Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisations

Scientific conclusions

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

Zinacef contains cefuroxime sodium, a second generation cephalosporin antibacterial agent. Cefuroxime exerts a bactericidal action by inhibiting bacterial enzymes necessary for cell-wall synthesis (peptidoglycan synthesis), thereby causing cell death. Zinacef was first approved in Europe in the early 1980's and is available as parenteral formulations. Zinacef was included in the list of products for Summary of Product Characteristics (SmPC) harmonisation, due to divergent national decisions taken by Member States concerning the authorisation of the above-mentioned product. A referral under Article 30(2) of Directive 2001/83/EC was therefore triggered to resolve these divergences and thus to harmonise the Product Information (PI) across the EU.

Section 4.1 - Therapeutic indications

The CHMP noted the large degree of divergences in the nationally approved indications and therefore reviewed the available data supporting each indvidual indication and the patient age groups.

Community acquired pneumonia

The CHMP noted that although only one double-blind study was submitted, several other comparator-controlled and randomised studies were also submitted, several of which were performed recently and showed adequate efficacy of cefuroxime. The CHMP therefore concluded that there is enough data to support the indication in adults and that the adult efficacy data could be extrapolated to the paediatric population. The CHMP considered the indication to be acceptable for all populations.

Acute exacerbations of chronic bronchitis

The CHMP noted the submitted double blind, comparative, randomized study and considered it to be adequately designed. As the study demonstrated the non-inferiority of cefuroxime, the CHMP considered the indication to be acceptable.

Upper respiratory tract infections

The CHMP considered the proposed indication wording to be too general and noted that most upper respiratory tract infections respond well to oral therapy or are spontaneously cured. The CHMP reviewed the presented clinical studies but considered the data to be insufficient. The CHMP also noted that no comparative, placebo-controlled or double-blinded studies were available in the restricted indication severe ear, nose and throat-infections. The CHMP therefore recommended the removal of this indication.

Urinary tract infections

The CHMP considered the submitted data, consisting of eleven small, non-comparative studies and two open labelled, comparative studies. The CHMP noted the large amount of clinical experience supporting the use of cefuroxime in this indication. The CHMP also noted that there are few treatment options available for pregnant women with pyelonephritis. In conclusion, the CHMP considered the indication "*complicated urinary tract infections, including pyelonephritis"* to be acceptable.

Skin and soft-tissue infections

The CHMP reviewed the submitted data and agreed that staphylococci and streptococci, the bacterial species most frequently involved in skin and soft tissue infections, are sensitive to cefuroxime. Based on the provided data, the CHMP considered the indication "*soft-tissue infections: cellulitis, erysipelas and wound infections*" to be acceptable.

Bone and joint infections

Having reviewed the available data, consisting of small non-comparative studies, the CHMP considered it to be very limited and of questionable methodology. The CHMP considered that the data on bone penetration did not outweigh the lack of supportive clinical data. The CHMP therefore recommended the removal of this indication.

Obstetric and gynaecological infections
The CHMP reviewed the two open studies submitted but stated that cefuroxime is not active against many of the bacterial species isolated in obstetric and gynaecological infections, either due to inherent resistance or due to acquired resistance. The CHMP considered this indication to be inadequately supported and therefore recommended its removal.

Gonorrhoea
The CHMP reviewed the submitted studies, the majority of which used cefuroxime in combination with probenecid rather than cefuroxime alone. The CHMP also noted that although the most common co-existing pathogen in patients with gonorrhoea is *Chlamydia trachomatis*, no data on combination therapy (cefuroxime with other antibiotic) for treatment of patients co-infected by *N. gonorrhoeae* and *C. trachomatis*, or by *N. gonorrhoeae* and anaerobic bacteria, was submitted. The CHMP considered that the available data did not support this indication and therefore recommended its removal.

Septicaemia and meningitis
The CHMP reviewed the studies on septicaemia which were old, non-comparative and included small numbers of patients. The studies were performed in a period in which acquired resistance was not a critical problem. Regarding meningitis, the CHMP noted that the majority of the studies identified *H. influenzae*, *N. meningitidis*, *S. pneumonia* and *S. aureus* (non-MRSA) as the predominant bacterial species, which does not reflect the present EU situation, where aerobic Gram-negative bacilli are increasingly important as causative agents. The CHMP concluded that the clinical data and the data from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) did not support the treatment of meningitis. In conclusion, the CHMP judged the data insufficient to support the septicaemia and meningitis indications and therefore recommended their removal.

