10 September 2012
EMA/CHMP/633654/2012

Assessment report for Zinacef and associated names

Pursuant to Article 30 of Directive 2001/83/EC

INN : cefuroxime (cefuroxime sodium)

Procedure no: EMEA/H/A-30/1158

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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1. Background information on the procedure

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

On 20 April 2010 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:

Zinacef 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 April 2010 meeting. The marketing authorisation holder was informed of the start of the procedure.

The CHMP appointed Michal Pirozynski (PL) as rapporteur and Liv Mathiesen (NO) as co-rapporteur. The rapporteurship and co-rapporteurship were transferred to Piotr Fiedor (PL) and Karsten Bruins Slot (NO) as of May 2010.

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

Zinacef medicinal products are currently not registered in the following EU Member States: Germany, Latvia, Slovakia and Spain.

2. Scientific discussion during the referral procedure

2.1. *Introduction*

Zinacef contains cefuroxime sodium, a second generation cephalosporin antibacterial agent. Cefuroxime is resistant to most beta-lactamases and has in vitro activity against a broad spectrum of Gram-positive and Gram-negative bacteria. Cefuroxime exerts a bactericidal action by inhibiting bacterial enzymes necessary for cell-wall synthesis (peptidoglycan synthesis) causing cell death. Zinacef was first approved in Europe in the early 1980's and is available as powder for solution for injection, at strengths of 250 mg, 750 mg, 1 g, 1.5 g and 2 g per vial, for intravenous (IV) or intramuscular administration. It is also available, for IV infusion only, at strengths of 1.5 g as a monovial. The product is approved in 23 EU member states as well as in Iceland and Norway and is used to treat certain infections caused by bacteria before the infecting organism has been identified or when caused by sensitive bacteria in adults and children including neonates. Originally approved indications included respiratory tract infections, septicaemia, peritonitis, bronchitis, gonorrhoea and infections of the ears, throat, sinuses, urinary tract, bone and joint and skin and soft tissue as well as for prophylaxis in surgery.

Zinacef was included in the list of products for Summary of Product Characteristics (SmPC) harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC. 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(2) of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised SmPCs and thus to harmonise the Product Information (PI) across the EU.

The main areas of disharmony were Sections 4.1, 4.2, 4.3 and 4.4. Nevertheless, the MAH was asked to review all other sections of the nationally approved EU SmPCs and suggest appropriate changes in the text where divergences exist. As a consequence, the entire PI was reviewed and harmonised by the CHMP. In response to the CHMP list of questions, the MAH provided proposals for a harmonised Product Information and an overview of the major differences between the current nationally authorised SmPCs.

The CHMP also consulted the Infectious Disease Working Party (IDWP) on 14 June 2011 and 23 September 2011 and took the reports into consideration during its assessment.

2.2. *Critical Evaluation*

Section 4.1 - Therapeutic indications

General comments:

The CHMP reviewed the overview of indications approved by the individual member states prepared by the MAH and noted the large degree of divergences. The CHMP reviewed the harmonised indications proposed by the MAH but revised the wording in line with current EU guidelines (NfG on Evaluation of Medicinal Products indicated for the treatment of bacterial infections, CPMP/EWP/558/95 rev. 1 , 2004). The CHMP inserted the statement: 'Consideration should be given to official guidance on the appropriate use of antibacterial agents' but deleted the introductory sentences describing Zinacef. Only relevant information for the discussion is presented per indication hereinafter.

1) Lower respiratory tract infections (LRTIs)

The MAH reviewed the nationally-approved SmPCs and proposed the following harmonised indication: "*Respiratory tract infections (e.g., acute and chronic bronchitis, infected bronchiectasis, bacterial pneumonia, lung abscess and post-operative chest infections)*", together with data from a number of studies to support the proposal. The studies evaluated the efficacy of i.v. cefuroxime in patients with LRTI, including pneumonia, bronchiectasis and AECB . The majority of the studies conducted were open and comparative, but with a limited number of study subjects in each study. The MAH provided an overview of the clinical and bacteriological success rates from these studies for both adults and children with LRTI (Pettersson, 1977, Bax, 1979, Pines, 1979, Samanta, 1980, Pines 1981, Miki, 1977, Stoney 1979, Mehtar, 1982, Schwigon, 1993, Geckler 1994, Rossof, 1995 and Vuori-Holopainen, 2000). The MAH also presented three studies investigating the efficacy of IV cefuroxime followed by oral cefuroxime axetil, compared to that of a similar regimen of amoxicillin/clavulanic acid (Flamaing, 2007, Brambilla, 1992 and the MAH-sponsored study CAET99).

In particular, Bax conducted an open, non-comparative study evaluating the efficacy of cefuroxime 750 mg TID by intramuscular injection in 274 patients diagnosed with LRTI (Bax, 1979). The clinical results showed a 90% success rate in the patients with bronchopneumonia (n=105), 91% in patients with post-operative pneumonia (n=74), and 89% in patients with acute exacerbations of chronic bronchitis (n=96). The corresponding bacteriological eradication rates were 88%, 92% and 73%, respectively.

The CHMP noted the MAH proposal but stated that general indications such as lower respiratory tract infections are no longer valid and should be replaced by specific conditions according to the clinical studies. The MAH was requested to substantiate the individual indications AECB and bronchiectasis, and perform a sub-categorisation presenting how many patients each of the studies provide for each of the sought indications, and the clinical and bacteriological cure rates obtained. The CHMP also considered that acute bronchitis is primarily of viral aetiology and therefore not an appropriate indication for antibacterial agents. The MAH agreed and revised its proposal to the following indications: "*Pneumonia*" and "*acute exacerbations of chronic bronchitis".*

1a) Pneumonia (CAP)

The MAH submitted data from a number of clinical trials evaluating the efficacy of parenteral cefuroxime (either as mono-therapy or as sequential therapy) in comparison to various antibiotics routinely used for the treatment of CAP. The MAH provided an overview of the clinical and bacteriological success rates from these studies for both adult and paediatric patients. Although one study was double-blind, the majority of these studies were open, comparative studies (CAEM15, Ducroix, 1991, Siegel, 1997, van den Brande, 1997, Vetter, 1997, Siegel, 1999, Stille, 2000, Vergis, 2000, Plouffe, 2000 and Kuzman, 2005). The MAH also submitted studies conducted in paediatric patients (Nelson, 1982, Shalit, 1994, Barlinski, 1994). The most common bacterial pathogens isolated were *S. pneumoniae*, *H. influenzae* and *S. aureus*. In all studies, patients were considered to have CAP if they had radiographic evidence of pneumonia and the presence of at least 1 of the following criteria: fever (>38°C), white blood cell count ≥10×109/L with immature forms, pleuritic pain and/or auscultatory findings consistent with pneumonia. Sequential therapy with IV cefuroxime followed by oral cefuroxime axetil was studied several studies. In recent comparative studies in adult patients with moderate to severe CAP, sequential therapy with intravenous cefuroxime followed by oral cefuroxime axetil (with or without erythromycin) had similar efficacy as: 1) a full parenteral course of cefuroxime, (Siegel, 1996), 2) intravenously administered followed by orally administered azithromycin (Vergis, 2000; Plouffe, 2000; Kuzman, 2005), 3) intravenously administered followed by orally administered clarithromycin (Vetter, 1997), or 4) intravenously administered ceftriaxone followed by cefetamet pivoxil (Stille, 2000). In these studies, 74-94% of cefuroxime axetil recipients achieved a satisfactory clinical response versus 74-94% of patients treated with comparator agents. In the studies that reported bacteriological eradication rates, eradication occurred in a similar percentage of patients in the cefuroxime axetil (ranging from 70-82%) and the comparators clarithromycin (67%) and azithromycin (75%) sequential therapy groups (table 8).

Lode demonstrated that sequential therapy of IV cefuroxime/cefuroxime axetil was as efficacious as oral gemifloxacin in patients with CAP, with a clinical efficacy rate of 93% vs. 92% and bacteriological efficacy rate of 87% vs. 91%, respectively (Lode, 2002). In one large open study (File, 1997) sequential therapy with IV ceftriaxone followed by oral cefuroxime, the clinical efficacy rate was considered to be inferior to the comparator IV levofloxacin followed by oral levofloxacin, despite the clinical efficacy rate being 90% for ceftriaxone/cefuroxime axetil vs. 96% for the comparator group (95% confidence interval (CI) of difference of -10.7 to -1.3) (File, 1997). The bacteriological efficacy was also considered superior for the comparator group (85% vs. 98%). However, the microbiological population had a small sample size and thus no firm conclusions can be made with regard to bacteriological efficacy. Of note, the eradication rates for patients with CAP due to *S. pneumoniae*, *S. aureus* and *M. catarrhalis* were similar for the ceftriaxone/cefuroxime and levofloxacin groups. However, the efficacy rate in patients with *H. influenzae* was slightly lower for the ceftriaxone/cefuroxime group compared with the levofloxacin group (79% vs. 100%).

In a small double blind study, the efficacy of IV cefuroxime for 2 days followed by oral cefuroxime axetil for either 5 or 8 days was of similar efficacy in veterans with moderately severe CAP (Siegel, 1999). In addition, a dose-finding study for sequential therapy with IV cefuroxime given BID or TID followed by cefuroxime axetil was submitted (CAEM15/van den Brande, 1997).

Several of the studies submitted by the MAH were performed recently and have shown an adequate efficacy of cefuroxime. Regarding the submitted data, the CHMP acknowledged that only one, small double-blind study of cefuroxime in treating pneumonia in an adult population was submitted, nevertheless, several other comparator controlled, randomised but open-label studies were submitted in support of this indication, allowing the CHMP to conclude that there is enough data to support an indication of community acquired pneumonia for cefuroxime in adults. Regarding paediatric patients, the CHMP noted that no comparative, double-blind studies were submitted in the paediatric population, although one study included children with pneumonia and compared mono-therapy with cefuroxime with penicillin (Vuori-Holopainen, 2000). However, the CHMP considered that the efficacy data from studies in the adult population can to a large extent be extrapolated to the paediatric population. In conclusion, the CHMP considered the indication to be acceptable for all populations, although it

restricted the indication to "*community acquired pneumonia"*, as the submitted studies were performed in patients with CAP. In conclusion, the CHMP adopted the following harmonised indication:

"Community acquired pneumonia"

1b) Acute exacerbations of chronic bronchitis (AECB)

The MAH stated that earlier studies in patients with AECB were part of an evaluation of the efficacy in LRTI. The studies presented for CAP included many patients with AECB and the MAH considered them to demonstrate that cefuroxime is an effective treatment for this indication. Two MAH-sponsored published studies specifically evaluated the efficacy of sequential cefuroxime therapy in patients with AECB (Dellamonica, 1997; Vogel, 1997).

The study by Dellamonica, 1997 included a total of 110 patients with AECB treated with either a four-day course of cefuroxime 750 mg IM BID followed by eight days of oral cefuroxime axetil (250 mg twice daily), or a 12-day course of ceftriaxone injection (1000 mg once daily). The study was a double blind, comparative, randomised study. Clinical success was defined by a return to a previous stable state at the end of treatment. On completion of treatment the clinical success rate was 64% in the cefuroxime group and 63% in the ceftriaxone group. Both therapies were similar with respect to resolution of fever and change in sputum characteristics, with 90% of patients in the cefuroxime group improving and 85% in the ceftriaxone group. After one month the success rate was 93 % for cefuroxime treated patients and 96% for ceftriaxone group treated patients. The MAH considered that this study demonstrated that a sequential therapy of a 4-day course of cefuroxime IM followed by an 8-day course of cefuroxime axetil, is as effective and safe as a 12-day treatment course with ceftriaxone IM in adults with AECB.

Another prospective, randomised, open label study by Vogel, 1997, evaluated sequential therapy with cefuroxime 750 mg intravenously BID or TID for 48-72 hours followed by cefuroxime axetil 500 mg BID for 5-7 days, for the treatment of AECB. A total of 628 patients entered the study, of which 522 were clinically evaluable and 159 bacteriologically evaluable, with confirmed infection by one or more susceptible organisms. The predominant pathogens were *H. influenzae* (17%), *Haemophilus* spp. (15%), *S. pneumoniae* (15%) and *Enterobacteriaceae* (23%). The number of patients judged to be cured or improved following treatment was 230/267 (86%) amongst those who received intravenous cefuroxime TID and 225/255 (88%) of those on the BID dosing regimen. In both groups, the clinical cure rate was maintained in approximately 85% of patients at 14-28 days post-treatment. Bacteriologically, 73% of patients were cleared of infection by cefuroxime TID and 87% by cefuroxime BID dosing regimens. Superinfection occurred in 3% and 1% of patients respectively, while the original pathogen persisted (treatment failure) in 10% and 7%, respectively. The MAH considered that the study confirmed that a BID of parenteral cefuroxime was as efficacious as TID regimen of parenteral cefuroxime followed by oral therapy for the treatment of AECB.

The MAH stated that several studies have evaluated the penetration of parenteral cefuroxime into saliva, sputum, bronchial secretions and pleural fluid. In a study by Havard, 1980, 23 patients with bacterial pneumonia or AECB were enrolled to determine the sputum concentrations following a dose of 750 mg IV or IM cefuroxime TID, 1 g IM TID or 1.5 g TID. All dosing regimens resulted in substantial concentrations in the sputum. Mean sputum concentrations at 1 hour were 0.8 µg/mL and these concentrations were maintained in the sputum for up to 6 hours. By the fifth day of therapy, cefuroxime concentrations in the sputum were 1. 8 µg/mL. Pierce, 1980, studied cefuroxime concentrations in patients with LRTI requiring bronchoscopy. Patients received 750 mg or 1.5 g cefuroxime and were either sampled after the first dose or after the 7th dose. Patients who received a first dose of 750 mg had mean sputum concentration of 0.6 µg/mL in bronchial secretions. Concentrations rose with subsequent doses, reaching 0.95 µg/mL after the 7th dose. For the patients who received the 1.5 g dose the concentration of cefuroxime was 1.78 µg/mL in bronchial secretions after the first dose. In another study in patients with LRTI, the mean sputum concentration of cefuroxime achieved 1 hour after the first dose of 750 mg IM was 1 µg/g and this increased to 1.4 µg/g at day 5. In a paediatric study by Nelson, 1982, pleural fluid concentrations ranged from 2.2 µg/ml to 11 µg/ml, 30 minutes after a 15 minute infusion of 25 mg/kg IV. These studies show that

parenteral cefuroxime penetrates the RTI tissues with concentrations sufficient to be above the minimum inhibitory concentrations (MICs) of the key respiratory pathogens. The MAH considered that the clinical data from the cefuroxime axetil studies can be extrapolated to IV cefuroxime, where the PK/PD properties are enhanced in comparison to oral cefuroxime axetil and would therefore predict that IV cefuroxime would be efficacious in this indication.

The MAH also summarised a number of guidelines, including the European Respiratory Society (ERS) consensus guidelines for the antibiotic treatment of LRTI, which recommend a second generation cephalosporins as one of the parenteral treatment choices for patients with AECB with moderate or severe COPD without risk factors for *P. aeruginosa* (Woodhead, 2005). The MAH also stated that the global initiative for the management of chronic obstructive lung disease (GOLD) recommend second generation cephalosporins as one of the treatment choices for patients classed as having a moderate exacerbation (group B) with risk factors for a poor outcome but requiring parenteral therapy (GOLD, 2009). In addition, many countries in Europe have their own national guidelines and recommend cefuroxime for the treatment of community. The use of cefuroxime or second generation cephalosporins for the treatment of LRTI also feature in the guidelines of several hospitals which take into consideration local resistance patterns plus medical opinions.

Finally, the MAH stated that limiting the indication to the treatment of mild to moderate AECB was not supported by the available data. While acknowledging that *P. aeruginosa* is not included in the spectrum of activity for cefuroxime, the MAH stated that cefuroxime remains active against the three major bacterial causes of AECB, including those in elderly patients, are *S. pneumoniae, H. influenzae*, and *M. catarrhalis* (Sethi, 2001; Hayes, 2007). Less commonly, *Staphylococcus aureus*, *Pseudomonas*, and members of the Enterobacteriaceae family can be isolated in AECB (Sethi, 2001). The clinical criteria identified by Anthonisen are generally used to identify patients likely to be infected with bacterial pathogens and to benefit from antibacterial therapy. However these criteria have never been fully validated (Anthonisen, 1987). At present, there is no method for quantifying the severity of exacerbations (Jones, 2007; Torres, 2009). Consequently, various guidelines for the treatment of AECB recommend stratification of patients according to risk factors. Whilst the MAH accepted that cefuroxime axetil is more appropriate for the treatment patients with AECB without risk factors for a poorer outcome, parenteral cefuroxime is more likely to be used in patients with underlying severe COPD with an exacerbation with underlying risk factors for a poorer outcome or in elderly subjects who may require initial hospitalisation.

