Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of Tazocin and associated names (see Annex I)

Tazocin was included in the list of products for Summary of Product Characteristics (SPC) harmonisation, due to the divergent national decisions taken by Member States concerning the authorisation of the product. 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. 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 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 procedure, in line with the notification. After the initial assessment, a number of lists of outstanding issues were discussed. A CHMP drafting group was convened on two occasions.

Section 4.1 – Therapeutic indications

The MAH proposed a list of harmonised indications based upon current guidelines (the EC guideline on SPC, September 2009 and *CPMP/EWP/558/95 rev 1 - Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections, 2004*) and on the MAH core data sheet (CDS). The CHMP provided general comments on Section 4.1, noting that the Note for Guidance 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. 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. For all indications, differences in clinical practices and national treatment recommendations are addressed by the sentence "*Consideration should be given to official guidance on the appropriate use of antibiotics."*

1. Lower Respiratory Tract Infections

The CHMP assessed the submitted data but considered 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 and therefore separated the discussion into community acquired pneumonia (CAP) and hospital acquired pneumonia (HAP), including ventilator acquired pneumonia (VAP).

Regarding CAP, the CHMP noted that the non-comparative studies submitted in the context of the initial MAA were performed involving patients with respiratory tract infections including lower respiratory tract infections and acute exacerbation of chronic bronchitis (AECB). The CHMP considered that AECB could not be accepted due to the lack of a superiority study.

Regarding HAP, the CHMP noted the presented comparative studies 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 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. Therefore, the CHMP considered the evidence sufficient to support the use of Tazocin in the treatment of HAP and VAP.

The CHMP concluded that the MAH provided satisfactory evidence demonstrating the efficacy of Tazocin in the treatment of LRTIs. The CHMP considered Tazocin to be a very valuable agent due to its broad antibacterial activity including many Gram-positive and Gram-negative pathogens, anaerobes as

well as several multi-drug resistant organisms common in nosocomial infections. This is why the drug should not be used in less severe infections, where more appropriate alternatives are available and instead be used in severely ill patients for cases of CAP that require hospitalisation. In conclusion, in line with the position of the CHMP drafting group, taking into account the extensive clinical experience and despite the limited data, The CHMP considered that Tazocin covers most organisms responsible for causing severe CAP, HAP and VAP. The CHMP adopted the following harmonised indication:

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

2. Urinary tract infections

The CHMP assessed the submitted data and noted that most member states list urinary tract infections (UTIs) 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 as well as in compliance with clinical practice. 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)"

3. Gastrointestinal, Biliary and Abdominal Infections

The CHMP assessed the submitted data and 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 every 8 hours 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"

4. Skin and Soft Tissue Infections

The CHMP assessed the data submitted but noted that the comparative studies were all performed at the initial US-approved regimen of 3.375 g every 6 hours. The CHMP considered that the studies suggests that Tazocin is efficacious in the treatment of cSSTI and 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. However, the wording proposed by the MAH was not in line with the common European terminology or with the wording used in several recently finalised procedures for generics. 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 skin and soft tissue infections (including diabetic foot infections)"

5. Infections in Neutropenic Patients

The CHMP noted the data submitted. 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"

6. Septicaemia, bacteraemia

The CHMP noted the data submitted and acknowledged that several studies have demonstrated the safety and efficacy of Tazocin in the management of patients with septicaemia and that broad-spectrum agents such as piperacillin-tazobactam are widely used in clinical practice in these situations. The CHMP noted that the supporting evidence is mainly derived from studies in febrile neutropenia and that 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 and that all cases of "bacteraemia" were in patients with one or more of the other indications. 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. However, taking into account the view of the CHMP drafting group and despite the very limited data 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 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".

7. Gynaecological Infections including postpartum endometritis and pelvic inflammatory disease
The CHMP noted the submitted data but considered inadequate to support the broad indication claimed or any qualified version of this indication. The CHMP therefore deleted the indication.

8. Bone and Joint Infections
The CHMP noted the submitted data and that the indication bone and joint infections were approved in about half the EU member states. However, the single study supporting the initial European application for Tazocin for the indication bone- and joint infections was an open-labelled non-comparative study and no additional data from any comparative study was provided. Results from three single-dose, open label studies to characterize the tissue penetration of piperacillin-tazobactam were provided but these data alone could not justify the indication claimed. Although pharmacokinetic data suggest that piperacillin and tazobactam concentrations in both bone and synovial tissue are sufficient to treat the majority of infections caused by susceptible organisms, the available clinical documentation is considered too limited and insufficient to justify an indication in treatment of bone and joint infections. The CHMP therefore deleted the indication.

