Reconstitution' was added. The MAH proposed a harmonised wording for Section 6.3.

The CHMP considered the change in shelf-life to up to 36 months to be supported. The stability data for reconstituted solution also supports the in-use shelf-life. The CHMP adopted a harmonised wording for Section 6.3.

Section 6.4 - Special precautions for storage

The MAH stated that 26 out of 27 member states included the storage condition 'do not store above 25°C'. Based on the available stability data (Module 3, section 3.2.P.8) and in accordance to the

'Guideline on: A. Declaration of Storage Conditions in the Product Information of Medicinal Products' CPMP/QWP/609/96/Rev 2, 2007, the MAH proposed a harmonised wording for Section 6.4:

The CHMP considered that the storage condition is in compliance with the updated data, however, the statement 'Keep vials in the outer carton' was not supported by any data and was removed. The stability data for reconstituted solution supports the in-use shelf-life. The CHMP adopted a harmonised wording for Section 6.4.

Section 6.5 - Nature and contents of container

The MAH stated that the nature of the container is the same in all countries; only the presentations approved and described in the SPC section '6.5 Nature and contents of container' are different. The MAH stated that detailed information on the container of the drug product was presented in Module 3 and section 3.2.P.7. The CHMP adopted a harmonised wording for Section 6.5.

Section 6.6 - Special precautions for disposal and other handling

The MAH stated that information on special precautions for disposal and other handling is presented in all countries but that the statements differ in the depth of elaborations. The MAH conducted several studies to verify the compatibility and the suitability of the container closure system with the drug product as reported in Module 3, sections 3.2.P.2.4 and 3.2.P.2.5. Furthermore, studies were conducted on admixtures of piperacillin and tazobactam (EDTA formulation) in various intravenous fluids, including Lactated Ringer's injection or Ringer's acetate and Ringer's acetate/malate. Compound sodium lactate intravenous infusion (synonym Hartmann's Solution) has also been shown to be a suitable infusion fluid for use with piperacillin and tazobactam (Section 3.2.P.2.6). Storage stability for both reconstituted vials and admixture solutions, were also verified (Section 3.2.P.2.6). Piperacillin and tazobactam for injection (EDTA Formulation) drug product was shown to be compatible for co-administration via a Y-site intravenous tube with amikacin, tobramycin and, gentamicin (Module 3, section 3.2.P.2.6). The wording of the harmonised SPC section '6.6 Special precautions for disposal and other handling' is based on the Module 3. The MAH provided a detailed overview of the country specific information and proposed a harmonised wording for Section 6.6.

The CHMP agreed with the proposal but noted that Water for Injection that complies with Ph. Eur does not contain any benzyl alcohol or parabens. Furthermore, bacteriostatic water for injection with benzyl alcohol and parabens is not commonly used in the EU and was therefore deleted. The CHMP agreed on the list of IV diluents compatible with Tazocin and noted that the use of EDTA increases the compatibility with aminoglycosides. The CHMP adopted a harmonised wording for Section 6.6.

Module 3

The MAH stated that all of formulations without EDTA have by now been replaced by updated formulations which contain EDTA (first authorised in the EU in 2006) and there are currently no MAs in the EU, Norway and Iceland without EDTA. Module 2 (QOS) was also updated in line with Module 3. The MAH provided a 'CMC-Divergence Overview' document with the harmonized dossier where changes performed to all the existing national dossiers are briefly described. Additionally, a tabular comparison of all the sections of module 3 that vary between member states was provided. Piperacillin and tazobactam are combined in a single intravenous formulation to treat gram-negative and anaerobic infections. Piperacillin has a European Pharmacopoeia (Ph. Eur.) monograph while tazobactam is described in a monograph of the USP. Divergence summaries were provided by the MAH indicating the differences between the dossiers approved in each member state. For each of the three drug substance manufacturers (the two separate manufacturer for piperacillin and the tazobactam manufacturer), the MAH presented and discussed general information, the manufacture, the control of drug substance, the reference standard or materials, the container closure system and the stability. For the drug product, the MAH presented and discussed the description and composition of the drug product, the pharmaceutical development, the manufacture, the control of excipients, the control of drug products, the reference standard, the container closure system and the stability.

