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 Tienam and associated names (see Annex I)

A referral under Article 30 of Directive 2001/83, as amended, was started in May 2009 for Tienam and associated names. During the course of the procedure, a Drafting Group meeting was convened by the CHMP. Tienam is a broad spectrum antibacterial agent that belongs to the group of carbapenems and consists of a fixed combination (1:1 ratio) of imipenem (a carbapenem antibiotic which is a derivative of thienamycin) and cilastatin (an inhibitor of dehydropeptidase I, a renal enzyme which metabolizes and inactivates imipenem). Imipenem has activity against a wide variety of bacteria, including Gram-positive aerobic cocci, Gram-positive aerobic bacilli, Gram-negative aerobic bacteria, and anaerobes. In particular, four divergent indications (i.e., gynaecological infections, septicaemia, bone and joint infections, and endocarditis) and the use in paediatric patients less than 3 years of age were discussed. Tienam was approved in the EU in 1985 and is currently authorised in 28 European countries (Norway, Iceland and all EU countries with the exception of Denmark). Tienam is approved as an intravenous (IV) formulation: Powder for solution for infusion, 250 mg/250mg and 500 mg/500 mg.

Section 4.1 - Therapeutic indications

4.1.1 Intra-abdominal infections

The CHMP considered that the data provided by the MAH included sufficient evidence that imipenem/cilastatin is efficacious in most studies in treating complicated intra-abdominal infections including e.g., intra-abdominal abscesses, peritonitis, complicated appendicitis, gall bladder empyema. The CHMP also noted the additional information in the form of abstracts or brief publications and considered that an indication for complicated intra-abdominal infections was supported. In conclusion, the CHMP adopted the following harmonised indication:

"complicated intra-abdominal infections"

4.1.2 Lower respiratory tract infections

The CHMP noted the proposed indication "lower respiratory tract infections" but considered the indication to be non-specific and therefore no longer appropriate, according to the Guideline on Antibacterial agents. The MAH discussed a number of specific indications, including community acquired pneumonia (CAP), cystic fibrosis, nosocomial pneumonia or ventilator associated pneumonia. In conclusion, the CHMP adopted the following harmonised indication:

"severe pneumonia including hospital and ventilator-associated pneumonia"

4.1.3 Gynaecological infections

The CHMP noted the proposed indication "gynaecological infections" but commented that the discussion of the available documentation focused primarily on intra- and post-partum infections. The MAH acknowledged that the spectrum of imipenem/cilatstatin does not cover *Chlamydia trachomatis*, and that there is insufficient evidence that *Neisseria gonorrhoeae* is a good target for therapy with this agent. Although data supporting this indication is limited, the CHMP considered the following harmonised indication to be acceptable:

"intra- and post-partum infections

4.1.4 Septicaemia

The CHMP noted the proposed the indication "septicaemia" but remarked on the limited and old clinical trial data available. There were no useful comparator-controlled clinical trials conducted and published in the peer-review literature from 2000 through 2010 in this indication and the epidemiological studies were of questionable quality and not sufficiently informative, in particular with regards to the used imipenem/cilastatin dosage. However, the CHMP acknowledged that high clinical cure rates were

reported in a large number of patients with bacteraemia associated with the approved indications. In conclusion, based on the presented data, the CHMP considered the indication to be acceptable and adopted the following harmonised indication:

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

4.1.5 Genitourinary infections

The CHMP noted the proposed indication "genitourinary infections" but stated that imipenem/cilastatin should be used only in severe bacterial infections suspected or due to pathogens resistant to other beta-lactams and susceptible to imipenem/cilastatin. In addition, the term "genitourinary tract infections" was considered outdated. Although most studies were outdated and/or of poor quality, the CHMP was of the opinion that a restricted indication would be justified and in conclusion, adopted the following harmonised indication:

"complicated urinary tract infections"

4.1.6 Bone and joint infections

The CHMP noted the proposed indication "bone and joint infections" but considered the data submitted to be insufficient. The CHMP also assessed the limited data from literature sources and concluded that the claimed broad indication in the treatment of bone and joint infections could not be supported. The CHMP also discussed the possibility of limiting the indication to "*Osteomyelitis"* however there were not enough data to support this indication. In addition, potential failure of Tienam therapy might lead to surgical interventions or amputations which should be considered as serious adverse outcomes. In conclusion, the CHMP was of the opinion that this indication was inadequately substantiated, and therefore deleted the indication.