9. Neonates and children
The CHMP noted the submitted data and considered that the data from adults was considered relevant and that the pharmacokinetic information can be used to extrapolate efficacy to the paediatric population. 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 in neutropenic children 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 and the safety of piperacillin-tazobactam is well documented in immunocompetent patients. Similarly, the clinical and pharmacokinetic data from comparative studies in adults and children, as well as wide clinical experience in children aged > 2 years, support the safety and efficacy in the treatment of intra-abdominal infections in paediatric patients. 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

With regards to the method of administration, the CHMP recommended intravenous infusion over 30 minutes based on the relationship between efficacy and the time during which the free (unbound) drug concentration in blood exceeds the MIC of the organism (T > MIC). 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. Regarding adult and adolescent patients (> 12 years of age), the dosage depends on the severity, location of the infection and the indication. The CHMP agreed on a dosage of 4 g piperacillin/0.5 g tazobactam given every 6 to 8 hours. The CHMP also implemented a tabular presentation of the doses. The CHMP also agreed that no dose adjustment is necessary in patients with hepatic impairment. Regarding children aged 2-12 years with normal renal function, the CHMP agreed to a dosage of 80/10 mg/kg every 6 hours for neutropenic children and 100/12.5 mg/kg every 8 hours for complicated intra-abdominal infections. The CHMP agreed on a statement that the usual duration of treatment for most indications is in the range of 5-14 days but that the duration of

treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress. In conclusion, the CHMP adopted a harmonised wording for Section 4.2.

Section 4.3 - Contraindications

Information on hypersensitivity to the active substances or any of the other ingredients and class specific hypersensitivity to β-lactams and β-lactamase inhibitors was included and the MAH proposed a harmonised wording in line with its current Core Data Sheet. The CHMP adopted a harmonised wording for Section 4.3.

Section 4.4 - Special Warnings and Precaution for Use

The MAH proposal was in line with its Core Data Sheet. The CHMP agreed with the MAH proposal but enforced some additions, in particular by inserting a caution regarding use in patients without severe hypersensitivity reaction to non-penicillin β-lactams but who may have had non-severe reactions and by supplementing the warning on pseudomembranous colitis. A statement on the emergence of resistant organisms was inserted. The CHMP adopted a harmonised wording for Section 4.4.

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

The MAH listed the following interactions: non-depolarizing muscle relaxants, oral anticoagulants, methotrexate, probenecid, aminoglycosides, and vancomycin and provided an overview of the divergences between the nationally approved wordings for Section 4.5. The MAH proposed a harmonised Section 4.5 in line with its Core Data Sheet. The CHMP agreed with the available information on the interaction studies 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 its Core Data Sheet. The CHMP considered the justification provided by the MAH to be acceptable but included a mention of studies showing developmental toxicity in animals. The CHMP adopted a harmonised wording for Section 4.6.

Section 4.7 - Effects on ability to drive and use machines

The MAH proposed a wording in line with its Core Data Sheet. The CHMP adopted a revised harmonised wording for Section 4.7.

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. 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. The section 4.8 is in all countries consistent with the MAH Core Data Sheet. The CHMP considered that the justifications provided by the MAH for the proposed wording were acceptable 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 its Core Data Sheet. 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 a harmonised wording for Section 4.9.

Section 5.1 - Pharmacodynamic properties

The MAH stated that all required information 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. The CHMP required a complete re-write of the section, 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. Only EUCAST MIC breakpoints and only species relevant for the approved indication were listed. The MAH 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 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 its Core Data Sheet and provided supporting data. A harmonised wording was adopted for Section 5.2.

Section 5.3 - Preclinical safety data

The MAH stated that 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 its Core Data Sheet. The CHMP included only the preclinical information relevant to prescribers and also 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 a harmonised wording for Section 5.3.

Section 6 - PHARMACEUTICAL PARTICULARS

The CHMP agreed with the MAH proposals and adopted harmonised wordings for Section 6.1 – List of excipients, Section 6.2 Incompatibilities, Section 6.3 Shelf life, Section 6.4 - Special precautions for storage, Section 6.5 - Nature and contents of container and Section 6.6 - Special precautions for disposal and other handling.

Module 3

The MAH provided a 'CMC-Divergence Overview' document describing the changes performed to all the existing national dossiers. 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, control of excipients, the control of drug products, the reference standard, the container closure system and the stability. Following a number of clarifications, the MAH proposal was accepted and the CHMP adopted a harmonised Module 3. Module 2 (QOS) was also updated in line with Module 3.

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas

- the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet
- the summary of products characteristic, labelling and package leaflet proposed by the marketing authorisation holders have been assessed based on the documentation submitted and the scientific discussion within the Committee

the CHMP has recommended the amendment of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Tazocin and associated names (see Annex I).