DRUG SUBSTANCE – Piperacillin (manufacturer 1)

The MAH confirmed that the Piperacillin Monohydrate (PMH) drug substance used in the manufacturing of Tazocin powder for solution for injection/infusion (EDTA Formulation) drug product complies with both USP and Ph. Eur. monographs. The manufacturer holds a valid Certificate of Suitability (CEP) for

the manufacture of piperacillin monohydrate. The CHMP raised a number of issues for further discussion.

Regarding the analytical methods for the control of the drug substance section, the MAH was requested to replace the USP methods used in testing piperacillin by their equivalent Ph. Eur methods. The MAH committed to do so or alternatively submit a statistical equivalence study between USP and EP methods within the 1st quarter of 2011. The response was accepted by the CHMP and the issue was considered to be resolved.

The MAH was also requested to provide the report for validation of the GC method for determination of ethyl acetate. The MAH included this report in a revised Section 3.2.S.4.3 of the dossier relative to the PMH drug substance. The CHMP noted that the report was provided and that the method has also shown to be capable of detecting ethanol and triethyl amine. The response was accepted by the CHMP and the issue was considered to be resolved.

Finally, the MAH was requested to provide a validation report for test of microbial contamination and bacterial endotoxins. The MAH provided this validation report in a revised Section 3.2.S.4.3 of the dossier relative to the PMH drug substance. The response was accepted by the CHMP and the issue was considered to be resolved.

Regarding the reference standards or materials section, the MAH was requested to use the available EP chemical reference substance (CRS) is available for piperacillin and ampicillin as primary reference standards instead of the USP reference standards. The MAH confirmed that the primary reference standards used for the testing of PMH drug substance will be EP CRS within the 1st quarter of 2011. The response was accepted by the CHMP and the issue was considered to be resolved.

Regarding the container closure system section, the CHMP noted that the dry piperacillin monohydrate drug substance is packaged in a low density polyethylene bag, which is sealed with a crimp seal. This bag is placed into a second polyethylene bag, which again is crimp-sealed. The CHMP requested a declaration from the supplier of the plastic bags for its compliance with the European standards 2002/72/EC for plastic material in immediate contact (food contact). The MAH included the certification of compliance according to European standards 2002/72/EC, regarding the plastic bags in immediate contact with the PMH drug substance in a revised relevant Section 3.2.S.6. The response was accepted by the CHMP and the issue was considered to be resolved.

Regarding the stability section, the CHMP noted that no data under accelerated storage conditions was provided and the MAH was therefore requested to commit to perform full stability testing as per ICH recommended storage conditions. If available, this data should be included in the dossier to support the retest period. The MAH stated that all the provided stability studies in Section 3.2.S.7.3 carried out on the drug substance were performed at a storage temperature of 8 ± 2 °C, which represents a worst case scenario with respect to the ICH recommended storage condition (5 ± 3 °C) and although the testing frequency have not been set strictly according to the current ICH guidelines, it can be considered sufficient to establish the drug substance stability profile. However, additional stability data have been included in Section 3.2.S.7.3 for one batch of piperacillin monohydrate stored at 5 ± 3°C for up to 24 months tested according to a stability protocol complying with ICH guidelines. Moreover, the MAH confirmed that all future stability studies on batches of the drug substance will be conducted according to ICH recommended storage conditions available to any of the European Health Authorities upon request. Nevertheless, based on the stability data collected over the years that has been sufficient to establish the stability profile of PMH drug substance, the testing frequency for the stability protocol was reduced as reported in Section 3.2.S.7.2 in compliance with ICH Q7/11-54. The CHMP agreed with the commitment to conduct all future stability studies in line with ICH requirements and noted that the MAH has extensive experience in the manufacture and control of piperacillin, supporting the retest period of 24 months.