The CHMP noted the submitted the single double blind, comparative, randomized study with a total of 110 patients comparing sequential therapy with cefuroxime/cefuroxime axetil with ceftriaxone monotherapy, showing similar clinical success rates in the two groups. The CHMP considered the study to be adequately designed and that the non-inferiority of cefuroxime has been demonstrated. The CHMP therefore considered the indication to be acceptable. In conclusion, the CHMP adopted the following harmonised indication:

"*Acute exacerbations of chronic bronchitis*"

2) Upper respiratory tract infections (URTI)

The MAH reviewed the nationally-approved SmPCs and proposed the following harmonised indication: "*Ear, nose and throat infections (e.g., sinusitis, tonsillitis, pharyngitis and otitis media)*". The MAH stated that there are relatively few published papers on the use of parenteral cefuroxime in these indications as most URTIs respond well to oral therapy or are spontaneously cured. The MAH presented three open, non-comparative studies conducted with parenteral cefuroxime.

The study by Costa, 1979, was an Italian open, non-comparative study reported the use of cefuroxime (average dose 2 g per day in adults, 1 g per day in children) dosed for 4 to 15 days in 160 patients with ENTI (20, acute tonsillitis; 2, peritonsillar abscess; 12, acute or chronic pharyngitis; 7, furunculosis of the ear; 2, acute mastoiditis; 12, AOM; 10, chronic otitis; 17, sinusitis and 72, requiring treatment following ear, nose and throat (ENT) surgery). Within 48-72 hours of commencing treatment, 86 % of patients (138/160) were apyrexic and free of symptoms. In a further 10 patients the drug had a good, though less than excellent effect, giving an overall clinical response rate of 93%. There were eight treatment failures in patients with pharyngitis, some of which were considered probably viral in origin. A further four patients with a long history of chronic otitis media despite having a cessation of

secretion were also not considered cured. The study demonstrates that parenteral cefuroxime is a useful therapeutic option in patients with more serious ENT infections.

The 1984 Boner study was an open, non-comparative study investigating the efficacy of cefuroxime (50-80 mg/kg/day) and N-acetyl-cysteine, a mucolytic agent (15-25 mg/kg/day), administered IM for 10 days was evaluated for the treatment of chronic sinusitis in 24 asthmatic children with allergic rhinitis aged 8 to 14 years. Clinical efficacy was evaluated during treatment and on completion of treatment. Radiological efficacy was evaluated by means of x-rays obtained before treatment, three or four days after treatment and two weeks after treatment. Nasal or nasopharyngeal cultures were not obtained. Patients were considered cured if they responded clinically and radiologically (decrease in mucosal thickening of or loss of opacification or air fluid level). Patients who failed therapy were those whose symptoms persisted and maxillary sinus remained opacified. Treatment was effective in 95.8 % of the children with 37.5% of them able to reduce their anti-asthma medication. The authors concluded that cefuroxime is an appropriate treatment for maxillary sinusitis particularly in patients whose previous treatment has failed.

The study by Sugita, 1985, evaluated the efficacy of cefuroxime IV in treating otorhinolaryngological infections which included an evaluation of the susceptibility to cefuroxime of bacteria cultured from these infections and tissue concentrations in the target tissues. Fifty-one patients with otorhinolaryngological infections (24, tonsillitis; 6, peritonsillar abscess; 9, pharyngitis; 3, AOM; 2, sinusitis and 7 with other ENT infections) were treated with cefuroxime, 750 mg or 1.5 g once or twice daily by bolus IV injection or IV drip infusion. The most common pathogens isolated from these patients were *S. pyogenes* (20 isolates), *S. aureus* (5 isolates), *S. pneumoniae* (5 isolates) and *H. influenzae* (5 isolates). Efficacy was 96% in tonsillitis, 100% in peritonsillar abscess and 100% in pharyngitis, sinusitis and acute otitis media. The overall efficacy rate was 94%. Only two cases of chronic otitis media failed to respond. Bacteriological eradication was 90% for β-haemolytic streptococci, and 100% for *S. pneumoniae, S. aureus*, and *H. influenzae*. The study demonstrates that parenteral cefuroxime effectively penetrates the tonsillar tissue and maxillary sinus mucosa with concentrations above the MIC of the key pathogens isolated from ENT infections and was clinically effective in treating ENT infections.

The MAH also stated that many different classes of antibacterial have been successfully used and recommended for the treatment of more serious infections of sinusitis, which have included cefuroxime or a combination of cefuroxime and metronidazole (Desrosiers, 2006; Brook, 2007). In acute mastoiditis the aim of antibiotic treatment is to control the infection and avoid the complications associated with mastoiditis. Treatment of mastoiditis is guided by cultures and susceptibility testing and includes parenteral antimicrobials able to penetrate into bone and myringotomy with tympanostomy tube. Parenteral cefuroxime is one of the recommended treatments for this indication frequently used to treat acute mastoiditis (Brook, 2009). The treatment of peritonsillar abscess requires both the selection of appropriate antibiotics and aspiration or drainage of the abscess and in some cases tonsillectomy. The choice of antibiotics is usually based on gram stain and culture of the fluid obtained from the abscess. Penicillin used to be the antibiotic of choice for the treatment of peritonsillar abscess, but in recent years the emergence of beta-lactamase-producing organisms has required a change in antibiotic choice (Brook, 2004). Antibiotic therapy such as cefuroxime, either as mono-therapy or in combination with metronidazole) is also recommended for the treatment of peritonsillar abscesses (Steyer, 2002; Brook, 2004). Cefuroxime is considered an appropriate choice in both adults and children as it provides the cover for the major pathogens implicated in epiglottitis (Felter, 2009, Bowman, 2010).

The MAH also provided an overview of national guidelines within Europe recommending cephalosporin group 2 / cefuroxime as a treatment option for ENTI.

The CHMP considered the proposed indication wording to be too general and noted that as acknowledged by the MAH, most URTIs respond well to oral therapy or are spontaneously cured. Furthermore, broad spectrum antibiotics such as cefuroxime are usually reserved for severe or complicated infections. The CHMP reviewed the presented clinical studies in support of the claimed indication but considered that the inclusion criteria for parenteral instead of oral antibiotic therapy and the need for parenteral therapy were unclear. The CHMP therefore considered the data presented to be insufficient to support the proposed indication. In addition, the CHMP discussed the suitability of restricting the indication to severe ENT-infections (mastoiditis, peritonsillar infections, epiglottitis, acute bacterial sinusitis accompanied by severe signs and symptoms) but noted that no comparative, placebo-controlled or double-blinded studies have been conducted and only two studies relevant

studies have been presented (Costa 1979 and Boner 1984), both of which were open, non-comparative, and included very few patients with severe ENT-infections (<10 in each). The CHMP therefore concluded that this indication is not acceptable.

In conclusion, the CHMP recommended the removal of the proposed indication "*Severe ear, nose and throat infections (mastoiditis, peritonsillar infections, epiglottitis, acute bacterial sinusitis accompanied by severe signs and symptoms)*" from the harmonised SmPC.

3) Urinary tract infections (UTI)

The MAH reviewed the nationally-approved SmPCs and proposed the following harmonised indication: "*Urinary tract infections (e.g., acute and chronic pyelonephritis, cystitis and asymptomatic bacteriuria)*". The MAH stated that several MAH-sponsored studies (Daikos, 1977a, Gardikas, 1977, Nilsson, 1977, Hanninen, 1977, Kosmidis, 1977) and published studies (Naide, 1977, Iversen, 1981, Faro, 1984, Copland, 1977, Gomez-Luz, 1977, Graninger, 1977, Hofstetter, 1977 and Friman, 1989) have demonstrated the efficacy of parenteral cefuroxime in the treatment of uncomplicated UTI (uUTI) and complicated UTI (cUTI) and provided an overview of these studies. A review article by Brogden, 1979, summarises the earlier studies evaluating cefuroxime in UTI, the majority of which were open, non-comparative studies, as per the standards of evaluation of efficacy at the time parenteral cefuroxime was developed. In all studies, the primary efficacy parameter was the bacteriological response rate at the end of treatment and this was evaluated quantitatively.

In order to further support the indication, the MAH discussed the pharmacokinetics and pharmacodynamics (PK/PD) of cefuroxime. An effective %*f*T>MIC for cephalosporins such as cefuroxime is considered to be 40% or more of the dosing interval (Bulitta, 2009). High probability of target attainment (PTA) expectation values (>90% for a %*f*T>MIC of 50%) against *Escherichia coli* and *Klebsiella pneumoniae* were achieved by IV dosing of 750 mg and 1500 mg every 8 hours for an MIC of 4 µg/mL and 8 µg/mL, respectively (Ambrose, 2004). 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 MICs up to and including 8 µg/mL. The susceptibility breakpoint for IV cefuroxime has been revised by EUCAST and CLSI to 8 µg/mL, with the recommendation that, the higher cefuroxime IV dosage (1500 mg given every 8 hours) be used for infections with Enterobacteriaceae (Kahlmeter, 2008).

Urinary excretion of unaltered cefuroxime over a 24-hour period accounts for over 95 % of each dose (Foord, 1976). High concentrations of cefuroxime are therefore achieved in the urine, with average levels of 500 - 2000 µg/mL 1 - 2 hours after 250 – 500 mg and 1000 - 7000 µg/mL after 750 mg and 1.0 g doses (Foord, 1976). Levels in excess of 150 µg/mL can persist in urine for 8 hours (Daikos, 1977a). Therefore based on urinary levels, cefuroxime achieves high concentrations in the urine which indicates that it is a suitable antibiotic for the treatment of urinary tract infections.

The MAH stated that recent surveillance data among *Enterobacteriaciae* showed that cefuroxime resistance rates were quite variable; for *Proteus* spp. resistance rates ranged from 0% (112 *Proteus mirabilis* from Spain) to 56.4% (39 strains from Turkey), for *Klebsiella* spp. resistance rates ranged from 1.2–15% and for *E. coli* resistance rates ranged from 2.4– 26% (Jacobs, 2009; Garcia Garcia, 2007; Cetin, 2009; Gobernado, 2007, Katsarolis, 2010; Oudhuis, 2005; Sanchez Merino, 2008; Schito, 2009; Willemsen, 2009; Cuevas, 2010; Azap, 2010; Eryilmaz, 2010).

With regards to the clinical programme, the MAH stated that studies conducted with parenteral cefuroxime have shown that it is clinically and bacteriologically effective and that most patients benefit within one to three days of starting treatment. Infections with *E. coli*, *Klebsiella* spp., *Proteus* spp., staphylococci and streptococci have all been successfully treated with resolution of symptoms and sterilisation of the urine. In patients with complicated infections or pyelonephritis, relapse is not uncommon and was noted in a number of studies with many having predisposing factors for relapsing or recurrent UTIs (Faro, 1984; Iversen, 1981; Graninger, 1977; Hanninen, 1977). In the two comparative studies cited, relapse rates were similar for cefuroxime and cefazolin (62% and 63%, respectively), and cefuroxime and aztreonam (33% and 27%, respectively) and were noted to be similar to those reported for a range of other antibacterial agents used to treat such infections (Iversen, 1981; Friman, 1989). Superinfection with *P. aeruginosa* and *E. faecalis* has been noted in a small

percentage of patients in some studies (Gomez-Lus, 1977; Nilsson, 1977). Several studies have also shown that high concentrations of cefuroxime are achieved following dosing (Foord, 1976; Daikos, 1977a).

A further published clinical study has been found which used cefuroxime IV as initial treatment followed by step down therapy with other class of antibiotics (Cronberg, 2001). This double-blind, multicentre study was performed at nine centres on a total of 171 patients who presented with fever (>38.5°C) and signs of acute pyelonephritis. All were initially treated with intravenous cefuroxime 750 mg or 1.5 g TID. After 2–3 days, when the fever had subsided and patients were switched to oral administration of ceftibuten 200 mg BID or norfloxacin 400 mg BID for 10 days. The patients were followed for signs of bacterial or clinical relapse 7–14 days after the end of treatment.
The initial clinical and bacteriological cure was excellent in both groups, but there were significantly fewer bacterial relapses after oral treatment with norfloxacin than with ceftibuten. *E. coli* was the predominant pathogen. In infections caused by *E. coli* the causal strain was eradicated without relapse in 75% of patients in the ceftibuten group and in 87% of patients in the norfloxacin group. This study demonstrates that parenteral cefuroxime followed by oral therapy it an effective treatment for acute pyelonephritis.

Hofstetter, 1992, reviewed data on 5 clinical studies which evaluated the efficacy of cefodizime (CDZ) in upper urinary tract infections (uUTI) and complicated lower urinary tract infections. The review included 70 patients treated with cefuroxime 1.5 g TID which was one of the comparative agents used for the treatment of cUTI. The median duration of treatment was 7 days. The most frequent pathogen at baseline was *E. coli*. Both clinical and bacteriological cure rates were above 90% for all treatments evaluated. This study further demonstrates that parenteral cefuroxime is an effective treatment for cUTI and acute pyelonephritis. The clinical data demonstrates that parenteral cefuroxime can be used successfully to treat pyelonephritis and complicated UTIs caused by many commonly encountered urinary tract pathogens which are susceptible to the antibiotic. Approximately 85 to 90% of the administered cefuroxime dose is recovered in the urine within 24 hours. The elimination of cefuroxime by the kidneys results in high therapeutic concentrations of cefuroxime in urine. Following IM administration of a 750 mg single dose high urinary concentrations (1300 µg/mL) are achieved during the first 8 hours. Intravenous doses of 750 mg and 1.5 g also produced high urinary levels averaging 1150 and 2500 µg/mL, respectively, during the first 8 hour period. These high urinary concentrations hence indicate that cefuroxime is a suitable antibiotic for the treatment of urinary tract infections. Given the diverse nature of cUTIs and varying severity, various cefuroxime dosing regimens are therefore appropriate for the treatment of these infections and therefore for mild to moderate infection in adults 750 mg TID is recommended. For more severe infections in adults a dosing regimen of 750 mg every four hours or 1.5 g every six to eight hours is recommended. In children, a dose of 60 mg/kg per day will be appropriate for most infections in infants and children with doses ranging from 30 to 100 mg/kg per day given six to eight hourly.

The MAH also discussed the current consensus and evidence based national guidelines which recommend cephalosporins for the treatment of urinary tract infections. In particular, the guidelines for the treatment of urinary tract infections by the European Society of Urology (Grabe, 2009 recommend that for empirical treatment of complicated UTI, knowledge of the spectrum of possible pathogens and local antibiotic resistance patterns, as well as assessment of the severity of the underlying urological abnormality are required. These guidelines consider that group 2 cephalosporins are an alternative empirical treatment option in patients with cUTI. A further consideration is that there are limited antibacterial treatment choices in pregnant women with pyelonephritis. Cephalosporins such a cefuroxime are considered to have good safety when used in pregnancy and are generally considered as first-line therapy in this setting (Jolley, 2010).