Intra-abdominal infections
The CHMP reviewed the submitted data and considered the distributions of infections in the two largest submitted studies to be supportive of the proposed indication, although cefuroxime is not suitable for the treatment of infections caused by Gram-negative non-fermenting bacteria. In conclusion, the CHMP considered the indication to be acceptable.

Prophylaxis
Having reviewed all submitted data to support the various prophylaxis indications proposed for cefuroxime, the CHMP considered the indication "*Prophylaxis against infection in gastrointestinal (including oesophageal), orthopaedic, cardiovascular and gynaecological surgery (including caesarean section)*" to be acceptable.

Indication in neonates
The CHMP reviewed the data in neonates, including the data on dosing range and dosing interval. The CHMP defined neonates as infants younger than 3 weeks, including newborns and agreed that cefuroxime has been used in neonates for many years without any serious safety concerns. The CHMP agreed that neonates may be given a similar total daily dose as recommended for infants (30 to 100 mg/kg/day) but at a reduced daily frequency of 2 or 3 divided doses, due to the longer serum half-life.

In conclusion, the CHMP adopted the following harmonised indications and wording for Section 4.1:

"Zinacef is indicated for the treatment of the infections listed below in adults and children, including neonates (from birth) (see sections 4.4 and 5.1).

- *Community acquired pneumonia.*
- *Acute exacerbations of chronic bronchitis.*
- *Complicated urinary tract infections, including pyelonephritis.*
- *Soft-tissue infections: cellulitis, erysipelas and wound infections.*
- *Intra-abdominal infections (see section 4.4).*
- *Prophylaxis against infection in gastrointestinal (including oesophageal), orthopaedic, cardiovascular, and gynaecological surgery (including caesarean section).*

In the treatment and prevention of infections in which it is very likely that anaerobic organisms will be encountered, cefuroxime should be administered with additional appropriate antibacterial agents.

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

Section 4.2 - Posology and method of administration

The CHMP noted the large degree of divergences in the nationally approved posologies and recommendations and therefore reviewed the available data to support a harmonised Section 4.2. The CHMP reviewed the dosage recommendations for each individual indication. The CHMP agreed that the commonly used intravenous and intramuscular dosing regimens (e.g., 750 mg to 1500 mg given every 8 hours) are expected to provide efficacy for organisms with minimum inhibitory concentrations (MICs) up to, and including, 8 µg/mL. The CHMP considered that for parenteral cefuroxime, the less susceptible bacteria include mainly Enterobacteriaceae (i.e. *E. coli, P. mirabilis* and *Klebsiella* spp).The CHMP therefore followed the EUCAST breakpoints for Enterobactariaceae at 8ug/mL to recommend a dosing regimen of 1500 mg every 8 hours for the treatment of infections caused by the above bacteria.

The CHMP recommended the removal of the option of parenteral-to-oral sequential therapy for all patients, due to the significant reduction in exposure to active drug when switching to the oral formulation.

Regarding patients with renal impairment, the CHMP reviewed the data and considered the proposed dosing guidelines to be acceptable. Regarding patients with hepatic impairment, the CHMP stated that hepatic dysfunction is not expected to affect the pharmacokinetics of cefuroxime. Regarding the method of administration, the CHMP stated that Zinacef should be administered by intravenous injection over a period of 3 to 5 minutes directly into a vein or via a drip tube or infusion over 30 to 60 minutes, or by deep intramuscular injection. In conclusion, the CHMP adopted a harmonised wording for Section 4.2.

Minor divergences in other sections of SmPC, labelling and package leaflet

The CHMP also adopted a harmonised wording for the remaining sections of the Zinacef SmPC and brought the labelling and the package leaflet in line with the adopted harmonised SmPC.

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

The basis for this referral procedure was a harmonisation of the summary of product characteristics, labelling and package leaflet. Having considered the data submitted by the Marketing Authorisation Holder, the rapporteur and co-rapporteur assessment reports and the scientific discussions within the Committee, the CHMP was of the opinion that the benefit-risk ratio of Zinacef and associated names is favourable.

Whereas

- The committee considered the referral under Article 30 of Directive 2001/83/EC,
- The committee considered the identified divergences for Zinacef and associated names regarding the therapeutic indications and the posology and method of administration sections, as well as in the remaining sections of the SmPC,
- The committee reviewed the data submitted by the MAH, including data from clinical trials, published literature and clinical documentation, justifying the proposed harmonised Product Information,
- The committee agreed the harmonisation of the summary of product characteristic, labelling and package leaflet proposed by the marketing authorisation holders,

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