DRUG SUBSTANCE – Piperacillin (manufacturer 2)

The manufacturer holds a drug master file for the manufacture of piperacillin monohydrate, with a current version dated 2003. Piperacillin monohydrate is manufactured from ampicillin and satisfactory details for structure elucidation and characterisation were provided. The drug substance specification is based on the *Ph. Eur.* and includes acceptable test parameters. A retest period of 24 months for storage under refrigerated conditions was approved. No further issues were raised.

DRUG SUBSTANCE – Tazobactam

The drug substance specification complies with the USP monograph and includes relevant tests such as description, identification, water content, pH, specific optical rotation, assay, bacterial endotoxins and microbial limits to ensure quality. These are adequate. The MAH provided a detailed description of the manufacturing process for tazobactam; however the CHMP raised a number of issues for further discussion.

Regarding the Control of Drug Substance section, the CHMP noted that in some in the tazobactam specification, there was confusion over the name one the main degradation compounds and the MAH was requested to clarify. The MAH clarified the correct name of the main degradation product of tazobactam. The response was accepted by the CHMP and the issue was considered to be resolved.

Regarding the Analytical methods, the MAH provided satisfactory descriptions of all the analytical methods used in testing of tazobactam, however references to USP methods for testing tazobactam should be replaced by equivalent Ph. Eur methods. The MAH stated that the tazobactam active pharmaceutical ingredient (API) has no compendial reference in the European Pharmacopoeia and that they therefore chose to use USP as a compendial reference for this Drug Substance. The MAH also agreed to use a European Pharmacopoeia standard for tazobactam drug substance when and if this will be included as one of the European Pharmacopoeia monographs. The response was accepted by the CHMP and the issue was considered to be resolved.

In addition, the CHMP noted that for residual solvents, the GC method is used. However, no validation report for the GC method was included and the MAH was therefore requested to include the reports for validation of GC method used for determination of residual solvents in the dossier. The MAH included the report for validation of the GC method for determination of residual solvents in a revised Section 3.2.S.4.3 of the dossier relative to the tazobactam Drug Substance. The response was accepted by the CHMP and the issue was considered to be resolved.

Finally, the CHMP requested the MAH to provide a validation report for test for microbial contamination and bacterial endotoxins. The MAH included the reports for validation of microbial contamination and for the validation of bacterial endotoxins in a revised Section 3.2.S.4.3 of the dossier relative to the tazobactam Drug Substance. The response was accepted by the CHMP and the issue was considered to be resolved.

Regarding the justification of specification, the specifications for tazobactam are established based on the requirements of the current United States Pharmacopoeia (USP). This is acceptable considering that there is no Ph. Eur monograph of tazobactam. In general the limits of impurities were justified by batch analysis data and controlled to a limit of not more than (NMT) 0.1%. Only one impurity, CL 181,643-degradation impurity is outside the ICH qualification threshold and the MAH was requested to include a justification for the limit for CL 181,643. The MAH stated that the current limit for tazobactam is in line with the requirements of USP which is currently the most acknowledged compendial reference for this drug substance. From a toxicological point of view, this impurity has been shown to be the main metabolite of tazobactam in the human body and as such it can be considered that its safety has been assessed at much higher levels during clinical studies. The MAH therefore considered the levels set at “Not More Than 1.0%” to be justified for this impurity. The response was accepted by the CHMP as the limit of NMT 1.0% on the basis of the presented batch data and stability data. Moreover, the CHMP acknowledged that the USP monograph supports the limits. The issue was considered to be resolved.

