EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 August 2012
EMA/CHMP/633839/2012

Assessment report for Zinnat and associated names

Pursuant to Article 30 of Directive 2001/83/EC

INN: cefuroxime (cefuroxime axetil)

Procedure no: EMEA/H/A-30/1157

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

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1. Background information on the procedure

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

On 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:

Zinnat 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 was transferred to Piotr Fiedor (PL) in June 2010 and the co-rapporteurship to Karsten Bruins Slot (NO) in May 2010.

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

2. Scientific discussion during the referral procedure

2.1. Introduction

Zinnat contains cefuroxime axetil which is an oral pro-drug of cefuroxime, a second generation cephalosporin antibacterial agent. Cefuroxime axetil undergoes rapid hydrolysis and de-esterification by non-specific esterases in the intestinal mucosa when administered, releasing the active parent compound cefuroxime. Cefuroxime 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), thereby causing cell death. Zinnat was first approved in Europe in the late 1980's and is available as oral formulation (film-coated tablets and granules for oral suspension). The product is approved in all 27 EU member states, as well as in Iceland and is used to treat certain infections caused by bacteria, such as upper and lower respiratory tract infections, urinary tract and skin and soft tissue infections, Gonorrhoea and Lyme disease. Zinnat 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/EMA 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 wording 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 added the statement "Consideration should be given to official guidance on the appropriate use of antibacterial agents and deleted the introductory statement describing Zinnat. Only relevant information for the discussion is presented per indication hereinafter.

1) Upper respiratory tract infections (URTI)

The MAH proposed the following indication "*Upper respiratory tract infections (e.g., ear, nose and throat infections, such as otitis media, sinusitis, tonsillitis and pharyngitis)*" and submitted several studies evaluating the efficacy of cefuroxime axetil in the treatment of acute otitis media, acute bacterial sinusitis and tonsillitis. Review articles by Scott, 2001 and Perry, 1996 have assessed the clinical studies conducted in URTI. Some of the earlier studies conducted with cefuroxime axetil enrolled all patients in one study with URTI, irrespective of the specific underlying disease

The CHMP stated that general indications such as URTI are no longer valid and should be replaced by specific conditions according to the clinical studies. The MAH agreed and therefore proposed the following upper respiratory tract indications: "*acute streptococcal tonsillitis and pharyngitis*", "*acute bacterial sinusitis*" and "*acute otitis media*".

1a) Acute streptococcal tonsillitis and pharyngitis

The MAH provided data to support the indication "*acute streptococcal tonsillitis and pharyngitis*". In a prospective, multicentre study by Aujard, 1995, 308 children aged 2 to 15 years with symptoms of tonsillopharyngitis were randomised to receive either cefuroxime axetil suspension (10 mg/kg twice daily, n=152) for four days, or penicillin V suspension (15 mg/kg three times daily, n=156) for 10 days. 200 children (97 in the cefuroxime group, 103 in the penicillin V group) were evaluable for efficacy and were culture-positive for group A beta-haemolytic streptococcus (GABHS). The overall clinical response rate at the end of treatment was 94.8% (92/97) and 96.1% (99/103) for cefuroxime axetil and penicillin V respectively, but sore throat and dysphagia resolved significantly ($p<0.05$) more quickly in the cefuroxime group. Between two and four days after treatment, DNA typing indicated that the primary pathogen had been eradicated in 87.6% of the cefuroxime group compared to 87.4% of the penicillin V. At follow-up on day 28-32, bacteriological relapse rates were low at 2.8% (2/80) and 2.3% (2/101) respectively, with eradication of the initial pathogen being confirmed in 94.4% (68/72) and 91.9% (79/86) patients treated with cefuroxime axetil and penicillin V respectively.

The clinical and bacteriological efficacy of cefuroxime axetil and penicillin V were also compared in 533 children aged two to 13 years with one or more clinical signs and symptoms of acute pharyngitis and a positive throat culture for GABHS by Gooch, 1993. In this investigator-blind, multi-centre trial, patients were randomised to 10 days of treatment with either cefuroxime axetil suspension (10 mg/kg twice daily with meals, n=259) or penicillin V suspension (16.7 mg/kg three times daily). Two hundred and