4.1.7 Skin and soft tissue infections

The CHMP noted the proposed indication "skin and soft tissue infections" (SSTI). These infections are mostly caused by Gram-positive bacteria, *S. aureus* being the most important. Imipenem/cilastatin is not considered to be the best anti-staphylococcal agent, as other agents like semi-synthetic penicillins are generally considered to be more effective. Furthermore imipenem/cilastatin has no activity against MRSA and is therefore not considered to be an appropriate antibiotic for the empiric treatment of SSTIs caused by staphylococci since the risk of selecting for MRSA is quite high. The CHMP noted and assessed the available clinical trial and publication data showing that imipenem/cilastatin is effective and well tolerated in the treatment of "Complicated Skin and soft-tissue infections". In conclusion, the CHMP adopted the following harmonised indication:

"complicated skin and soft-tissue infections"

4.1.8 Endocarditis

The CHMP noted the proposed indication "*endocarditis*" but considered that the claimed indication in the treatment of endocarditis was insufficiently substantiated. The presented data were very scarce and imipenem/cilastatin is not considered one of the most effective agents against staphylococci and methicillin-resistant staphylococci are known to be resistant to imipenem/cilastatin. Moreover, the use of imipenem in the management of any type of endocarditis has not been mentioned in the EU endocarditis Guideline, 2004. Therefore, the CHMP did not consider imipenem/cilastatin to be an appropriate antibiotic for the empiric treatment of this life-threatening infection as the risk of selecting for MRSA is especially high. In conclusion, the CHMP therefore deleted the indication.

4.1.9 Prophylaxis

The CHMP noted the proposed indication "prevention of certain post-operative infections in patients undergoing contaminated or potentially contaminated surgical procedures or where the occurrence of post-operative infection could be especially serious" and the data provided to support the indication, including several published studies evaluating imipenem or imipenem/cilastatin as prophylaxis antibiotic therapy to prevent post-surgical infections as a result of colorectal surgery, appendectomy, and endoscopic sclerotherapy. The CHMP considered that imipenem/cilastatin is a broad spectrum antibiotic which should be used in the treatment of severe/life-threatening infections accompanying

with microbial resistance and/or when microbial resistance is demonstrated. Unjustified and non-substantiated prophylactic use is not acceptable. The CHMP therefore deleted this indication.

4.1.10 Management of bacterial infections in patients with febrile neutropenia

The CHMP noted that, overall, although no high quality, double blind studies were submitted together with data from a substantial number of randomised, comparative open-labelled studies and concluded that imipenem/cilastatin appears to be suitable for the management of neutropenic patients. The issue of seizures in paediatric patients with systemic malignancies during therapy with imipenem/cilastatin was also discussed and the CHMP was reassured by the absence of evidence in support of an increased risk of seizures in this population. In conclusion, the CHMP adopted the following harmonised indication:

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

4.1.11 Mixed infections

The CHMP noted the proposed indication "mixed infections" but was of the opinion that this wording is not in line with the current antimicrobial guidelines and recent European regulatory decisions, which require a site of infection to be specified. The CHMP therefore deleted this indication.

4.1.12 Non-indication in the treatment of meningitis.

The CHMP did not consider this to be an indication and removed this information from section 4.1.