The CHMP noted the data submitted by the MAH, consisting of eleven small, non-comparative studies conducted in the 1970's and 80's. Further, two open labelled, comparative studies were submitted: a study by Iversen (comparator cefazolin) with 58 patients with cUTI, and a study by Friman (comparator aztreonam) with 173 patients with Gram-negative upper cUTI (Iversen, 1991; Friman, 1989). However, the CHMP noted the large amount of clinical experience for the use of cefuroxime in this indication, which should be considered as important when reassessing old antibiotic in the scope of a harmonization referral. The CHMP stated that although the resistance pattern for urinary tract pathogens has changed markedly in the last decades, there are few treatment options available for pregnant women with pyelonephritis. In conclusion, the CHMP considered the indication to be acceptable and adopted the following harmonized indication:

"Complicated urinary tract infections, including pyelonephritis"

4) Skin and soft-tissue infections (SSTI)

The MAH reviewed the nationally-approved SmPCs and proposed the following harmonised indication: "*Soft-tissue infections (e.g., cellulitis, erysipelas and wound infections)*". The MAH submitted data from a multi-centre, randomised, prospective, comparative open label trial conducted by Parvin, 1999, that enrolled 234 paediatric patients (3 months through 11 years of age) with SSTIs. Patients received 150 to 300 mg/kg/day ampicillin/sulbactam in equally divided intravenous doses every 6 hours. Cefuroxime was given in a dosage of 50 to 100 mg/kg/day either intravenously or intramuscularly in equally divided doses every 6 or 8 hours. Efficacy was evaluated in those patients who had a pre-treatment pathogen isolated. Fifty-nine of the 154 randomized patients who received ampicillin/sulbactam and 39 of the 80 who were treated with cefuroxime were evaluable for efficacy. Among the patients evaluable for efficacy in the ampicillin/sulbactam group, 37 were diagnosed with cellulitis, 24 had wound infections, 5 had impetigo, 2 had folliculitis, 1 had erysipelas and 13 were diagnosed with other conditions. Among the cefuroxime efficacy patients, 18 had cellulitis, 25 had wound infections, 1 had impetigo, 2 had erysipelas and 3 were diagnosed with other conditions. The predominant pathogens isolated were *S. aureus* and *S. pyogenes*. In the ampicillin/sulbactam treatment arm, 46 of the 59 evaluable patients (78%) were cured and 13 patients (22%) were improved. Thirty patients (76.9%) were cured and nine patients (23.1%) improved in the cefuroxime comparator arm. Bacteriological eradication was achieved in 93.2% and 100% of patients, respectively, in the ampicillin/sulbactam and cefuroxime treatment arms. No statistically significant differences in clinical or bacteriological efficacy were observed. The MAH also submitted data from four small and relatively old non-comparative studies.

In a study by Zide, 1986, 55 hospitalised patients suffering from severe odontogenic or maxillofacial infections were treated with cefuroxime (750 mg TID for three to 30 days). The majority of infections involved one or more fascial spaces, and were of mixed aerobic and anaerobic aetiology. *Bacteroides* spp., *Streptococcus* spp. and *S. epidermidis* were the most frequent isolates. Fifty-two patients received the drug intramuscularly, and three received it intravenously. Adjunctive surgical drainage was performed in all cases. A satisfactory clinical response was obtained in 91% of patients (50/55).

In a study by Barson, 1985, 36 children, ranging from 3.5 to 57 months of age, received IV cefuroxime (75 mg/kg/day in three divided doses) for the treatment of soft tissue infections of the face or epiglottis. Infections treated included preseptal (n=19) and buccal (n=13) cellulitis and epiglottitis (n=4). Blood cultures were positive for *H. influenzae* type b in 17 cases, non-typeable *H. influenzae* in one and *S. pneumoniae* in four. Five additional patients with buccal cellulitis had negative blood cultures but *H. influenzae* type b antigenuria. A satisfactory clinical improvement was obtained in all cases, with resolution of pyrexia and inflammation. Bacteriological cures were documented in all bacteraemic patients.

Hugo, 1980, conducted an open non-comparative study of IM or IV cefuroxime to 33 patients including 24 patients with proven bacterial SSTIs, mostly caused by *S. aureus* or *S. pyogenes*. Serum levels of cefuroxime were also evaluated. The majority of patients received 750 mg cefuroxime IM TID, though doses of up to 6 g daily were used. The mean duration of treatment was 11.4 days, with three patients treated for 28 days or more. Of the 28 clinically evaluable patients, 16 were cured, 11 improved, and there was only one treatment failure.

An open, non-comparative study by Gold, 1981, used intravenous cefuroxime (50 mg/kg/day in four divided doses) to treat 53 children with soft tissue infections (cellulitis). The main pathogens were *S. aureus*, *S. pyogenes*, *S. pneumoniae*, *H. influenzae* and mixed aerobic and anaerobic organisms. Five patients with *H. influenzae* infection also have bacteraemia. Clinical results were good in 50, fair in 1, and unevaluable in 2 children. All 5 patients with bacteraemia were cleared.

The MAH stated that in general, *S. aureus* including MRSA, and streptococci, are by far the most common causes of uncomplicated and complicated SSTIs (Abrahamian, 2008). An effective %T>MIC for unbound concentrations of cefuroxime is considered to be 40 or more of the dosing interval for key Gram-positive aerobic bacteria such as *S. aureus* (Craig, 2003, Bulitta, 2009). 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 MICs up to and including 8 µg/mL. Therefore the MAH considered that parenteral cefuroxime would be an appropriate antibiotic to use for the treatment of skin and soft tissue infections, based on PK/PD principles.

The MAH stated that adequate cefuroxime concentrations have been demonstrated in the cellular mass of soft tissues and in subcutaneous interstitial fluid (Gold, 1983; Smith, 1983), and skin blister fluid concentrations of 12 µg/mL have been obtained with continuous intravenous cefuroxime infusion of 0.166 g/hour (Simon, 1977). A number of non-comparative clinical studies have been performed for the treatment of SSTIs (Gold, 1983). The study in adult patients carried by Hugo, 1980, demonstrated a satisfactory clinical outcome in 96% of cases, including examples of Gram-positive and Gram-negative infection, and patients with septicaemia. Excellent results have also been obtained in paediatric patients with various forms of cellulitis involving the predominant pathogens in this age group, *S. aureus*, *H. influenzae* and *S. pyogenes*, with satisfactory clinical outcomes of 90-100% of cases (Barson, 1985; Gold, 1981; Parvin, 1999). One comparative study with ampicillin/sulbactam demonstrated that cefuroxime had comparable clinical and bacteriological efficacy, with 100% of patients in the cefuroxime and ampicillin/sulbactam treatment groups deemed clinical successes (cured and improved). The eradication rate achieved for cefuroxime was a 100% compared to 93% for ampicillin/sulbactam (Parvin, 1999). Cefuroxime effectively cleared bacteraemia in patients with SSTI, and promoted resolution of fever and inflammation (Barson, 1985; Gold, 1981). More refractory conditions such as severe maxofacial infections caused by mixed aerobic and anaerobic flora have also been shown to respond well to parenteral cefuroxime following adequate surgical drainage (Zide, 1986).

The MAH also provided an overview of current guidelines, including the IDSA guidelines for Skin and soft tissue infections, which recommend both oral and parenteral second generation cephalosporins such as cefuroxime for the treatment of skin and soft tissue infections (Stevens, 2005).

The CHMP reviewed the data submitted by the MAH and agreed that the bacterial species most frequently involved in SSTIs, staphylococci and streptococci, are sensitive to cefuroxime, although cefuroxime has no activity against MRSA. Based on the provided data, the CHMP considered the indication to be acceptable. In conclusion, the CHMP adopted the following harmonised indication:

"*Soft-tissue infections: cellulitis, erysipelas and wound infections*"

5) Bone and joint infections

The MAH reviewed the nationally-approved SmPCs and proposed the following harmonised indication: "*Bone and joint infections (e.g., osteomyelitis and septic arthritis)*". The MAH stated that Gram-positive organisms, particularly staphylococci and streptococci, are responsible for the majority of bone and joint infections (Lew, 2004). There are few well-designed randomised controlled trials in patients comparing efficacy of different antibiotics. This was confirmed by a recent metaanalysis of 93 published trials of antibiotic treatment for osteomyelitis, which concluded that despite three decades of literature the available literature on the treatment of osteomyelitis is inadequate to determine the best antimicrobial agent(s), route or duration of antibiotic therapy (Lazzarini, 2005).

The above meta-analysis confirmed the findings of a previous Cochrane systematic review and meta-analysis by Stengel, 2001, which concluded that the current clinical studies fail to provide a reliable answer to the clinical question of whether any antimicrobial leads to better healing rates than any other such agent in patients with bone and joint infections. No striking differences were found between the investigated antibiotics, which included ceftazidime. While their safety profiles appeared quite similar, the choice of antibiotic agent will be influenced by economic considerations, availability, and the preferential route of administration. A further recent Cochrane systematic review by Conterno, 2009 of the treatment of chronic bone infection, also concluded that there is insufficient evidence from controlled trials as to what the most appropriate antibiotic is to treat this infection. Hence currently, there is no consensus on what the optimal antibiotic of choice is for the treatment of osteomyelitis.

Regarding pharmacokinetics and pharmacodynamics, the MAH stated that numerous *in vitro* models and animal studies have assessed the effect of various concentration-versus-time profiles on the rate of bacterial killing of β-lactam antibiotics. Using *in vitro* models with varying concentrations of drug, T>MIC expressed as percentage of the dosing interval has been well correlated with bactericidal activity for cephalosporins (Craig, 2003). An effective %T>MIC for unbound concentrations of cefuroxime is considered to be 40% or more of the dosing interval for key Gram-positive aerobic bacteria such as *S. aureus* (Craig, 2003, Bulitta, 2009). 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 MICs up to and including 8 µg/mL.

The MAH stated that cefuroxime *in vitro* activity remains high among other Gram positive organisms. For other *Streptococcus* spp., specifically *Streptococcus agalactiae* and *Streptococcus pyogenes*, cefuroxime continues to retain excellent activity (MIC90 ≤0.12 mg/L) (Garcia Garcia, 2007; Jansen, 2007). A European study of 60 viridans streptococci reported MIC50/90 of ≤0.12/2 mg/L (Soriano, 2004). Two German studies reported good cefuroxime activity against *S. aureus* with susceptibility rates of 86.2% and 97% (Jacobs, 2009; Niebuhr, 2008). No recent studies specific for methicillin susceptible *S. aureus* were available.

The MAH stated that the rate and extent of penetration of antimicrobials into human bone has been assessed and shown to be important for successful treatment in numerous studies, including several studies with cefuroxime. Cefuroxime diffuses into bone in measurable amounts, although reported concentrations vary markedly, probably reflecting differences in methods of collection and assay. Dornbusch used agar diffusion to assay for cefuroxime in human bone and found concentrations that ranged from 0.4 - 1.9 g/g of bone, two to eight hours after a 750 mg IV dose (Dornbusch, 1980,). Similar results were observed in a study by Nungu, where bone concentrations of 1-2 g/g were obtained (Nungu, 1995a). The concentration achieved in bone is dose-dependent, with a level of 9.5 g/g being reported after intravenous administration of 1.5 g cefuroxime (Alvarez Ferrero, 1993). Leigh, 1989a, evaluated bone and serum concentrations of cefuroxime (750 mg IV) . measured by high performance liquid chromatography (HPLC) in 21 patients undergoing hip and knee joint replacement surgery. The mean concentrations in the femoral head bone supernatant in hip replacements were 8•0mg/kg of cefuroxime. In knee replacement the femoral condyle bone and tibial bone concentrations were 4.2 mg/kg and 4.6 mg/kg, respectively. Hughes evaluated the penetration of cefuroxime in patients following hip and knee replacement surgery (Hughes, 1982). In patients who received 1g cefuroxime IV at induction of anaesthesia followed by IM injections of 1 g 6 and 12 hourly after the operation, the overall mean concentrations of cefuroxime were 10.8 mg/kg (femoral head), 22.1 mg/kg (hip capsule), 14.7 mg/kg (lower femur) and 20.5 mg/kg (knee capsule). In patients who received 1.5 g cefuroxime IV at induction of anaesthesia with 750 mg IM 6 and 12 hours later, the corresponding cefuroxime concentrations were: 14.5 mg/kg (femoral head), 28.5 mg/kg (hip capsule), 16.9 mg/kg (lower femur) and 18.3 mg/kg (knee capsule). Twelve patients undergoing total hip anthroplasty received, at the induction of anaesthesia, cefuroxime 1.5 g; further doses cefuroxime were given at 8 and 16 h after the operation (Lovering, 1997). Routine total hip arthroplasty was performed and at timed intervals during operation samples of bone, fat and blood were collected for assay for HPLC analysis. Samples of the haematoma fluid that formed around the operation site and further blood samples were also collected at 7 and 15 h after the operation. Although considerable variation was observed in the bone and fat concentrations, the mean values for bone of cefuroxime was 36.0 mg/L (95% CI 29.0–43.0 mg/L) and for fat of cefuroxime 15.0 mg/L (95% CI 11.1–18.9 mg/L). When corrected for blood concentrations the penetration of cefuroxime into bone was 43.6% and 16.0% for fat, cefuroxime. Cefuroxime concentrations in haematoma drain fluid at 6–8 h after the operation were 17.8 mg/L and at 14- 16 h 7.7 mg/L. Time–kill curves for cefuroxime against five clinical isolates of *S aureus* failed to identify any significant differences between the rates of kill for the two agents at the concentrations seen in bone, fat or haematoma fluid. The concentrations of cefuroxime exceeded the MICs for potential pathogens for the duration of the operation also in the haematoma which surrounds the operation site for up to 24 h after the operation. The MAH considered that the submitted studies demonstrate that cefuroxime penetrates into bone and achieves concentrations that are generally in excess of MICs of common pathogens such as *S. aureus*.

Regarding clinical data, the MAH stated that there are few well-designed randomised controlled trials in patients comparing efficacy of different antibiotics. This was confirmed by a recent meta-analysis of 93 published trials of antibiotic treatment for osteomyelitis, which concluded that despite three decades of literature the available data on the treatment of osteomyelitis is inadequate to determine the best antimicrobial agent(s), route or duration of antibiotic therapy (Lazzarini, 2005). Hence, currently there is no consensus on what the optimal antibiotic of choice is for the treatment of osteomyelitis.

Nelson, 1983, conducted an open comparative study in seventy-five children with suppurative bone and joint infections (arthritis, osteomyelitis, osteoarthritis) comparing IV cefamandole (100 mg/kg/day every six hours, n=48) to intravenous cefuroxime (75 mg/kg/day every eight hours, n=27). *S. aureus*, *Streptococci* spp. were the predominant pathogen but *H. influenzae* type b was more prevalent in patients with suppurative arthritis. Therapy was completed with oral antibiotics, in most cases with either cefaclor or cephalexin. In the 75% of patients where a pathogen was identified, *S. aureus, H. influenzae* and streptococci predominated, and all were susceptible to cefuroxime at ≤2.5 μg/mL. All patients showed clinical improvement whilst receiving cefuroxime. One eventual treatment failure was

reported in a child with extensive staphylococcal disease involving the ankle and distal fibula, the patient was initially treated with parenteral cefuroxime for nine days followed by oral cloxacillin.

A series of 17 patients, 14 with bacteriologically confirmed septic arthritis caused by *S. aureus*, *S. epidermidis*, *S. pyogenes* or *Acinetobacter* spp., were treated with cefuroxime at either 750 mg IM TID (n=6) or 1.5 g in a short intravenous infusion three times (n=11) daily (Hedström, 1984). The cefuroxime regimens were compared with ampicillin and/or cloxacillin treatment in 10 similar patients. Twelve of the 14 patients treated with cefuroxime became culture-negative from joint fluid within 4 days of commencing treatment, and were afebrile with regression of inflammation in 3-7 days. Two treatment failures occurred at the lower cefuroxime dose, prompting the adoption of the higher intravenous regimen for the remainder of the study. These failures failed to eradicate *S. aureus*. Antibiotic penetration measurements indicated that using this dosage, joint fluid levels reached 16-80 mg/L after two hours, and exceeded 5mg/L for at least eight hours after dosing. One patient who initially was a success had a relapse with *S. pyogenes* infection. There were no reported side effects. In the control group, bacteria were eradicated during therapy in all cases.

Herold, 1983, treated 21 cases of osteomyelitis or septic arthritis with cefuroxime in an open non-comparative study. For adults the drug was administered intravenously at 1.5 g 8-hourly, while children received 50 mg/kg/day in three divided doses. The duration of treatment ranged from nine to 22 days, the average being14 days. After two weeks, 14 patients were clinically cured with no persisting signs of infection, and five showed marked improvement including resolution of acute inflammation. Two treatment failures occurred, one in a diabetic patient with gangrene and osteomyelitis of the foot with polymicrobial infection including *E. faecalis*, and in a patient with compound fractures also with a polymicrobial infection including *Pseudomonas* spp. In 11 patients for whom a microbiological outcome could be determined, all infecting organisms were cleared, with the exception of one isolate of *Pseudomonas* spp. in a patient who also received colomycin, and was clinically cured. Additionally, two patients responded to cefuroxime after the failure of previous antibacterial therapy.