The CHMP also noted that the 2-mercaptobenzothiazole used in the manufacturing process is a potentially genotoxic compound and therefore requested the MAH to present evidence of its absence in the final drug substance. Additionally, a routine test for determination of 2-mercaptobenzothiazole should be added to the tazobactam control specification. The MAH clarified the rationale for including 2-mercaptobenzothiazole in the tazobactam synthetic process and presented the removal process, stating that the likelihood of 2-mercaptobenzothiazole being present in the final active pharmaceutical ingredient (API) is extremely low, and is therefore considered as a potential theoretical impurity in tazobactam drug substance. The MAH agreed to develop and validate an analytical method that will be suitable for the determination of 2-mercaptobenzothiazole in tazobactam drug substance. The MAH stated that the maximum daily dose of tazobactam drug substance which can be given to a patient (based on 4g of piperacillin and 0.5g of tazobactam 4 times a day) is 2g/day. The threshold of toxicological concern (TTC) for 2-mercaptobenzothiazole is 1.5µg/day. Therefore, in order not to exceed the TTC the levels of 2-mercaptobenzothiazole detectable in batches of finished tazobactam API should not exceed 0.75ppm. The MAH tested ten batches of tazobactam finished API using a validated

method with a detection limit for 2-mercaptobenzothiazole of 0.25ppm. In all ten batches, the presence of 2-mercaptobenzothiazole was not detected, confirming that any hypothetical trace of 2-mercaptobenzothiazole is below 0.25ppm. These findings are in line with the manufacturing process step during which 2-mercaptobenzothiazole is completely removed during the synthesis. Based on these findings the MAH believed that it is not necessary to implement a routine test for 2-mercaptobenzothiazole. The CHMP considered that the method has been satisfactorily validated and the issue was considered to be resolved.

Regarding the container closing system, the CHMP noted that bulk tazobactam is packaged using double polyethylene bags and a steel drum. The polyethylene bags are in compliance with the standards set by the Japan Hygienic Olefin and Styrene Plastics Association (JHOSPA). However, the CHMP requested the MAH to provide confirmation that the primary packaging material (polyethylene bags in direct contact with tazobactam) is in compliance with the food contact requirements of Directive 2002/72/EC. The MAH provided certification of compliance according to European standards 2002/72/EC, regarding the plastic bags in immediate contact with the tazobactam drug substance in a revised Section 3.2.S.6. The response was accepted by the CHMP and the issue was considered to be resolved.

Drug Product

The piperacillin-tazobactam drug product is formulated as sterile powder for solution for injection/infusion (EDTA formulation) as a freeze-dried powder for intravenous infusion and is currently marketed in all member states. The approved formulation contains an 8:1 weight ratio of piperacillin to tazobactam (present as their sodium salts) and is packaged in clear Type I glass vials with crimp-sealed butyl rubber closures. The EDTA formulation contains disodium edetate dihydrate (as a chelating agent) and citric acid monohydrate (as a buffering agent). Both disodium edetate dihydrate (EDTA) and citric acid are associated with inhibition of particulate formation. The EDTA containing formulation has been demonstrated to have better compatibility with commonly used IV diluents and is also compatible with certain aminoglycosides. The manufacturing process involves solubilisation of piperacillin and tazobactam in water by using sodium hydrogen carbonate. The solution is by sterilisation by filtration. The sterile solution is then filled in vials and lyophilised. The partially stoppered vials are fully closed while in the lyophiliser. These vials are unloaded and labelled and packed. Adequate details of the manufacturing process are provided. The drug product control specification is adequate. Modifications to the drug product specifications have been fully justified. Stability data has been provided to support the shelf life of the product is adequate. The stability data has been updated to support the shelf-life claim of 3 years.