4.1.13 Paediatric use

The CHMP assessed the available data regarding use in children, in particular taking into account 2 large efficacy/safety paediatric studies (*Paediatric Study 1* and *Paediatric Study 2/3*) and the available peer-review medical literature. The overall clinical efficacy of imipenem/cilastatin was high and evaluable patients and the used dosage was effective and safe. The MAH provided a categorised summary of the enrolled patients, according to age groups to provide a basis for a discussion on the need for limiting the use of imipenem/cilastatin to children above 1 year of age for safety reasons. The MAH provided a cumulative review of adverse event reports received for imipenem/cilastatin in paediatric patients between 3 months to 3 years of age, which identified a total of 163 events in 82 reports. The CHMP considered that the frequency of seizures in the paediatric population < 1 year was unacceptably high and that this risk was confirmed by spontaneous adverse event reports. The CHMP therefore considered that the benefit-risk for imipenem/cilastatin in children under 1 year of age is negative and inserted a statement that the clinical data are insufficient to recommend dosing for children under the age of 1 year. With regards to safety, the CHMP considered that the available documentation supports a similar safety profile of imipenem/cilastatin in children compared to adults.

4.2 Posology and method of administration

<u>Adults and adolescents.</u>
The CHMP was of the opinion that in light of the present clinical and PK/PD data, a standard dose of 500 mg every 6 hours or 1g every 8 hours can be accepted, provided that a recommendation is inserted in the SPC stating that for infections suspected or proven to be due to less susceptible organisms (e.g. *P. aeruginosa*) and for very severe infections (e.g. in neutropenic patients with a fever), the 1000 mg q.i.d should be used.

<u>Paediatric patients above 1 year of age</u>
The CHMP was of the opinion that in light of the present clinical and PK/PD data, for paediatric patients ≥1 year of age, a standard dose of 15 or 25 mg/kg/dose administered every 6 hours is recommended. Advice to physicians was provided regarding infections suspected or proven to be due to less susceptible bacterial species (e.g. *Pseudomonas aeruginosa*) and very severe infections (e.g. in neutropenic patients with a fever), recommending treatment with 25 mg/kg every 6 hours.

<u>Elderly population</u>
Based on information from the submitted studies, the CHMP considered that no dose adjustment is required in elderly patients, except in cases of moderate to severe renal impairment.

Doses ≥ 4 gm/day
The CHMP requested the MAH to carry out a relevant safety analysis across dose levels to confirm that the reason for not recommending the higher dose of 1 g q6h in several indications was not driven by safety aspects. The CHMP observed that no new safety issues or increased ADRs were observed with the use of imipenem/cilastatin doses of ≥ 4 gm/day as compared to doses of <4 gm/day, based on the review of clinical trial data in the original WMA, PMS data and the literature.

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

"Adults and adolescents
For patients with normal renal function (creatinine clearance of >70 ml/min/1.73 m^2), the recommended dose regimens are:

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

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

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

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

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

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

Section 4.4 - Special warnings and precautions for use

The CHMP noted the MAH proposal for this section and made a number of revisions. The CHMP adopted a harmonised wording for section 4.4 and in particular, the following statement concerning the limited susceptibility of specific pathogens and the concomitant use of an appropriate anti-MRSA agent or of an aminoglycoside was included:

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

Sections 4.3 – Contraindications, 4.5 - Interaction with other medicinal products and other forms of interaction, 4.6 – Fertility, Pregnancy and Lactation, 4.7 - Effects on ability to drive and use machines, 4.8 - Undesirable effects, 4.9 – Overdose, 5.1 - Pharmacodynamic properties, 5.2 - Pharmacokinetic properties and 5.3 - Preclinical safety data

The CHMP adopted a harmonised wording for these sections.

SECTION 6 – PHARMACEUTICAL PARTICULARS

In sections 6.3 and 6.6, a warning was added to state that diluted solutions should be used immediately and that the interval between beginning of reconstitution and the end of intravenous infusion should not exceed two hours. In addition, the recommended solutions were specified as being 0.9% sodium chloride solution and water for injection, while the use of 5% glucose was restricted to exceptional circumstances where 0.9% sodium chloride cannot be used for clinical reasons.

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 Tienam and associated names (see Annex I).