Graninger, 1977 used parenteral cefuroxime (2-3 mg IV every 12 hours or 1 mg IM every eight hours for 16-22 days) to treat six patients with osteomyelitis of two to 10 years duration. The causative organisms were *S. aureus*, *P. mirabilis* and *Klebsiella* spp. A clinically favourable result was obtained in five cases, all treated intravenously. Two patients were considered cured and two showed marked improvement. None of them relapsed during the 3-14 month follow-up period. In one patient, cefuroxime therapy was followed by intramedullary nail extraction and subsequent healing. The patient considered a treatment failure developed a subperiosteal abscess during intramuscular cefuroxime therapy, but recovered quickly without further antibiotic therapy after surgical drainage.

Parsch, 1997, treated 24 neonates and small infants with septic arthritis of the hip joint, a minority of which had simultaneous osteomyelitic infection of the femoral neck or acetabulum. After emergency arthrotomy to relieve the joint from septic effusion, capsular biopsy and collection of bacteriological specimens, treatment was initiated with parenteral cefuroxime and continued for three weeks, followed by three weeks of oral therapy. Seven patients were infected with β-haemolytic streptococci or *S. viridans*, two with *S. aureus*, two with *S. epidermidis* and two with *E. coli*. Cultures were negative in a further eight patients. Antibiotic therapy consisted of 150 mg/kg parenteral cefuroxime initiated during surgery and continued for three weeks. A successful outcome without sequelae was obtained in 18 patients where treatment was carried out promptly, whereas moderate osteomyelitic changes were evident in patients where treatment was delayed, and one child suffered destruction of the femoral head with permanent deformity.

Six children with osteomyelitis and six children with arthritis were treated by Gold, 1981, using cefuroxime at 150 mg/kg per day. Five children with osteomyelitis caused by *S. aureus* or *S. pyogenes* had a good clinical outcome. One further patient with osteomyelitis of unknown aetiology was unevaluable. The results from arthritis patients were more variable. The clinical outcome was good in three patients (one with an infection due to *H. influenzae* type b and two with infections of unknown aetiology), fair in one patient with arthritis due to *H. influenzae* and poor in one patient with arthritis due to *S. aureus*. The sixth patient was unevaluable.

The MAH also stated that no consensus guidelines on antibiotic therapy for bone and joint infections are currently available either in Europe or the USA (Lazzarini, 2005; Lew, 2004; Stengel, 2001).

The CHMP was of the opinion that the data provided in support of this indication was very limited. Osteomyelitis is difficult to treat, and data from controlled studies are considered necessary to support

this indication. Only one small comparative study in children was submitted (Nelson, 1983), with questionable methodology while the remaining submitted documentation consisted of small non-comparative studies (n=5-24). Even though the CHMP acknowledged the data on the penetration of cefuroxime into the bone, this did not outweigh the lack of supportive clinical studies. Furthermore, bone and joint infections include prostheses infections, which have a high frequency of formation of biofilm and a different bacteriology with the most important pathogen being MRSE, for which cefuroxime is not active. The CHMP considered the data to be insufficient to support this indication.

In conclusion, the CHMP recommended the removal of the proposed indication "*Bone and joint infections (e.g., osteomyelitis and septic arthritis)"* from the harmonised SmPC.

6) Obstetric and gynaecological infections

The MAH reviewed the nationally-approved SmPCs and proposed the following harmonised indication: "*Obstetric and gynaecological infections (e.g., pelvic inflammatory diseases)*". The MAH stated that the term pelvic inflammatory disease (PID) encompasses a wide spectrum of female pelvic infections. The causative pathogens usually reflect the normal microflora of the lower genital tract, but may include sexually transmitted organisms such as *N. gonorrhoeae* and *C. trachomatis*, and various aerobic and anaerobic organisms of faecal or dermatological origin, such as *Enterobacteriaceae*, enterococci, staphylococci, *Bacteroides* spp. and *H. influenza* (Bevan, 1995; Barrett, 2005; Judlin, 2010). Mixed infections are not uncommon. The relative importance of different pathogens varies in different countries and regions within Europe (Ross, 2007). The majority of obstetric infections occur postpartum and the placental bed is the most common site of infection. Obstetric infections are caused by a variety of different anaerobic and aerobic organisms. The most common aerobes are Streptococci, Enterococci, *S. aureus*, *E. coli*, *Klebsiella* spp. and *Proteus* spp. Anaerobic organisms include the Peptostreptococci, *Bacteroides* spp. and *Clostridium* spp. (Male, 2000). Antimicrobial regimens for the treatment of acute PID must be effective against the pathogens most frequently associated with this disease, notably *N. gonorrhoeae* and/or *C. trachomatis* and anaerobes. Cephalosporin antibiotics have been effectively used for the management of PID and are usually combined with doxycycline to cover for *C. trachomatis* or metronidazole to cover for anaerobes (Judline, 2010). The high mortality from infections during pregnancy makes early, aggressive therapy imperative. Due to the variety of potential pathogens in obstetric infections, therapy usually consists of a combination of antibiotics to cover both Gram-positive and Gram-negative pathogens as well as providing anaerobic cover. Cephalosporins such as cefuroxime in combination with metronidazole have been used to treat such infections (Male, 2000). In support of the indication, the MAH submitted two open studies which have evaluated the efficacy of parenteral cefuroxime.

Gertsner ,1993, investigated the efficacy of intravenous cefuroxime (1.5 g TID) in a study of 251 gynaecological and obstetric patients (). Conditions being treated included adnexitis, wound infections, endomyometritis, UTIs, abscesses and mastitis. Bacteriological evaluation on 47 patients indicated the predominant pathogens were *E. coli* and *S. aureus*. Other pathogens included aerobic streptococci, anaerobic peptostreptococci, *Bacteroides* spp., gonococci and *Chlamydia* spp. Thirty-four patients received adjuvant metronidazole, five were given clotrimazole, and one each was given clindamycin, tobramycin, josamycin and fluconazole. The mean treatment period was five days. Eighty-two women had additional oral cefuroxime therapy (500 mg BID) for periods of 3 to 15 days. Treatment was completely successful in 77.5% of cases with a further 17.2% showing improvement. Only five cases were classed as non-responders and required a change of therapy. Two of these had UTIs caused by resistant organisms, two had chorioamnionitis which was treated with erythromycin, and one was treated with metronidazole for bartholinitis.

Voropeva, 1982, studied the efficacy of parenteral cefuroxime in 24 obstetric and gynaecological patients, of whom eleven were suffering from puerperal endometritis, four from lactational mastitis, five from pyelonephritis gravidarum and four from complications following gynaecological surgery. Three of the post-surgery patients were treated with 1.5 g cefuroxime IV TID, while the remainder received 750 mg IM TID. All treatments were continued for 6–7 days. A good clinical outcome was obtained in all those suffering from endometritis, with normalisation of body temperature and

disappearance of symptoms within 2-3 days. A variety of organisms including *E. coli*, *S. aureus* and *Klebsiella* spp. were isolated from these patients, together with enterococci and, in some cases, anaerobes. A marked decrease in the numbers of enterococci and other pathogens was evident after 4-5 days of treatment. *S. aureus* was the causative pathogen in the cases of mastitis, all of which responded well to treatment. One recurrence of infection occurred 12 days after treatment, but with a different strain of staphylococcus. Clinical improvement was seen in the five cases of pyelonephritis, three of which were associated with high counts of *E. coli*, *P. mirabilis* or *P. rettgeri*, with the urine becoming sterile in 3-4 days. Three of the four patients with post-surgical infections also improved rapidly. The fourth developed pneumonia caused by *P. aeruginosa* and required a change of therapy. No adverse effects were encountered in any of these patients.

The CHMP reviewed the two open studies submitted by the MAH, both relatively old, which evaluated the efficacy of parenteral cefuroxime. The CHMP stated that cefuroxime is not active against many of the bacterial species isolated in obstetric and gynaecological infections either due to inherent resistance (*Bacteroides* spp., and *Clostridium* spp., *Chlamydia* spp., *Mycoplasma* spp. *Enterococcus* spp.) or due to acquired resistance (*E. coli*, *Proteus* spp., *Klebsiella* spp.) of the bacterial species isolated in obstetric and gynaecological infections. Due to the variety of potential pathogens in obstetric infections, therapy usually consists of a combination of antibiotics to cover both Gram-positive and Gram-negative pathogens, aerobe and anaerobe, extracellular as well intracellular bacterial species. The CHMP therefore considered this proposed indication to be inadequately supported by the submitted data.

In conclusion, the CHMP recommended the removal of the proposed indication "*Obstetric and gynaecological infections (e.g., pelvic inflammatory diseases)"* from the harmonised SmPC.

7) Gonorrhoea

The MAH reviewed the nationally-approved SmPCs and proposed the following harmonised indication: "*Gonorrhoea particularly when penicillin is unsuitable*". The MAH submitted three comparative and five non-comparative studies.

In a comparative study (blinding and design not specified) the efficacy of a single 1.5 g cefuroxime plus 1 g oral probenecid was compared with that of a 2 g dose of spectinomycin given intramuscularly in 365 culture positive patients, (Chitwarakorn 1985). Of note, this study was conducted in Thailand, where there is a high incidence of penicillin resistance (approximately 40%) in gonococci. At 3 to 13 days after treatment, 98% of those treated with either drug were cured, irrespective of sex or the presence of penicillinase-producing organisms. Dysuria and discharge were slightly more prevalent in the cefuroxime group in comparison to the spectinomycin group (12% vs. 6%, respectively).

A study by Morrison, 1980, compared the response to single dose of IM cefuroxime given at various dosages (cefuroxime 1 g plus probenecid 1 g, cefuroxime 750 mg plus probenecid 1 g, and cefuroxime 1.5 g only) to benzylpenicillin (penicillin G) 5 million units with probenecid 1g. A total of 625 men and 423 women were randomly assigned to the different regimens. The cure rates were almost identical for men (95.3% vs. 94.0%) and for women (98.8% vs. 98.4%), when comparing penicillin G to cefuroxime 1 g (both with probenecid). Cefuroxime at a lower dosage (750 mg plus 1 g probenecid) and cefuroxime 1.5 g alone gave similar cure rates for men (95.0% vs. 96.5%) and for women (98.0% vs. 98.7%). Six out of seven patients with pharyngeal gonorrhoea were cured with cefuroxime, as were four out of five cases of rectal gonorrhoea in men. Between 21% and 39% of patients treated with cefuroxime experienced post-gonococcal urethritis, with continuing discharge but negative cultures. A similar effect occurred in 35% of patients treated with benzylpenicillin.

Lossik, 1982, reported the results of a double-blind randomised trial comparing cefuroxime 1.5 g with aqueous procaine penicillin G (4.8 x 106 IU) IM plus 1 g probenecid for the treatment of uncomplicated gonorrhoea in 358 culture positive men and women. The cure rate of 96% and 95% respectively, was not statistically different, nor was the rate of post-gonococcal urethritis. Antibiotic susceptibility studies of 365 isolates of *N. gonorrhoeae* from the study population showed that cefuroxime was more active

than penicillin. There was no significant difference between cefuroxime and penicillin in terms of post-gonococcal urethritis rates (20% and 15.3% respectively; p=0.5).

In an open, non-comparative study, a single IM 1.5 g dose of cefuroxime was found to be effective within four days of commencing treatment in 97% of 100 evaluable patients with culture confirmed gonorrhoea, with resolution of symptoms and infecting pathogens (Bello 1983). Of the three patients who failed therapy, all had signs of dysuria after treatment but no *N. gonorrhoeae* was cultured from these patients.

A study of adult male and female patients with gonorrhoea conducted by Price compared the efficacy of intramuscular cefuroxime, 1 g alone (n=31, all males) vs. 1 g with 1 g of oral probenecid (n=45, all males), or vs. 1.5 g with 1 g oral probenecid (n=201, 143 males, 58 females) (Price 1977). Of the patients treated with 1 g cefuroxime alone, only 14 were assessable of which 12 were cured. The failure rate was therefore 14.3%, whereas all 32 (100%) assessable patients were cured by 1 g cefuroxime plus 1g probenecid. Ninety eight male patients given 1.5 g cefuroxime plus 1g probenecid were assessable. In 95 (97%) of these the gonococcus was successfully eradicated. Amongst female patients, 50/51 (98%) of those assessable were cured, including 19 with positive rectal cultures. The postgonococcal urethritis rate in males was 15.6% for the 1 g dose and 4.2% for the 1.5 g dose.

Fowler, 1977, conducted an open non-comparative study to evaluate the efficacy of 1.5 g cefuroxime IM in 151 men suffering from gonorrhoea. In the 122 evaluable patients followed there was one treatment failure and 8 cases which were considered to be reinfections. Three of these had negative tests for gonococci at the first follow-up examination, while another had negative tests at both first and second follow-up visits. These cases presented again with acute gonorrhoea 12 or more days after their last visit. Post-gonococcal urethritis developed in 18 (15%) of the 113 cases in which the gonococcal infection responded satisfactorily to cefuroxime therapy and there was no reappearance of the infection during the follow-up period.

Fowler, 1978, used cefuroxime to treat 856 male and 340 female patients with uncomplicated gonorrhoea caused by penicillin susceptible *N. gonorrhoeae*. The diagnosis of gonorrhoea in men was made when both smears and cultures gave positive results in 796 patients. In women, smears and cultures gave positive results in 196 patients. The cefuroxime dosage for men was 1.5 g, 1 g or 750 mg administered intramuscularly with 1g probenecid. Women received only the lower two doses. Patients were evaluated two to three days after screening and then at intervals of one, two, four and six weeks. Cure rates for the 1.5 g cefuroxime group ranged from 96.2% to 99.3%. For 1 g cefuroxime group the cure rates ranged from 96.1% to 98.5% and the corresponding rates for the 750 mg dose plus probenicid group was 94.8 to 99.6%. The postgonococcal urethritis rate ranged from 15.6-16.5% at the various doses.

A study by Patamasucon, 1981, enrolled 26 children between one and 15 years of age with purulent genital discharge and a Gram stain indicative of gonococcal infection. Treatment was initiated with cefuroxime 25 mg/kg IM. Gonococci were recovered from pharyngeal cultures in 3 of 26 (12%), from anal cultures in 8 of 26 (31%) and from vaginal or urethral cultures in 96 % of instances. Nineteen patients had only *N. gonorrhoeae* isolated, and of these 17 became asymptomatic in less than two days. The remaining two became asymptomatic in 3 to 5 days. In the remaining seven patients, *Chlamydia spp* was recovered in addition to *N. gonorrhoeae*. Two of these became asymptomatic within two days, but the remaining five had genital discharge continuing beyond five days. In-vitro, some of the *N. gonorrhoeae* strains were non-susceptible to penicillin, with MICs higher than 0.08µg/mL. None of them produced β-lactamase.

The CHMP reviewed the studies submitted by the MAH. The most common co-existing pathogen in patients with gonorrhoea is *Chlamydia trachomatis* and many studies performed during the last three decades have given remarkably consistent results: 15- 25% of heterosexual men, 10-15% of men who have sex with men, and 35-50% women with gonorrhoea have concurrent *Chlamydia* infections (Dicker et al 2003, Sex Transm Dis. 30:472-476; Datta et al., 2007. Ann. Intern Med. 149: 89-96).

The CHMP therefore considered 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, to be missing. The CHMP also noted that in most of the provided studies, cefuroxime was used in combination with probenecid for treatment of gonorrhoea. The CHMP concluded that the available data did not support the use of cefuroxime in this indication.

In conclusion, the CHMP recommended the removal of the proposed indication "*Gonorrhoea particularly when penicillin is unsuitable"* from the harmonised SmPC.

8) Other infections

The MAH reviewed the nationally-approved SmPCs and proposed the following harmonised indication: "*Other infections including septicaemia, meningitis and peritonitis*".

8a) Septicaemia

The MAH provided five non-comparative studies and one meta-analysis to support the proposed indication. Mott, 1981, reported the use of cefuroxime and gentamicin in combination as empirical antibiotic coverage in 41 children with leukaemia and 16 children with solid tumours who developed fever while neutropenic (< 1000/mm3). The combination was effective in all cases. Susceptible Gram-positive organisms were recovered in 13 patients and Gram-negative organisms in four others. Pathogens were, however, not isolated in the majority of these febrile episodes.