Regarding the compatibility section, the CHMP noted that the information provided with regards to the Pharmaceutical Development contained a summary of the historical pharmaceutical development data together with all the information provided to all of the national European Health Authorities when the Drug Product was reformulated. In addition the dossier also contained three additional studies for the new formulation which have been subsequently presented to the Health Authorities of only a limited number of countries. The first of these three studies was RPT-65972 which served to provide additional solidity to the claim of compatibility of piperacillin and tazobactam for Injection with amikacin and gentamicin via a Y-site infusion set. The second was RPT-70423 which contains data generated upon request of the German Health Authorities to support the claim of compatibility of piperacillin and tazobactam for Injection with gentamicin. The third study, RPT-74066, was presented to the Health Authorities of a limited number of Northern European countries and provided evidence of compatibility of piperacillin and tazobactam for Injection with Ringer's acetate and Ringer's acetate/malate. The MAH was requested to provide the compatibility studies RPT-65972 and RPT-70423. The MAH included these studies in the revised Section 3.2.P.2.6. The MAH also included reports were provided to FDA for Tazocin label expansion for the Y -site co-infusion of gentamicin at all clinically relevant concentrations in presence of 5% dextrose or 0.9% sodium chloride (RPT- 76099 and RPT-75934).

The CHMP also considered the data presented to support the claimed Y-site-compatibility with aminoglycosides (in particular gentamicin) to be insufficient and that evidence of the reliability of the presented results for the content of the aminoglycosides was missing. Gentamicin is a complex mixture of several compounds and an High Performance Liquid Chromatography-assay for gentamicin might therefore not be able to differentiate between different (active) compounds and (inactive) impurities. However, neither the methods used nor any validation data have been presented. Furthermore, the acceptance criteria for compatibility presented were not state of the art. The formation of impurities, in particular the adduct of piperacillin with the aminoglycoside were not investigated. Further proof of compatibility with gentamicin should be provided. For amikacin, the method used including validation

data should be provided. For the solutions with amikacin, data for related substances (known and unknown) should be provided. The content of the detected impurities should be assessed with regard to safety. The MAH provided responses to this outstanding issue. As per the theoretical calculation provided, the maximum length of time the gentamicin and piperacillin will be in contact is approximately 10 minutes in clinical conditions. There is a possibility of adducts between gentamicin and piperacillin forming, however, as per the data provided, the mixture is stable for more than 30 minutes. The NMR method used was satisfactorily discussed and it was noted that the SPC of most member states since 2006 that administration along with gentamicin through Y-site should be restricted to critical circumstances only. The response provided satisfactorily addresses the outstanding points. Since there is a difference in the composition of Tazocin and other generic equivalents already on the EU market, the compatibility of these products is also different. Section 6.6 comparability profile of the SPC of Tazocin and associated names, should be include a condition 'in line with module 3 data'. This will require each generic manufacturer to generate data to support the compatibility profile. The response was accepted by the CHMP and the issue was considered to be resolved.

The MAH was requested to include process validation data of commercial batches of Tazocin manufactured at both the sites. The MAH included validation data of commercial batches of Tazocin 2.25g and 4.5g manufactured in Section 3.2.P.3.5 Process Validation Summary. Three consecutive commercial scale (validation) batches of Tazocin (EDTA Formulation) drug product presentations 2.25g and 4.5g were successfully validated. The response was accepted by the CHMP and it was noted that these sites are already approved for the manufacture of EDTA for national licenses for all the MS and have extensive experience in manufacture of this product. The issue was considered to be resolved.

The MAH provided sterile filter validation for Tazocin manufactured at both production sites in the revised Section 3.2.P.3.5 Sterile Filter Validation Summary and described the validation process. The MAH also provided media-fill simulation runs for the manufacturing process due to the manufacturing process involving substantial aseptic handling. The MAH stated that media fill validation runs were performed for Tazocin (EDTA Formulation) drug product presentations 2.25g and 4.5g to demonstrate that acceptable sterile manufacturing processes are established. The results were reported in the revised Sections 3.2.P.3.5 Aseptic Process Simulation (Media Fill) Data and 3.2.P.3.5 Aseptic Process Simulation (Media Fill) Summary and the MAH provided a description of the process. The responses were accepted by the CHMP and the issue was considered to be resolved.