Hugo, 1980, conducted an open non-comparative study evaluating IM or IV cefuroxime in 33 patients, including 6 patients with proven bacterial septicaemia. The pathogens isolated from 6 septicaemia patients were *Klebsiella* spp., *P. mirabilis*, *E. coli* (2 cases) *S. epidermidis* and *S. aureus*. The majority of patients received 750 mg cefuroxime IM TID, though doses of up to 6 g daily were used. The mean duration of treatment was 11.4 days, with three patients treated for 28 days or more. All six patients with septacaemia were successfully treated with cefuroxime.

A non-comparative study by Goberando, 1977, evaluated the efficacy of parenteral cefuroxime (750 mg to 1 g TID or QID) in 25 critical patients with serious infections, including 7 patients with bacteraemia. The pathogens isolated from these 7 patients were *Serratia* spp. (6 patients) and *P. mirabilis* (1 patient). All seven patients had successfully eradicated the causative pathogen and were clinical successes.

Miki, 1977, reported on the efficacy of varying dosing regimens of cefuroxime (750 mg and 1500 mg) given IM or IV in 70 Japanese patients, 5 of whom had bacteraemia. The causative pathogens were *E. coli* (2 patients), *Klebsiella* spp. (1 patient), *Salmonella typhimurium* (1 patient) and unidentified Gram- positive anaerobe (1 patient). TID regimens were generally administered to patients with severe infections. Treatment with parenteral cefuroxime resulted in clinical cure in 2 patients with a further 1 patient showing considerable improvement. Outcome was poor in 2 patients. Of the causative pathogens isolated at screening, both *E. coli* isolates and a Gram-positive anaerobe were eradicated. In one case, *S. typhimurium* was not eradicated (this patient also had a poor outcome). Bacteriological outcome for the patient who failed with *Klebsiella* spp. could not be determined.

An open, non-comparative study by Gold, 1981, studied intravenous cefuroxime (50 mg/kg/day in four divided doses) to treat 53 children with soft tissue infections (cellulitis), which included five patients with bacteraemia. The causative pathogens were *S. pyogenes* (1 patient) and *H. influenzae* type b (4 patients). Blood cultures became sterile within 48 hours in all five patients and all did well clinically.

Several clinical studies conducted between 1978 and 1981 were pooled to evaluate the efficacy of cefuroxime in patients with bacteraemia (Gold, 1983). One hundred and ten evaluable cases of bacteraemia were treated with cefuroxime. All bacteraemic patients were considered to have cleared their infection following cefuroxime treatment. The MAH provided a summary of the pathogens successfully treated in these studies.

The CHMP reviewed the data provided by the MAH but noted that they were old, non-comparative and included small numbers of patients. The studies were performed in a period in which acquired resistance, particularly among aerobe Gram-negative bacteria, was not a problem. The CHMP considered the results from some of the studies to be questionable (Gorebando 1977; Gold 1983) and considered it unclear how bacterial species such as *Serratia* spp., and *Enterococcus faecalis*, which are inherently resistant to cefuroxime, could be "successfully" treated in these studies. The CHMP therefore concluded that the submitted data was insufficient to accept the proposed indication.

In conclusion, the CHMP recommended the removal of the proposed indication "*Septicaemia/bacteraemia*" from the harmonised SmPC.

8b) Acute bacterial meningitis

The MAH submitted 3 comparative 2 non-comparative studies to support the proposed indication, together with two recently published case studies. A prospective, randomised study conducted by the Swedish Study Group, 1982, compared cefuroxime with a combination of ampicillin and chloramphenicol in 40 evaluable patients with culture proven bacterial meningitis. Cefuroxime was administered in doses of 180 – 225 mg/kg/day to children in 3 doses, while adults received 9 g/day in three divided doses. Pathogens isolated were *H. influenzae* (20), *N. meningitidis* (11), *S. pneumoniae* (5) and other bacterial species (4). Satisfactory clinical results were obtained in 18 of 21 patients treated with cefuroxime and in 14 of 19 patients treated with standard antibiotic therapy. Two patients in each treatment group died. Although the CSF became sterile in a fourth patient who was receiving cefuroxime for *S. aureus* meningitis, this patient died. Two patients (one in each treatment group) had significant hearing loss, and two patients (one in each group) had some degree of paresis. One patient treated with cefuroxime developed epilepsy. These complications were regarded as recognised sequelae of the meningitis.

Marks, 1986, conducted a multicentre study comparing cefuroxime to ampicillin plus chloramphenicol in 107 children with bacterial meningitis. CSF isolates included *H. influenzae* type b (25% β-lactamase positive), *S. pneumoniae* and *N. meningitidis*. Overall, clinical cure rates were similar and very high for both treatments (95%). In the cefuroxime group, secondary bacteraemia developed in one patient on day 10, and three patients had relapse or reinfection. One patient who received cefuroxime for 10 days had a relapse of epiglottitis 17 days later. Of the patients given ampicillin plus chloramphenicol, one had a relapse of meningitis one week after completing 7 days therapy. Bacteraemia developed in one patient 42 days after completion of 10 days therapy. Four patients treated with ampicillin/chloramphenicol and five treated with cefuroxime had sensorineural hearing loss.

To assess the comparative efficacy of cefuroxime and ceftriaxone for the treatment of bacterial meningitis, Lebel, 1989b, reviewed the records of four prospective trials conducted in their medical institution using comparable patients. The majority of infections were caused by *H. influenzae* type b (255 cases) with a lower number caused by *S. pneumoniae* (34), *N. meningitidis* (29), Group B streptococci (4) or no identified pathogen (11). A total of 159 subjects received cefuroxime at 240-300 mg/kg/day iv at 8-hourly intervals, while 174 patients received ceftriaxone either at an initial dose of 75 mg/kg followed by 100 mg/kg/day 12-hourly or as 80 mg/kg at 0, 12 and 24 hours then once daily treatment was continued for 7-10 days. Some patients in each group also received dexamethasone 0.6 mg/kg/day. After 24 hours of therapy 14 out of 157 patients (8.9%) treated with cefuroxime still had positive CSF cultures, whereas all samples from patients treated with ceftriaxone were sterile ($p<0.001$, Chi-square analysis). In 24 hour specimens where cephalosporinase was added before culture, 9/58 (15.5%) were positive from the cefuroxime group and 11/158 (7%) in the ceftriaxone group. At the time of hospital discharge there were significantly more patients with neurological abnormalities in the cefuroxime group (39/159 vs. 25/174,$p=0.018$), but the difference was no longer statistically significant at 6-week and one year follow-up, and psychometric evaluations were similar. However, the incidence of hearing impairment was higher in the cefuroxime group (18% vs. 11%).

In a non-comparative study, Schaad, 1984, prospectively evaluated 84 paediatric patients with bacterial meningitis while receiving cefuroxime (200 mg/kg per day in four equal intravenous doses) as single drug therapy for nine to 13 days. Bacterial cultures on admission yielded the following organisms (*H. influenzae*, 43; *N. meningitis*, 20; *S. pneumoniae*, 10; unknown 5). Six cases were admitted in extremis and died within a few hours. Bacteriological and clinical responses in the remaining 78 patients were good. All responded with rapid improvement in clinical signs and symptoms, and there were no cases of recrudescence or relapse. Six patients experienced prolonged fever for 10 or more days before defervescence, and 12 had transient reappearance of fever after a non-febrile interval. On follow-up examination, 15% of patients had neurological sequelae. Hearing impairment was slight in four patients, moderate in three, and one had severe bilateral hearing loss.

A study by Bahaeldin, 1983, evaluated the efficacy of cefuroxime (dose ranging from 90 mg/kg to 300 mg/kg during the first two days of treatment and subsequently 45 to 149 mg/kg for the next six to nine days) in 48 infants and children (aged from birth to 14 years) with bacterial meningitis. Cefuroxime was clinically and bacteriologically effective in 40 patients (83%). All isolates of *S. pneumoniae*, *N. meningitides* and *S. typhi* were susceptible to cefuroxime. Of the *H. influenzae* isolates cultured, 14 were susceptible to cefuroxime and one was of intermediate susceptibility. Nine of the *S. aureus* isolates were susceptible but three were resistant to cefuroxime as was the *P. aeruginosa* isolate. Of the patients who failed, three patients who had a resistant *S. aureus* isolated died, one patient with meningococcal meningitis experienced gastro-intestinal haemorrhage with purpura and ecchymoses covering the body and died soon after cefuroxime was administered. A further patient with meningococcal meningitis received less than one dose of cefuroxime and died. One patient with *S. pneumoniae* meningitis failed to respond to treatment and died on the sixth day after admission.

In the first case study, the efficacy of beta-lactam antibiotics given every 8 hour to adult patients with community-acquired acute bacterial meningitis was retrospectively analysed (Brink 2006). The most common pathogens noted were *S. pneumoniae* (47.5%), *N. meningitidis* (12.5%), and *Listeria monocytogenes* (5.0%). Other bacteria were diagnosed in 16.3% of all episodes, but the bacteriological aetiology remained unknown in 18.8%. The 80 medical records identified in the period 1999-2004, included10 single treatment courses with IV cefuroxime (750 mg to 3 g). The mortality rate in these patients was 6.3%, with an incidence of permanent neurological deficiencies of 24.1%.

The second case study was a retrospective review of patients (aged 0.5 – 53 years) with bacterial meningitis due to *S. aureus* (Norgaard 2003). *S. aureus* meningitis was confirmed in 45 patients, and 5 additional patients had a brain abscess. 44 cases were nosocomial (mortality 16%) and 6 were community acquired (mortality 83%). None of the isolates was methicillin resistant and 6 were penicillin susceptible. Intra-ventricular antibiotic treatment was given to 28 patients, systemic therapy included cefuroxime in 32 patients (64%) as either a primary or secondary choice., Among 31 nosocomial cases treated systemically with cefuroxime the mortality was 10% (95% exact confidence limits 2-26%). The authors concluded that cefuroxime seems to be a valid choice for *S. aureus* meningitis in the nosocomial setting.

The CHMP stated that the bacterial species that cause meningitis vary by age group and that the most commonly isolated bacterial species are *Neisseria meningitides*, *Haemophilus influenza*, *Streptococcus pneumonia*, *Listeria monocytogenes*, *Streptococcus agalaectiae*, as well as staphylococci (*S. aureus* and *S. epidermidis*). Aerobic Gram-negative bacilli like *Klebsiella*, *Escherichia coli*, *Serratia marcescens*, *Pseudomonas aeruginosa* and *Salmonella* species have been increasingly important as causative agents in patients with bacterial meningitis. Therefore, the CHMP was concerned that the majority of the studies provided by MAH, which were conducted in the late 1970's, identified *H. influenzae*, *N. meningitidis*, *S. pneumonia* and *S. aureus* (non-MRSA) as the predominant bacterial species. This does not reflect the present situation in the EU. *H. influenza* is no longer the predominant bacterial species in meningitis, due to current vaccination programmes.

In conclusion, the CHMP recommended the removal of the proposed indication "*Meningitis"* from the harmonised SmPC.

8c) Peritonitis

The MAH submitted data to support the proposed indication "*peritonitis*". A randomised, open, comparative study by Ohlin compared the efficacy of piperacillin/tazobactam to cefuroxime/metronidazole in the treatment of patients with intra-abdominal infections (Ohlin, 1999). In total, 269 patients with intra-abdominal infections were randomised and treated with at least one dose of each study drug. Patients were given piperacillin 4 g/tazobactam 0.5 g every 8 hours or cefuroxime 1.5 g every 8 hours plus metronidazole 1.5 g every 24 hours. Each patient was to be treated for a minimum of 3 days and no more than 10 days. Two hundred five patients (205) were evaluable for efficacy, 105 patients treated with piperacillin/tazobactam and 100 patients with cefuroxime. In the intention to treat analysis, treatment was equally successful for piperacillin/tazobactam (103/140, 74%) and the cefuroxime/metronidazole groups (90/129, 70%) (p = 0.6). Corresponding figures for the clinically evaluable group were 102/105 (97%) and 94/100 (94%) for piperacillin/tazobactam and cefuroxime/metronidazole groups, respectively. At late follow up, 92/105 (88%) and 83/100 (83%) in the two groups, respectively, remained free of infection.

In a large open, randomised, comparative multicentre trial the efficacy, safety and tolerance of cefuroxime/metronidazole and imipenem/cilastatin combinations were compared in patients with intra-abdominal infections (Hall Angeras, 1996). Two hundred and fifty seven patients (mean age 54 years) were treated with cefuroxime (3.0-4.5 g/day) plus metronidazole (1.0-1.5 g/day) for at least three days, and 258 patients were treated with imipenem/cilastatin (1.5-2.0 g/day), for at least three days. 16% and 21% of patients in the imipenem/cilastatin and cefuroxime/metronidazole group, respectively, were considered to be seriously ill with Apache II scores between 11 and 20. Appendicitis (39%), perforated colon (18%), abscess (10.5%) and ulcer (10%) were the most common intra-abdominal infections. One-hundred-and-twenty-four of 145 clinically evaluable patients (85.5 %) treated with the cefuroxime/metronidazole combination were cured. The corresponding cure rate for imipenem/cilastatin was 80.7% (130 of 161 evaluable patients). The bacteriological eradication rates were 90.8 % for cefuroxime/metronidazole group and 86.9 % for imipenem/cilastatin group (no statistically significant difference). The mortality rate was 7.4% and 4.7% for the impenem/cilistatin and cefuroxime treatment groups, respectively.

Cefuroxime given by IV infusion at a dose of 1.5 g TID with 0.5 g metronidazole (IV infusion TID) for at least 5 days has been successful in treating purulent peritonitis with and without lavage in patients with perforation of the appendix or colon (Hallerbäck, 1986). No post-operative abscesses or other complications were found in any patient. This dosage regimen was equally effective as piperacillin given four times daily in 85 patients with diffuse peritonitis who were randomly allocated to receive one of the two treatments. To ensure the groups were comparable with respect to origin of the infection, patients were stratified into those with appendicitis or colonic perforation (n=45) and those with perforated ulcers or biliary disease (n=38). A successful outcome was achieved in 29/45 (64%) in the cefuroxime/metronidazole group compared with 27/38 (71%) in the piperacillin group. However, there were significantly more recurrent infections in the piperacillin group among patients treated for perforated appendix 5/11 vs. 1/15, p=0.02), and more wound or intra-abdominal infections in those with anaerobic infections.

In another study, 85 patients were randomly allocated to receive either piperacillin (n = 38) or cefuroxime plus metronidazole (n = 45) after surgical treatment of diffuse peritonitis (Paakkonen, 1991). A total of 78 patients were evaluable for the efficacy analysis. A mean of 1.5 (piperacillin group) and 1.7 (cefuroxime/metronidazole group) pathogens/patient were identified. Twenty-seven patients (71%) were successfully treated in the piperacillin group compared with 29 (64%) in the cefuroxime/metronidazole group.

Antibiotic treatment with intravenous cefuroxime alone (1.5 g TID) and intravenous cefuroxime in combination with metronidazole (1.5 g + 0.5 g TID) for at least three days was compared in a prospective randomised study of 122 patients undergoing surgery for diffuse peritonitis (Tornqvist,

1985). Pre-operative cultures indicated that most patients had mixed aerobic/anaerobic infections. Post-operative infectious complications occurred in 22% of patients treated with cefuroxime alone and 17.5% of those given combination therapy, leading the authors to conclude that both treatments were equally effective. The mortality rate was 5% for patients treated with cefuroxime alone in comparison to 8% for those given the combination treatment. Tissue concentrations of cefuroxime were all above the MIC values for the pathogens isolated.