Regarding the control of the drug product, the CHMP made a number of remarks. The CHMP noted that the changes to the drug product specification were based on the specification already approved in other member states and that the limits were more stringer than approved in most member states. The main change was to include all the degradents for each drug substance. The MAH updated Sections 2.3.P.5 and 3.2.P.5.1 to include impurity CL 287,835 (originating from piperacillin) in the shelf life specification and stated that the impurity is already present in the information relevant to release testing as presented in Section 3.2.P.5.1. Sections 3.2.P.5.6, 3.2.P.8.2 and 3.2.P.8.3 were also revised and integrated as a consequence of this change. The response was accepted by the CHMP and the issue was considered to be resolved.

The CHMP endorsed the change of calculation of the related substances and subsequently of the specification limits to weight/weight related to the parent substance. However, the results for 'total related compounds' as well as for 'any other related compound (total)' should be calculated as the sum of the single results reported and separated as total (other) related compounds of piperacillin and tazobactam, respectively to ensure the link between the single results and the total impurities. The MAH revised Sections 2.3.P.5 and 3.2.P.5.1 to report 'Total Related Compounds from piperacillin' and 'Total Related Compounds from tazobactam' as well as 'Other Related Compound (Total) from piperacillin' and 'Other Related Compound (Total) from tazobactam', respectively. Sections 3.2.P.5.2, 3.2.P.5.4, 3.2.P.5.6 and 3.2.P.8.2 were consequently revised and integrated to reflect this change. The changes to representation of limits for total related substances response were accepted by the CHMP and the issue was considered to be resolved.

The CHMP also noted that the specification limit for impurity CL 181,643 (tazobactam penicillamin) might be qualified, as it is a metabolite and also proposed to tighten the limit for this impurity to NMT 1.0 % (release) and NMT 3.8 % (shelf-life), based on actual batch data. After evaluating a consistent number of drug product batches manufactured at both proposed manufacturing sites, the MAH agreed to accept the tighter limits proposed of NMT 1.0 % (release) and NMT 3.8 % (shelf-life) for impurity CL 181,643 (tazobactam penicillamin). The MAH revised Sections 2.3.P.5, 3.2.P.5.1, 3.2.P.5.4, 3.2.P.5.6, 3.2.P.8.2 and 3.2.P.8.3 to reflect this change. The response was accepted by the CHMP and the issue was considered to be resolved.

The CHMP requested the MAH to tighten the limits for residual solvents in the drug product in line with Ph. Eur. 5.4 as the maximum daily dose is 16 g piperacillin which in turns means that the daily dose of the whole mixture is 18.83 g. This is above 10 g which is the usual base for stating the limits of option 1. The limits for the residual solvents should be tightened accordingly (NMT 2656 ppm for Ethyl acetate). After evaluating a consistent number of drug product batches manufactured at both proposed manufacturing sites, the MAH agreed to accept the tighter limits proposed. However, in line with the capability of the analytical method, the proposed limit for ethyl acetate was NMT 0.26%. The MAH revised Sections 2.3.P.5, 3.2.P.5.1, 3.2.P.5.4 and 3.2.P.5.6 to take this change into account. The response was accepted by the CHMP and the issue was considered to be resolved.