Following concerns raised by the CHMP regarding the proposed indication, due to the lack of clarity on the number of patients with peritonitis included in the two largest studies submitted (Ohlin 1999 and Hall Angeras 1996), the MAH proposed to revise the indication to "*Intra-abdominal infections*" and presented information on the type of intra-abdominal infections (IAIs) included in the study by Hall Angeras, 1996 and the clinical cure rate by diagnosis. 124 of 145 clinically evaluable patients (85.5 %) treated with the cefuroxime/metronidazole combination were cured. The overall cure rate for imipenem/cilastatin was 80.7% (130 of 161 evaluable patients). The bacteriological eradication rates were 90.8 % for cefuroxime/metronidazole group and 86.9 % for imipenem/cilastatin group (no statistically significant difference). The mortality rate was 7.4% and 4.7%, for the impenem/cilistatin and cefuroxime treatment groups, respectively. The authors concluded that intra-abdominal infections can be treated equally successfully with the combination of cefuroxime plus metronidazole with similar efficacy to imipenem/cilastatin. The MAH also presented the clinical diagnoses of patients with intra-abdominal infections enrolled in the study by Ohlin, 1999. The most common diagnosis was appendicitis, followed by peritonitis and diverticulitis. The MAH provided an overview of several European guidelines recommending the use of cefuroxime with or without metronidazole for the first- or second-line treatment of IAIs.

The CHMP noted the change in proposed indication and considered it acceptable, based on the distributions of infections in the two largest submitted studies (Ohlin 1999 and Hall Angeras 1996). However, as a large proportion of the study subjects in both studies had appendicitis, the CHMP added a cross-reference to Section 4.4, to state that due to its spectrum of activity, cefuroxime is not suitable for the treatment of infections caused by Gram-negative non-fermenting bacteria. In conclusion, the CHMP adopted the following harmonised indication:

"*Intra-abdominal infections (see section 4.4)*"

9) Prophylaxis

The MAH reviewed the nationally-approved SmPCs and proposed the following harmonised indication: "*Prophylaxis against infection in abdominal, pelvic, orthopaedic, cardiac, pulmonary, oesophageal and vascular surgery where there is increased risk from infection*". The MAH stated that most surgical site infections (SSIs) are believed to be acquired during a surgical procedure with the responsible pathogens originating from the patient's endogenous flora. Generally, the causative pathogens depend on the type of surgery; the most commonly isolated organisms are *S. aureus*, coagulase-negative staphylococci, *Enterococcus* spp. and *E. coli*; however, the pathogens isolated will also depend on the surgical procedure (Owen 2008; Uckay 2010). An increasing number of SSIs are being caused by multidrug resistant organisms, such as methicillin-resistant *S. aureus* (MRSA). Clean surgical procedures typically result in SSIs due to Gram-positive aerobes representing common skin flora pathogen. Clean-contaminated, contaminated or dirty surgical procedures usually result in poly-microbial infections containing enteric Gram-negative and anaerobic organisms in addition to skin flora pathogens (Nichlos 2004). Short courses of antimicrobial prophylaxis are widely used to reduce SSI risk. The choice of agent is usually based on the pathogens most commonly associated with the procedure being performed. In practice, broad-spectrum β-lactam antibiotics such as cefuroxime are most widely used as prophylactic agents, particularly for clean contaminated surgical procedures, with an agent such as metronidazole being added if necessary to provide cover against anaerobes (Owen 2008; Hedrick 2006; Uckay 2010). Cefuroxime has been comprehensively evaluated as a prophylactic agent for the prevention of SSIs in many different types of surgical prophylaxis as presented below.

9a) Prophylaxis for prevention of respiratory tract infections

Sirvent, 1997, performed an open, prospective, randomised, controlled clinical trial using prophylactic cefuroxime with the aim of reducing the incidence of ventilator-associated pneumonia (VAP) in head-injured patients and patients with stroke requiring mechanical ventilation. 100 patients with head injury or coma caused by medical stroke and with Glasgow coma scores ≤ 12 and mechanical ventilation > 72 h, were included. Patients received cefuroxime IV (n=50; two 1,500 mg doses 12 hours apart after intubation) and 50 patients in the control group received no cefuroxime. In the former group patients did not receive any other antibiotics before the end-point determination, whereas in the latter, 17 patients received prophylactic antibiotics as prescribed by the attending physician. The global incidence of microbiologically confirmed pneumonia was 37% (n = 37); 12 (24%) in the cefuroxime group, and 25 (50%) in the control group (p = 0.007). Early-onset pneumonia accounted for 70% of all the pneumonia episodes (n = 26), eight (67%) occurred in the cefuroxime group, and 18 (72%) belonging to the control group (p = 0.02). In the control group, four of 17 (23%) patients receiving prior antibiotics developed pneumonia, whereas 21 of 33 (64%) patients who did not receive antibiotics developed pneumonia (p = 0.016). The multivariate analysis revealed that the duration of mechanical ventilation was an independent risk factor significantly associated with the development of pneumonia. Furthermore, the use of cefuroxime and/or prior antibiotics in the control group, before the pneumonia episode, had a protective effect against its development. No differences were found with regard to mortality and morbidity when comparing the study population with the control group. Nevertheless, when comparing patients with pneumonia (from both study and control groups) with those without it, there was a decrease in total hospital stay (35 ± 13 days versus 25 ± 14 days, p = 0.048) and ICU stay (20 ± 11 days versus 11 ±7 days, p = 0.001).

The CHMP noted that only one small study was provided by the MAH, which showed no differences between cefuroxime and control group with regard to mortality and morbidity, although total hospital stay was shorter in the cefuroxime group compared with the control group. Due to the lack of supportive data, the CHMP did not consider the indication "*prophylaxis against infections in pulmonary surgery"* to be acceptable.

9b) Prophylaxis in gastrointestinal and biliary surgery

A consecutive series of 509 patients undergoing abdominal surgery were entered into a randomised, observer and patient blind, controlled, prospective, study to evaluate the efficiency of amoxicillin/ clavulanate compared with cefuroxime/metronidazole for the prevention of post-operative wound infections (Palmer, 1994). One or three doses of antibiotics were given depending on the type of surgery and operative factors. Amoxicillin/clavulanate was given to 230 patients and resulted in a total wound infection rate of 5.6%; cefuroxime/metronidazole was given to 225 patients and resulted in a total wound infection rate of 3%. The difference between infection rates was not significant. Both groups were comparable in terms of demographic details, type and duration of surgery, risk factors associated with surgical procedures and post-operative management. Although not statistically significant, a difference in the wound infection rate for those patients undergoing colorectal surgery was seen: 8/69 (12%) for the amoxicillin/clavulanate group and 2/79 (3%) for the cefuroxime/metronidazole group.

A randomised, observer blind controlled trial was undertaken by Cann, 1988, to compare the role of mezlocillin, as the sole prophylactic agent, with a combination of cefuroxime and metronidazole in 346 patients undergoing biliary and gastrointestinal surgery. Mezlocillin was administered at induction of anaesthesia and further doses of 2 g mezlocillin TID was administered every 8 hours for 48 hours to those patients who had undergone contaminated surgery. In the comparator group, patients received 750 mg cefuroxime at induction of anaesthesia and then 12 hourly for 24 hours. Patients who were undergoing contaminated surgical procedures received 750 mg cefuroxime plus 500 mg metronidazole at induction of anaesthesia and then 8 hourly for 48 hours. No difference in wound infection rates was seen in patients following appendectomy, biliary or gastro-oesophageal surgery. A significantly higher wound infection rate was seen in patients undergoing colorectal surgery who received mezlocillin alone (30.2%) compared with those receiving cefuroxime and metronidazole (11.5%). The wound infections seen in patients receiving mezlocillin alone were polymicrobial involving organisms of faecal origin,

including non-sporing anaerobes, predominately *B. fragilis*, which were predominantly susceptible to mezlocillin. Infections due to *S. aureus,* resistant to mezlocillin, were more frequent in patients receiving mezlocillin and usually secondary in nature.

A prospective, randomised, controlled trial, was conducted evaluating the efficacy a single intravenous dose of 1.5g of cefuroxime (n = 207) or 3g of ampicillin-sulbactam (group B, n = 211) administered during induction of anaesthesia in patients undergoing elective open or laparoscopic cholecystectomy (Dervisoglu, 2006). Patients were evaluated post-operatively for 1 month for the development of surgical site infections. Postoperative surgical site infection was noted in 19 (4.5%) of 418 patients, 18 in the cefuroxime group and 1 in the ampicillin-sulbactam group (P<.001). In the group that received cefuroxime, 15 (83.3%) of 18 surgical site infections were due to *Enterococcus* species.

A prospective randomized trial compared mezlocillin plus metronidazole with cefuroxime plus metronidazole for the prophylaxis against the aerobic organisms encountered during elective colonic surgery (Ambrose, 1983). Forty-nine patients received mezlocillin and metronidazole, and 47 patients received cefuroxime and metronidazole. The first dose of antibiotic (mezlocillin 2 g or cefuroxime 1.5 g with metronidazole 500 mg) was given intravenously on induction of anaesthesia. The second and last dose was given 8 hour after the initial injection. No other antimicrobial therapy was given in the preoperative period with a bowel preparation or in the immediate post-operative period. Severe wound infection occurred in three of the patients receiving mezlocillin and metronidazole (6 %) compared with six in the group receiving cefuroxime and metronidazole (13 %). Minor wound sepsis was recorded in 24 % of patients receiving mezlocillin and metronidazole compared with only 11 % after cefuroxime and metronidazole. There were two episodes of septicaemia, one in each group, and three abscesses, all of which occurred in patients receiving metronidazole and mezlocillin. The total number of surgically related infections was, however, significantly less with cefuroxime and metronidazole (13) compared with mezlocillin and metronidazole (23; P<0.03). *Escherichia coli* was the principal organism responsible for surgically related post-operative sepsis: (22 isolates: 14 mezlocillin and eight cefuroxime) all of which were susceptible to the agents used. *P. aeruginosa* was recovered from 10 patients (three mezlocillin and seven cefuroxime); all of the isolates were resistant to both antibiotics and were associated with severe morbidity. There were 11 isolates of *Staphylococcus* spp. (nine mezlocillin and two cefuroxime: P<0.03).

The purpose of one randomised prospective study of 416 patients with acute cholecystitis was to compare the prophylactic efficacy of three cephalosporins in preventing wound infections (Hurlow, 1981). Patients received either 1 g cefazolin, 750 mg cefuroxime or 1 g of cefamandole IM at the time of surgery. Wound infection rates were 3.1% with cefuroxime, and 6.0% with cefamandole, and 8.7% with cefazolin, but did not differ significantly between groups. The pathogens implicated in wound infections were predominately *Enterobactericae*.

Hares, 1981, studied the effectiveness of cefuroxime as prophylaxis in high risk gastro-oesophageal surgery in a prospective, placebo-controlled trial. In this study, 81 patients were randomly assigned to receive either a single 1.5 g IV dose of cefuroxime prior to surgery (n=27), 1.5 g cefuroxime instilled subcutaneously along the surgical incision (n=26), or no prophylactic antibiotics (n=28). Patients who received systemic cefuroxime showed a significant reduction in the number of cases of wound sepsis (7% vs. 32%, p<0.05), abscess formation (0% vs. 29%, p<0.01), and septicaemia (0% vs. 21%, p<0.01) when compared to untreated controls. The overall infection rate with systemic cefuroxime (7%) was significantly better than no prophylaxis (46%, p<0.01).

The CHMP reviewed the data submitted by the MAH and considered the indication "*prophylaxis against infections in gastrointestinal (including oesophageal) surgery*" to be acceptable.

9c) Prophylaxis in orthopaedic surgery

Cefuroxime was compared to cefazolin for prophylaxis against post-operative wound infection in a large double-blind, multicentre study of 1354 patients who had total hip or knee arthroplasty (Maurhan,

1994). The patients were randomised to receive 1.5g of cefuroxime, followed by 750mg, eight and sixteen hours later (for a total of one day of treatment) or 1g of cefazolin every 8 hours for nine doses (three days of therapy). The rate of deep wound post-operative infection was 0.5% (1 of 187 patients) for cefuroxime treated patients undergoing hip arthroplasty, compared to 1.2% (2 of 168) of patients treated with cefazolin. Similarly, the rates for those patients treated for knee arthroplasty were 0.6% (1 of 178) on cefuroxime compared to 1.4% (3 of 207) on cefazolin. It was concluded that there was no significant difference between the treatments.

A prospective, randomised study by Nungo compared cefuroxime (1.5 g at induction of anaesthesia or 750 mg TID at 8 hour intervals) with oral cefadroxil (1g cefadroxil 2 hours before surgery and 12 hours after surgery) for prophylaxis in intra- and subtrochanteric hip fracture surgery (Nungo 1994). Two hundred and forty two patients were randomised to receive cefadroxil and 210 patients to receive cefuroxime. All the patients were followed up for 4 months. There was one deep and five superficial infections observed for patients treated with cefuroxime and only one superficial infection for a patient treated with cefadroxil. The authors concluded that the two regimens were equally effective.

A non-comparative, randomised, multicentre trial was conducted by Wymenga, in which the prophylactic efficacy of one or three doses of parenteral cefuroxime was compared in 2651 hip replacement operations (Wymenga 1991). The incidence of distant infections and the number of post-operative complications was unaffected by the prophylaxis regimen. In this study, the incidence of joint sepsis was extremely low.

In a similar study, the prophylactic efficacy of one or three doses of parenteral cefuroxime was compared in 362 knee replacements (Wymenga 1991a). Patients received 1.5 g intravenously at induction of anaesthesia (30 minutes before the first incision). In the three-dose group, further doses of 750 mg were given after 8 and 16 hours. The incidence of wound infections over the 12-month follow-up period was higher in the three dose three-dose group (3.2% vs. 1.7%), but the difference was not statistically significant ($p<0.05$, one-tailed Chi-square test).

Hughes, 1981) studied patients undergoing total joint replacements who received cefuroxime 1 g or 1.5 g intramuscularly for surgical prophylaxis. Three doses were given: at the time of surgery, and 6 and 12 hours later. In this series of 106 total joint replacements in 96 patients, only two patients suffered bone or joint infections following surgery.

The CHMP noted the two large comparative studies and the three non-comparative studies provided by the MAH. The results from the comparative studies indicate that cefuroxime is as effective as cefazolin and cefadoroxil, which are well known antibiotics for prophylaxis in orthopaedic surgeries. Based on the submitted documentation, the CHMP considered the indication "*prophylaxis in orthopaedic surgery*" to be acceptable.

9d) Prophylaxis in cardiovascular surgery

A randomised, prospective study compared cefuroxime and vancomycin for the perioperative prophylaxis in coronary artery bypass surgery (Vuorisalo 1998). A total of 884 patients were randomized to receive either 1.5 g cefuroxime plus 2 additional doses of 750 mg at 8 hour intervals (n=444) or 1 g vancomycin plus another 1 g after 12 hours (n=440). The immediate surgical-site infection rate was 3.2% for cefuroxime as compared to 3.5% in the vancomycin group.

In a prospective, randomised, short-term prophylaxis trial cefuroxime (189 patients) was compared to cefazolin (196 patients) for patients undergoing cardiac surgery (Wellens 1995). A total of 3g of antibiotic was administered over 24h in both groups. There were 2 major and 6 minor wound infections reported for patients treated with cefazolin, as compared to 8 minor infections for patients treated with cefuroxime. It was concluded that cefuroxime and cefazolin were equally effective as short-term prophylaxis.

A prospective, randomised study, by Edwards compared the use of cefuroxime and cefazolin as prophylaxis in vascular surgery (Edwards, 1992). Cefuroxime was administered as a 1.5 g IV bolus injection before the operation at induction of anaesthesia, 750 mg every three hours during the operation and then 6-hourly after the operation for 24 hours. Cefazolin was given as a 1 g IV bolus before the operation, 500 mg every 4 hours during the operation and then 6-hourly after the operation for 24 hours. Deep wound infections developed in 7 of 272 (2.6 %) cefuroxime-treated patients and 3 of 287 (1.0 %) cefazolin-treated patients. There was no significant difference in the rate of infection between the treatments (p=0.2).

Another randomised, double blind, prospective study of vascular surgery compared the use of intravenous cefuroxime and oral ciprofloxacin as prophylaxis against postoperative infection (Risberg, 1995). Five-hundred-and-eighty patients undergoing arterial reconstruction of the legs involving an inguinal incision were randomised to receive either three doses of intravenous cefuroxime (1.5g per dose over 24 hours, n=287) or 2 doses of oral ciprofloxacin (750mg per dose over 12 hours, n=293). The first doses were given at premedication. The wound infection rates in the intent to treat population, occurring within 30 days postoperatively, were 9.1% (26/287) in the cefuroxime group and 9.2% (27/293) in the ciprofloxacin group, or 9.7 % (22/202) and 9.5% (23/218) in the corresponding clinically evaluable patients. *S. aureus* was the most common pathogen isolated (62/102, 60 %), followed by *S. epidermidis* (10/102, 10 %).

In a randomised, prospective study by Salma, a total of 337 patients undergoing coronary artery bypass grafting or cardiac valve replacement were randomly assigned to receive cefazolin (1 g every 8hours), cefamandole (2 g every 6 hours), or cefuroxime (1.5 g every 12 hours) as intravenous prophylaxis (Salma, 1986). All drugs were administered within 60 minutes prior to the initial incision and were continued for 48h postoperatively. The percentage of patients with postoperative infection was 9% for the cefazolin group, 6% for the cefamandole group, and 5% for the cefuroxime group. There were more infection sites in patients treated with cefazolin than in those treated with cefuroxime (p=0.05) or cefamandole (p=0.06), and fewer wound infections occurred with cefuroxime (p< 0.01) and cefamandole (p=0.06) than with cefazolin.

Cefuroxime prophylaxis has been evaluated in patients undergoing vein graft operations for coronary artery disease (Bain, 1981). Fifty-five patients were studied in a double blind, randomised trial. Some received cefuroxime for a 48 period beginning at the induction of anaesthesia (1.5 g IV twice plus 4 g IV infusion immediately postoperatively, n=29), while the remainder received no antibiotic prophylaxis (n=26). Eight of the 29 patients in the cefuroxime group showed clinical evidence of sternotomy wound infection, and nine had evidence suggesting leg wound infection. However, bacteriological confirmation was only obtained from two wounds at each site (6.9%). The relative rates of infection in the untreated group were 26.9% for the sternal wound and 7.7% for the leg wound. These results suggested that cefuroxime prophylaxis decreased the frequency of sternal wound infections, but the differences did not reach statistical significance. Probable and confirmed chest infections were also more common in the control group (18/26 vs. 11/29 probable; 9/26 vs. 1/29 confirmed, p<0.01 Fisher's exact test).

Based on the submitted data, the CHMP considered the indication in "*the prophylaxis of cardiovascular surgery"* to be acceptable.

9e) Prophylaxis in gynaecological procedures

Brouwer, 1990a, conducted a prospective randomised study comparing the efficacy of intravenous ciprofloxacin (200 mg single dose) to cefuroxime plus metronidazole regimen in 121 patients undergoing gynaecological procedures. Cefuroxime 1.5 g plus metronidazole 500 mg were administered IV at the start of each operation, and after 6 and 12 hours. Ciprofloxacin was administered at induction of anaesthesia. Febrile morbidity was found in 3 of 54 (6%) patients in the ciprofloxacin group, but in none of the patients in the cefuroxime plus metronidazole group. No patients had a vaginal cuff infection. Four of 54 (7%) patients in the ciprofloxacin group had a UTI,

versus 2 of 58 (3%) patients in the cefuroxime plus metronidazole group. *E. coli* was the predominant urinary tract pathogen. There was no difference between the two groups in the length of hospitalisation after operation.

Brouwer, 1995, conducted a prospective, randomised open comparative study comparing the prophylactic efficacy of 1 g ceftriaxone with 1.5 g cefuroxime plus 0.5 g metronidazole (given at the induction of anaesthesia) for the prevention of febrile morbidity and UTIs in 256 patients undergoing vaginal hysterectomy. Febrile morbidity occurred, in three of 114 patients (2.6%) in the cefuroxime plus metronidazole group and in five of 112 (4.5%) patients in the ceftriaxone group. None of the patients developed vaginal cuff infection. UTIs occurred more frequently in the cefuroxime plus metronidazole group (31 patients) than in the ceftriaxone group (13 patients) ($P < 0.001$). Twenty-five patients had pre-existing bacteriuria, 14 of those on cefuroxime plus metronidazole ($n = 16$) versus three on ceftriaxone ($n = 9$) had still bacteriuria post-operatively ($P < 0.01$). Enterococci and *E. coli* were predominant uropathogens in patients treated with cefuroxime plus metronidazole. Enterococci were also the main uropathogens in patients treated with ceftriaxone.

A placebo-controlled, prospective, randomised, observer blind, study was undertaken to evaluate the efficacy of a single dose of cefuroxime in alleviating infectious complications following non-elective caesarean section (Kristiansen, 1990). One hundred and two women were allocated to receive 750 mg of cefuroxime after cord clamping and 99 were allocated to a control group not receiving any antibiotic prophylaxis. The incidence of febrile morbidity was 2.0% in the cefuroxime group and 19.2% in the control group ($p<0.00l$). The incidence of endometritis in the two groups was 1.0% and 6.1%, respectively. The incidence of fever of unknown origin was 1.0% and 9.1 %, respectively.

Another placebo controlled double blind study involved 105 patients (Brouwer 1984). Three doses of antibiotic (cefuroxime 1.5 g plus metronidazole 0.5 g) were administered IV at the start of anaesthesia, then six and 12 hours later. Patients were classified according to whether they had undergone abdominal hysterectomy, vaginal hysterectomy, or vaginal hysterectomy with repair. For those having abdominal surgery, there was no statistically significant difference in the number of infections between treated (11/26) and control (5/26) groups. A statistically significant difference in favour of cefuroxime was, however, evident in those having a vaginal hysterectomy, both in terms of the number of infections (1/13 vs. 6/11, $p<0.05$) and the length of hospital stay (9.2 days vs. 11.1 days, $p<0.01$). Similar results were obtained in those having a vaginal hysterectomy with repair, where the number of infections (1/14 vs. 7/15, $p<0.025$) significantly favoured cefuroxime prophylaxis but there was no difference in hospital stay (12.6 days vs. 14 days).

Prophylactic use of cefuroxime in major gynaecological surgery was evaluated in a a randomised double-blind study involving 472 patients undergoing abdominal ($n=240$) or vaginal ($n=232$) procedures (Jandial, 1981). One group received a single 1.5 g dose of cefuroxime IV immediately postoperatively and the others received no antibiotic. In those having vaginal operations, postoperative pyrexia occurred in 11.5% treated with cefuroxime and 15% of the control group (no statistically significant difference). The corresponding figures for abdominal operations were 37% and 22% respectively in favour of cefuroxime prophylaxis ($p<0.02$). The urinary tract infection rate was also significantly lower after cefuroxime prophylaxis in this group (7 vs. 19, $p<0.05$). Sixty-four patients in the cefuroxime group required post-surgical antibiotics compared to 92 in the control group ($p<0.05$), mostly for suspected UTIs.

The efficacy of single-dose prophylaxis with intravenous cefuroxime 1.5 g plus 500 mg metronidazole in vaginal or abdominal hysterectomies was investigated in a randomised, double-blind, placebo-controlled study, involving 396 evaluable patients (Boodt, 1990). A significant reduction of the number in urinary tract infections was observed in the groups who received cefuroxime and metronidazole compared to placebo undergoing abdominal hysterectomy or vaginal hysterectomy with vaginal repair. Further, the incidence of wound infections and the duration of hospitalisation were significantly reduced in patients who received cefuroxime plus metronidazole in comparison to placebo in the same patient

groups. Body temperature normalised faster in all three groups receiving peri-operative antibiotic prophylaxis.

The prophylactic efficacy of three intravenous doses of cefuroxime 1.5 g plus metronidazole 500 mg in vaginal hysterectomy was compared with placebo in a prospective double blind randomised study in 53 patients (Brouwer, 1990). The antibiotics were administered IV at the start of each operation, and after 6 and 12 hours. Febrile morbidity occurred in 13 of 26 (50%) patients in the placebo group and none of the patients in the cefuroxime plus metronidazole group. UTIs occurred at a similar rate in both groups, 7 of 26 (27%) patients in the placebo group and 9 of 27 (33%) in the cefuroxime plus metronidazole group. *E. coli* was the predominant pathogen causing the UTIs. Duration of hospitalisation was significantly longer for placebo controlled patients compared with cefuroxime plus metronidazole patients, 12. 7 vs. 10.9 days (p = 0.02), respectively.

The CHMP noted the data provided by the MAH regarding prophylaxis against infection in gynaecological surgery and agreed that the data supported an indication for "*prophylactic use against infection in gynaecological surgery (including caesarean section)".* However, the proposed indication "*prophylaxis against infection in pelvic surgery"* was not accepted.

In conclusion, having reviewed all the data submitted by the MAH to support the prophylaxis indication for cefuroxime, the CHMP adopted the following harmonised indication:

"*Prophylaxis against infection in gastrointestinal (including oesophageal), orthopaedic, cardiovascular, and gynaecological surgery (including caesarean section)*"

10) Indication in neonates

Regarding the paediatric population and the associated dosage recommendations, the MAH stated that it does not have recent clinical data with regards to the use of cefuroxime in neonates; however, the proposed dosing regimen for neonates has been widely used in medical practice since the initial cefuroxime sodium clinical development programme. The MAH provided a literature review of several studies which have evaluated the pharmacokinetics of cefuroxime sodium in neonates and support the dosing regimen recommended in this population for the current harmonised SmPC.

In one study by Renland, 1977, the pharmacokinetics of cefuroxime was evaluated in 104 children aged less than 3 weeks with a variety of infections, receiving cefuroxime IM at a dose of 10 mg/kg TID. The study results demonstrated that the serum half-life of the cefuroxime varied in newborns (aged 4 to 14 days) and ranged from 3.5 to 5.5 hours depending on the age of the child. This was 3-5 times longer than in adults and infants (approximately 1-hour). Furthermore with a dosage of 10 mg/kg three times daily no accumulation was observed in neonates weighing >2000 g. The authors recommend that for neonates with a birth weight <2000 g, twice daily dosage of cefuroxime is appropriate. The dosing regimen of cefuroxime was clinically effective and well tolerated.

An additional study by Dash, 1980, in 20 neonates, observed a similar age dependency for cefuroxime elimination when dosed IM at 15 mg/kg BID or 25 mg/kg BID, with serum half-life decreasing from 5.1 hours on day one of life to 1.9 hours on day 6 in neonates of >2.5 kg birth weight. Cefuroxime was also efficacious and was not associated with any adverse events. The recommendation from this study is that twice daily dosage is suitable for neonates during the first week of life, but that for more severe infections larger doses and more frequent administration may be required. The study by Wilkinson, 1977, included 26 neonates treated with 100 mg/kg/day of cefuroxime IV for 3 to 18 days for septicaemia. Serum concentration curves after the initial dose of cefuroxime were constructed in 4 neonates 1-4 days old and revealed that the serum half-lives was 3 to 4 hours longer in comparison to a 23 day old neonate, with a corresponding serum half-life of 1-hour. The majority of patients in this study were clinical successes and the high dose of cefuroxime was well tolerated, with no evidence of any accumulation. Based on the observation of the prolonged serum half-life in neonates, the authors recommended that dosing of cefuroxime IV should be 12 hourly in neonates up to 4 days of age.

The study by Sorin, 1977, included 21 infants (age: 3 weeks to 24 months) suffering from broncho-pulmonary or urinary tract infection were treated with 30-60 mg/kg/day of IM or IV cefuroxime given as TID or QID. Cefuroxime did not accumulate in the serum after repeated injections. After 15 mg/kg IM and 12±2 mg/kg IV the serum half-lives were 64 and 60 minutes, respectively, and are comparable

to those observed in older children and adults. Observed serum cefuroxime concentrations provided good coverage for most pathogens with MIC of ≤4 ug/mL and high urinary concentrations of cefuroxime allowed successful treatment of urinary tract infections. Cefuroxime was shown to be effective and well tolerated by the infants. The author recommended a dosage of 15 mg/kg given TID by the IM or IV route.

The study by Rosachino, 1977, evaluated the efficacy and tolerance of cefuroxime IM at a daily dose of 50 mg/kg given as BID in 20 children (age: 6 months to 2 years). Clinical efficacy and tolerability was reported as 'excellent to good'. The absorption of cefuroxime from the injection site was rapid, with high peak levels and good overall serum concentrations of cefuroxime.

The study by del Rio, 1982, evaluated the pharmacokinetics of cefuroxime following single IV dose of 50 mg/kg (n=18) or 75 mg/kg (n=20) and 50 mg/kg QID (n=5) in infants and children (age: 4 weeks to 6.5 years) with bacterial meningitis. The pharmacokinetics of cefuroxime after doses of 50 and 75 mg/kg were similar with an elimination half-life of approximately 1.5 hours. The pharmacokinetics after multiple dosing was similar to those after single doses with no accumulation of cefuroxime after repeat dosing.

A further study by De Louvois, 1982, evaluated the efficacy and pharmacokinetics of cefuroxime in 28 neonates with suspected or proven infection. The treatment regimen consisted of intramuscular or intravenous cefuroxime (50 mg/kg twice a day) for 5 days. There was significant clinical improvement in 27 of the neonates after 5 days with no adverse clinical side effects. Cefuroxime was safe and well-tolerated in neonates. The mean half-life of cefuroxime in neonates aged less than 4 days was 5.8 hours and ranged from 1.6-3.8 hours in four neonates older than 8 days. In contrast to the studies by Renland, 1977, the authors of this study concluded that the elimination half-life was not associated with birth weight.

The study by Bahaeldin, 1983, evaluated the efficacy of IV bolus cefuroxime given TID (90-300 mg/kg during the first 2-4 days and 45-149 mg/kg during the subsequent 6-8 days) in the treatment of bacterial meningitis in forty-eight infants and children (age: 15 days to 14 years). Cefuroxime was clinically and bacteriologically effective and no toxicity was encountered.

The study by Sirinavin, 1984, evaluated the treatment of bacterial meningitis in infants and children (age: 25 days to 12 years) with 50 mg/kg IV dose of cefuroxime (N=25). Six patients were treated with 200 mg/kg/day and one with 250 mg/kg/day in 4 divided doses (QID) for 14 to 21 days. The author recommends a dosage of 200 mg/kg/day IV in 4 divided doses for therapy of HIB meningitis.

A GSK study evaluated cefuroxime for the treatment of serious infections in neonates, infants and children (aged; 5 days to 15 years). A total of 30 patients were enrolled. Treatment was given IM or IV and the dose in neonates was 100 to 150 mg/kg/day in four divided doses for 12 to 23 days. In children and neonates, cefuroxime was shown to be clinically and bacteriologically effective. In the study by Knoderer, 2011, IV cefuroxime dose of 50 mg/kg TID in paediatric patients (n=210; age: 3-days to 18 years) was shown to be effective and safe as prophylaxis treatment after cardiovascular surgery.

The study by Foord, 1976 evaluated the pharmacokinetics of cefuroxime following IM and IV injections and showed comparable PK properties (e.g., area under the curve, half-life, renal clearance, and duration serum cefuroxime concentrations were above certain target values).

The MAH concluded that neonates (aged <3 weeks) have serum half-life 3 to 5 times longer than those of adults and children (approximately 1-hour), however the drug is adequately excreted with no accumulation following repeat dosing. Neonates (aged >3 weeks) have a similar serum half-life to that of adults and infants. Neonates have been exposed to a total daily dose of cefuroxime ranging from 30 mg/kg/day to 100 mg/kg/day. Doses superior to the recommended doses of cefuroxime IV (up to 300 mg/kg/day given as TID, 200 mg/kg/day given as QID and 150 mg/kg/day given as TID) have been found to be safe and effective in infants and children aged 3 days and older.

The CHMP noted the data concerning the safety and efficacy of cefuroxime in neonates, including the pharmacokinetic parameters such as dosing range and dosing interval. The CHMP agreed that cefuroxime has been licenced for use in neonates in many EU countries for many years without any serious safety concerns. The CHMP defined neonates as infants younger than 3 weeks, including newborns. Based on the available information, 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 either 2 or 3 divided doses, due to the longer serum half-life observed in neonates.