The CHMP requested the MAH to qualify and if possible tighten the shelf-life limits for impurities relative retention time (RRT) 0.32 (NMT 0.4 %) and RRT 0.68 (NMT 0.3). The MAH agreed to the proposed tighter limits of NMT 0.2 % (shelf-life) for impurity RRT 0.32 and of NMT 0.15% (shelf-life) for impurity RRT 0.68. However, out-of-specification events were observed when using the new limits for the aforementioned impurities in the reconstituted samples of the stability batches. The MAH therefore proposed a revised label for usage of the reconstituted solution based on preliminary stability study which has purposely been conducted on reconstituted solutions. The revised stability protocol for the reconstituted solution was adopted for the Marketed Stability Program as reported in an updated Section 3.2.P.8.2. The new stability study shows that a vial of Tazocin for Injection drug product, after reconstitution, should be used within 12 hours when stored under refrigerated conditions. The new time limits and storage conditions proposed for a reconstituted solution will guarantee that the above mentioned impurities RRT 0.32 and RRT 0.68 will remain within the new proposed tighter limits. The MAH revised Sections 2.3.P.5, 3.2.P.5.1, 3.2.P.5.6, 3.2.P.8.1, 3.2.P.8.2 and 3.2.P.8.3 to take account of this change. The reduction in the recommended period of storage from 24h to 12 hour was accepted by the CHMP and the issue was considered to be resolved.

The CHMP noted that the maximum storage time of a reconstituted product as stated in the corresponding SPC does not necessarily mean that it will be used in this way every time. Therefore, any impurity developing after the maximum storage time of the reconstituted solution may not be considered qualified-by-use as this use is not properly documented. Usually the reconstituted solution will be used nearly immediately (i.e. within about two hours). Longer storage is not the normal use; therefore, qualification-by-use cannot be concluded. Qualification can be concluded if the impurity in question develops rapidly e.g. within 2 to 3 hours, but not after 24 hours. The older limit of NMT 1.0 % for ‘any other related compound (individually)’ cannot be considered as a qualification for the proposed limits as a general limit applied several years ago cannot qualify any concrete substance. 1.0 % of piperacillin corresponds to 160 mg based on the daily dose of 16 g. This amount of any unknown substance cannot be considered qualified without further information about the nature of the substance in question. The MAH stated that the previously submitted Section 3.2.P.5.1 had a limit of NMT 0.1% for ‘Any Other Related Compound (Individually)’ and agreed that the older limit of NMT 1.0 % for ‘Any Other Related Compound (Individually)’ cannot be considered as a qualification-by-use for any proposed limit. When necessary, the qualification of a proposed limit will be done based on historical data specifically relative to the impurity or based on data available in literature. Moreover, the MAH acknowledged and agreed that even specific data on an impurity cannot be used as qualification-by-use if this data is obtained from reconstituted solutions held for more than 2 hours. The response was accepted by the CHMP and the issue was considered to be resolved.

The CHMP requested the MAH to provide proposals for the degradation pathways leading to the impurities RRT 0.32, RRT 0.58, and RRT 0.68, as no supporting evidence of structure elucidation was presented for the uncommon structures of these impurities. The MAH included the degradation pathway leading to the formation of WYE 131175 (RRT 0.58) in the revised Section 3.2.P.5.5 and performed structure elucidation studies for the other two compounds to confirm the chemical structure. This allowed the confirmation of the chemical structure for the degradation compound WYE 125863-1 at RRT 0.32, using Electrospray (ESI) mass spectrometry and one and two-dimensional NMR. In addition, the structure elucidation performed on compound at RRT 0.68 revealed that the chemical structure which had originally been proposed for this compound was incorrect. The revised and correct chemical structure, along with details on the structure elucidation, was presented and a new structure ID was assigned to the RRT 0.68 degradant. The MAH revised Section 3.2.P.5.5 to reflect the latest findings, which now includes the correct chemical structure for the impurities found in the drug product, as well as the proposed degradation pathway for each of the impurities, including the proposed degradation pathway for impurities RRT 0.32, and RRT 0.68 as requested by the CHMP. The response was accepted by the CHMP and the issue was considered to be resolved.

Labelling and Package leaflet

The labelling and package leaflet were revised and brought in line with the adopted harmonised SPC.

2.3. Risk Management Plan

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

2.4. Recommendation

Based on the assessment of the MAH responses, the total body of available data and the input of the CHMP drafting group, the CHMP adopted a harmonised SPC, labelling and package leaflet for Tazocin and associated names.

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 Tazocin 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 Tazocin and associated names (see Annex I).