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 MAH proposal. However, the CHMP revised section 4.2 to reflect the changes resulting from the agreed indications as well as the posology for the individual indications. The CHMP also brought the presentation of the dose regimen and the duration of treatment courses in line with the NfG on Evaluation of Medicinal Products Indicated for Treatment of Bacterial agents (CPMP/EWP/558/95, rev.1). The MAH stated that according to Bulitta, 2009, an effective %*f*T>MIC for cephalosporins such as cefuroxime is considered to be 40% or more of the dosing interval. High probability of target attainment (PTA) expectation values (>90% for a %*f*T>MIC of 50%) against *Escherichia coli* and *Klebsiella pneumoniae* were achieved by IV dosing of 750 mg and 1500 mg every 8 hours for an MIC of 4 µg/mL and 8 µg/mL, respectively (Ambrose, 2004). The susceptibility breakpoint for IV cefuroxime has been revised by EUCAST and CLSI to 8 µg/mL; with the recommendation that the higher cefuroxime IV dosage (1500 mg given every 8 hours) be used for infections with Enterobacteriaceae (Kahlmeter, 2008). At the susceptibility breakpoint of 8 µg/mL, the PTA is approximately 59% and >90% for a %*f*T>MIC of 50% for a cefuroxime IV dosing regimen of 750 every 8 hour and 1500 mg every 8 hours, respectively. 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 MICs up to, and including, 8 µg/mL.

The CHMP considered that, taking into account the relevant indications for parenteral cefuroxime, the less susceptible bacteria include mainly Enterobacteriaceae (i.e. *E. coli, P. mirabilis* and *Klebsiella* spp). EUCAST has recently set the breakpoints for Enterobactariaceae at 8ug/mL, and the dosing regimen of 1500 mg every 8 hours is recommended for the treatment of infections caused by the above bacteria. The work of Ambrose (2004) supports the posology proposed by EUCAST. In this study, Monte Carlo simulations showed that high PTAs (>90% for the PK/PD target of %T>MIC: 50%) were achieved regarding the treatment of Enterobacteriaceae with the breakpoint of 8 ug/mL, using iv cefuroxime 1500 mg every 8 hours. The CHMP therefore accepted the MAH proposal. In conclusion, the CHMP adopted the following harmonised posology:

Posology

Table 1. Adults and children ≥ 40 kg

Indication	***Dosage***
Community acquired pneumonia and acute exacerbations of chronic bronchitis	*750 mg every 8 hours (intravenously or intramuscularly)*
Soft-tissue infections: cellulitis, erysipelas and wound infections.	
Intra-abdominal infections	
Complicated urinary tract infections, including	*1.5 g every 8 hours*

pyelonephritis	*(intravenously or intramuscularly)*
Severe infections	*750 mg every 6 hours (intravenously)* *1.5 g every 8 hours (intravenously)*
Surgical prophylaxis for gastrointestinal, gynaecological surgery (including caesarean section) and orthopaedic operations	*1.5 g with the induction of anaesthesia. This may be supplemented with two 750 mg doses (intramuscularly) after 8 hours and 16 hours.*
Surgical prophylaxis for cardiovascular and oesophageal operations	*1.5 g with induction of anaesthesia followed by 750 mg (intramuscularly) every 8 hours for a further 24 hours.*

Table 2. Children < 40kg

	Infants and toddlers > 2 months and children < 40 kg	***Infants (birth to 2 months)***
Community acquired pneumonia	*30 to 100 mg/kg/day (intravenously) given as 3 or 4 divided doses; a dose of 60 mg/kg/day is appropriate for most infections*	*30 to 100 mg/kg/day (intravenously) given as 2 or 3 divided doses (see section 5.2)*
Complicated urinary tract infections, including pyelonephritis		
Soft-tissue infections: cellulitis, erysipelas and wound infections		
Intra-abdominal infections		

Sequential therapy

The CHMP raised concerns over the MAH proposal for the use of Zinacef in parenteral-to-oral sequential therapy, including the proposed posology for both adults and paediatric patients. According to the MAH proposal, the dose and subsequent exposure to active drug is substantially lower with Zinnat than with the previous Zinacef treatment, with reductions of the available daily dose of up to 80%.

The MAH stated that the important consideration with regard to the sequential therapy is whether the oral formulation has the appropriate PK/PD to provide the appropriate coverage to eradicate the underlying pathogen causing the infection. The MAH presented a summary of the PK/PD properties of cefuroxime axetil. The MAH was of the view that an effective %fT>MIC for cephalosporins, such as cefuroxime axetil, is considered to be 40% or more of the dosing interval (Bulitta, 2009). High probability of target attainment (PTA) expectation values (>90% for a fT>MIC of 40%) was achieved by oral dosing of 250 mg or 500 mg BID for *S. pyogenes* and penicillin susceptible *S. pneumonia* (Bulitta, 2009). The 500 mg BID regimen is expected to provide higher PTA values against penicillin-intermediate *S. pneumonia*, *H. influenzae*, and *M. catarrhalis*. The commonly used oral dosing regimens (e.g., 250 mg to 500 mg given every 12 hours) are expected to provide efficacy for organisms with MICs up to and including 1 µg/mL. Therefore cefuroxime axetil would be an appropriate step down therapy where the pathogen is susceptible to cefuroxime. In addition, the convenient twice daily administration schedule of cefuroxime axetil provides the potential for good compliance. The MAH stated that several clinical trials evaluating the efficacy of cefuroxime IV therapy followed by cefuroxime axetil 250 mg and 500 mg BID compared to various antibiotic comparators routinely used for the treatment of respiratory tract infections have shown that step down therapy with cefuroxime axetil is efficacious. The MAH stated that the efficacy and safety of sequential therapy using the proposed doses in respiratory tract infections was established in controlled clinical trials at the time of authorisation and in subsequent clinical practice.

The CHMP considered that the PK/PD considerations seem reasonable with regard to the pathogens *S. pyogenes* and penicillin susceptible S*. pneumonia*. However, for pathogens with higher MIC values, the adequacy of the proposed dosage regimen was not acceptable (Bulitta 2009). Also, the choice of T>MIC of 40% as PK/PD target is not acceptable, especially concerning Gram negative, less-susceptible pathogens. The CHMP noted that the MAH did not provide additional PK/PD data to support proposed step down dosing schedule for sequential therapy and did not address the concern that a T>MIC of 50% and not of 40% should be chosen as PK/PD target. The CHMP therefore removed all references to sequential therapy, including dosage tables, from the SmPC, due to the significant reduction in exposure to active drug when switching to oral formulation.

Renal impairment

The MAH stated that cefuroxime is primarily excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function (i.e., Clcr<20 mL/minute) it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion. The pharmacokinetics of a single 750 mg intravenous dose of cefuroxime were investigated in 21 subjects with normal and impaired renal function (Bundtzen, 1981). In those with creatinine clearances of 60-120 mL/minute/1.73m^2 and 20-59 mL/minute/1.73m^2 the mean serum half-life was 1.7 and 2.4 hours, respectively. While in subjects with creatinine clearance below 20 mL/minute/1.73m^2, the half-life was increased to17.6 hours. Mean cefuroxime levels in excess of 8 µg/mL persisted for 30 hours in these subjects compared to 3 hours and 6 hours in those with normal and partially impaired renal function, respectively. Twenty-four hour urinary excretion was also reduced to 40% of the normal range in the subjects with most severe renal impairment, compared to a 100% excretion in the remainder. Cefuroxime distribution characteristics were independent of renal function. From this study it was concluded that the dosage of cefuroxime should be reduced in patients with a creatinine clearance of less than 20 mL/minute/1.73m^2.

Kosmidis, 1977, determined the half-life of cefuroxime to be 1.05 hours in patients with a creatinine clearance (C1cr) >80 mL/minute, 1.03 hours with C1cr of 50-79 mL/minute, 2.55 hours with C1cr of 25-49 mL/minute, 5.05 hours with C1cr of 10-24 mL/minute, and 14.8 hours with C1cr <10 mL/minute. Corresponding rates of urinary recovery decreased from 86.3% in those with Clcr >80 mL/minute to 5.4 % with C1cr <10 mL/minute. Urine levels of cefuroxime were >100 µg/mL for all groups except the most renally impaired, where the average level was 30 µg/mL. In this study, anuric patients not on dialysis had a serum half-life of 21.9 hours, which was reduced to 3.75 hours by dialysis. Peritoneal dialysis has been reported to decrease the half-life to between 13.6 and 5.4 hours (Bundtzen, 1981). Cefuroxime levels of 15-20 µg/mL have been found in peritoneal dialysate.

The pharmacokinetics of cefuroxime have been investigated in septic patients with acute renal failure (Clcr 19.3-29.5 mL/minute) treated by continuous arteriovenous haemodialysis (Davies, 1991). Patients were given intravenous cefuroxime 750 mg twice daily (n=11) or 500 mg twice daily (n=1) and at steady state showed a prolonged terminal elimination half-life of 12.6 ± 2.2 hours (mean ± SEM). In these patients, the volume of distribution was 22.8 ± 3.5L, and total body clearance was 22.3 ± 3.1 mL/min. Cefuroxime 500-750 mg twice daily would therefore be expected to produce therapeutic plasma concentrations, which are consistent with the recommendations for dosage of renally impaired patients.

The MAH recommended that is not necessary to reduce the standard dose (750 mg to 1500 mg three times daily) until the creatinine clearance falls to 20 mL/min or below. In adults with marked renal impairment (creatinine clearance 10 to 20 mL/min), a dose of 750 mg twice daily is recommended and in patients with severe renal impairment (creatinine clearance less than 10 mL/min) 750 mg once daily is adequate. For patients on haemodialysis a further 750 mg dose should be given IV or IM at the end of each dialysis. In addition to parenteral use, cefuroxime can be incorporated into the peritoneal dialysis fluid (usually 250 mg for every two litres of dialysis fluid). For patients in renal failure on continuous arteriovenous haemodialysis, or high-flux haemofiltration in intensive therapy units, a suitable dosage is 750 mg twice daily. For low-flux haemofiltration the physician should follow the dosage recommended under impaired renal function.

The CHMP reviewed the data submitted by the MAH and concluded that the proposed dosing guidelines in patients with renal impairment were acceptable. The CHMP adopted the following recommendations:

Recommended doses for Zinacef in renal impairment

Creatinine clearance	**$T_{1/2}$ (hrs)**	**Dose mg**
> 20 mL/min/1.73 m^2	1.7–2.6	It is not necessary to reduce the standard dose (750 mg to 1.5 g three times daily).
10-20 mL/min/1.73 m^2	4.3–6.5	750 mg twice daily
< 10 mL/min/1.73 m^2	14.8–22.3	750 mg once daily

Patients on haemodialysis	3.75	A further 750 mg dose should be given intravenously or intramuscularly at the end of each dialysis; in addition to parenteral use, cefuroxime sodium can be incorporated into the peritoneal dialysis fluid (usually 250 mg for every 2 litres of dialysis fluid).
Patients in renal failure on continuous arteriovenous haemodialysis (CAVH) or high-flux haemofiltration (HF) in intensive therapy units	7.9–12.6 (CAVH) 1.6 (HF)	750 mg twice daily; for low-flux haemofiltration follow the dosage recommended under impaired renal function.

Hepatic Impairment

Regarding patients with hepatic impairment, the CHMP noted and agreed with the MAH proposal: "*Cefuroxime is primarily eliminated by the kidney. In patients with hepatic dysfunction, this is not expected to effect the pharmacokinetics of cefuroxime*."

Method of administration

Regarding the method of administration, the CHMP accepted the wording proposed by the MAH stating 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.

Section 4.3 - Contraindications

The MAH reviewed the nationally-approved SmPCs and submitted a proposal for a harmonised wording together with justifications for not including contra-indications in patients with hepatic dysfunction and for the combination with aminoglycosides. The CHMP noted and agreed with the MAH proposal. In conclusion, the CHMP adopted a harmonised wording for Section 4.3.

Section 4.4 - Special warnings and precautions for use

The MAH reviewed the nationally-approved SmPCs and submitted a proposal for a harmonised wording. The MAH discussed the rationale for the proposed statements on hypersensitivity reactions, concurrent treatment with potent diuretics or aminoglycosides, overgrowth of non-susceptible microorganisms, intra-abdominal infections, interference with diagnostic tests and information about excipients, for which it also inserted appropriate headings. The CHMP revised the proposal, in particular to retain the statement on pseudomembraneous colitis and to add a statement on the interference of cefuroxime on the Coomb's test. The text regarding the ferricyanide test was reworded. In conclusion, the CHMP adopted a harmonised wording for Section 4.4.

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

The MAH reviewed the nationally-approved SmPCs and discussed the rationales for including statements on the potential effect of gut flora, on concomitant use of probenicid and on caution in patients taking strong-acting diuretics. The CHMP added a statement regarding an interaction with oral anti-coagulants. In conclusion, the CHMP adopted a harmonised wording for Section 4.5.

Section 4.6 - Pregnancy and Lactation

The MAH reviewed the nationally-approved SmPCs and submitted a proposal for a harmonised wording. The CHMP revised the proposal, in particular adding a warning on the potential for affection of the child's gastrointestinal and mouth flora, as well as the possibility of sensitisation of the infant. The

section was also brought in line with the current SmPC guideline. In conclusion, the CHMP adopted a harmonised wording for Section 4.6.

Section 4.7 - Effects on ability to drive and use machines

The MAH reviewed the nationally-approved SmPCs and submitted a proposal for a harmonised wording. The CHMP noted and agreed with the MAH proposal. In conclusion, the CHMP adopted a harmonised wording for Section 4.7.

Section 4.8 - Undesirable effects

The MAH reviewed the nationally-approved SmPCs and submitted a proposal for a harmonised wording, including the events present in the Core Safety Information, as identified from the cefuroxime sodium clinical trial programme and from data made available since launch. These data sources include spontaneous reports received by the MAH and the published medical literature. The CHMP revised the proposal, in particular, the frequency categorisation table, to bring the frequencies in line with the SmPC guideline, following clarifications from the MAH on the frequency assignment calculations. Some ADRs were reclassified accordingly and some ADRs were moved to more appropriate SOCs. "Injection site reactions" was added among the most common ADRs and *C. difficile* overgrowth was also added. Having reviewed the available data, the CHMP agreed that the safety profile of cefuroxime appears to be similar in adults and in children and included a paediatric sub-section, in line with the current SmPC guideline, stating that the safety profile for cefuroxime sodium in children is consistent with the profile in adults. In conclusion, the CHMP adopted a harmonised wording for Section 4.8.

Section 4.9 - Overdose

The MAH reviewed the nationally-approved SmPCs and submitted a proposal for a harmonised wording. The CHMP expanded the information provided on the potential consequences of overdose, including encephalopathy, convulsions and coma. In conclusion, the CHMP adopted a harmonised wording for Section 4.9.

Section 5.1 - Pharmacodynamic properties

The MAH reviewed the nationally-approved SmPCs and submitted a proposal for a harmonised wording. The CHMP revised the proposal, in particular, the breakpoints table was revised according the available EUCAST data, together with the table of susceptible species. In conclusion, the CHMP adopted a harmonised wording for Section 5.1.

Section 5.2 - Pharmacokinetic properties

The MAH reviewed the nationally-approved SmPCs and submitted a proposal for a harmonised wording. The CHMP noted the MAH proposal but moved the information on pregnancy and lactation to Section 4.6. The CHMP also obtained further data to justify the cut-off values for creatinine clearance in patients with improved renal impairment. In conclusion, the CHMP adopted a harmonised wording for Section 5.2.

Section 5.3 - Preclinical safety data

The MAH reviewed the nationally-approved SmPCs and submitted a proposal for a harmonised wording. The CHMP noted the MAH proposal but added a statement regarding the interference of gamma glutamyl transpeptidase activity on clinical laboratory tests. The text was also brought in line with the current QRD template. In conclusion, the CHMP adopted a harmonised wording for Section 5.3.

Section 6.6 - Special precautions for disposal and other handling

The CHMP harmonised the solutions for infusion, for which data was provided to support compatibility. Specifications for in-use stability and data supporting the storage temperature were also submitted

and the entire section was revised to clarify and simplify the instructions on reconstitution and infusion volumes and concentrations. In conclusion, the CHMP adopted a harmonised wording for Section 6.6.

Labelling and Package leaflet

The labelling and the package leaflet were revised and brought in line with the adopted harmonised SmPC. The CHMP assessed the readability testing report and considered the presentation and content of the package leaflet to be satisfactory.

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 and the total body of available data, the CHMP adopted a harmonised summary of product characteristics, labelling and package leaflet for Zinacef and associated names.

2.5. *Conclusions*

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 considered to be favourable. The CHMP adopted a positive opinion recommending the harmonisation of the summary of product characteristics, labelling and package leaflet as set out in Annex III of the CHMP opinion for Zinacef and associated names (see Annex I).