forty-four patients in the cefuroxime axetil group and 126 in the penicillin V group were clinically and bacteriologically evaluable. Amongst these evaluable patients, the pre-treatment serotype of GABHS was eradicated from 94.2% (244/259) of those treated with cefuroxime axetil and 84.1% (106/126) of those treated with penicillin V (p=0.001 in favour of cefuroxime axetil). The clinical success rate (complete resolution of pre-treatment signs and symptoms during treatment and throughout the follow-up period) was significantly greater for cefuroxime axetil than penicillin V (91.9% vs. 81.0%; p=0.001). The clinical recurrence (initial improvement followed by return of signs/symptoms during the follow-up period) occurred in 8.1% of the cefuroxime axetil group and 18.3% of the penicillin V group. Intention-to-treat analysis provided further support to the superiority of cefuroxime axetil. Out of the 533 patients enrolled in the study, the pre-treatment serotype was eradicated from 73.2% treated with cefuroxime axetil and 59.5% treated with penicillin V (p=0.0001). Similarly, clinical success was achieved in 71.3% and 55.3% of patients in these respective groups (p=0.0001).

In a prospective, open, randomised, multi-centre study by Scholz, 2004, children aged 1-17 years with acute tonsillopharyngitis and a positive culture for GABHS were treated with cefuroxime axetil (CXM) 20 mg/kg/day (max. 500 mg) BID for 5 days or with penicillin V 50,000 IU/kg (30 mg/kg) TID for 10 days. Patients were evaluated for clinical efficacy 2-4 and 7-9 days after the end of therapy, and throat swabs were taken at the same visits. Further follow-up visits were carried out 7-8 weeks, 6 months and 12 months after study inclusion. In the intent-to-treat analysis, 1,952 patients (CXM for 5 days, 496 patients/ penicillin V for 10 days, 1,456 patients) were included. Two to 4 days after completion of the treatment course, the bacteriological eradication in group A (1-5 years) and group B (6-17 years) was 90.52 and 89.53% (CXM) vs. 84.13 and 84.20% (penicillin V), respectively; p = 0.0172; 0.0382; clinical success was 98.30% (CXM) versus 93.25% (penicillin V), p = 0.0017. Recurrent infections were significantly higher in younger children (group A) under both treatment regimens. Post streptococcal sequelae (glomerulonephritis) were observed in only 1 case, in the penicillin V group. The study demonstrated that CXM BID for 5 days was at least as effective as penicillin V TID for 10 days. In countries with a low incidence of rheumatic fever, CXM for 5 days can be recommended for the therapy of tonsillopharyngitis due to GABHS - also in young children.

In response to concerns that shorter courses of treatment might lead to an increased incidence of post-streptococcal sequelae such as rheumatic fever or glomerulonephritis, the German Society for Paediatric Infectious Diseases (DGPI) undertook a large study of the efficacy of various antibiotics (penicillin/β-lactamase inhibitor, cephalosporins, macrolides) with potential for use in five day therapy regimens, and compared them with a standard 10-day course of penicillin V (50,000 IU/kg daily in three doses) (Adam, 1998; Adam, 2000). Clinical and bacteriological efficacy was determined two to four days after completion of therapy, with follow-up at seven to eight weeks, six months and one year to establish the effect on sequelae. The 4334 patients included in the intent-to-treat analysis had acute, culture-proven GABHS tonsillopharyngitis, with no history of rheumatic disease or glomerulonephritis in the household. In one arm of this study, cefuroxime axetil (250 mg twice daily) was evaluated, and was shown to be more effective than oral penicillin in eradicating GABHS at post-treatment assessment (90% (441/492) vs. 84% (1196/1422), p=0.001). Clinically, both agents were equivalent, and carriage rates were similar (11.1% vs. 13.8%, NS) at seven to eight weeks post-treatment. No post-streptococcal sequelae occurred in patients treated with cefuroxime axetil, whereas one case of glomerulonephritis was recorded at the first follow-up visit in a patient treated with penicillin V who had appeared to respond clinically and bacteriologically to treatment. This study therefore confirmed that short course cefuroxime axetil was comparable in efficacy to the standard 10-day penicillin V regimen, including prevention of serious complications of streptococcal infection. In the study as a whole, information on post-streptococcal sequelae was available from 3805 patients after seven to eight weeks, 3296 after six months and 2515 after one year. Only two events occurred, the one previously described in the penicillin V group, and one case of rheumatic fever after a five day course of treatment with an agent other than cefuroxime axetil. The overall incidence of post-streptococcal sequelae was thus very low, at less than 1 per 1000 patients, and no difference could be shown in risk and frequency between five day and 10-day therapy.

A total of 634 children aged two months to 12 years with symptoms of pharyngitis or tonsillitis, were entered into an open, parallel group MAH-sponsored study conducted in general practice centres in the UK, France and Germany in 1989. Patients were stratified by age and randomised to twice daily treatment with cefuroxime axetil suspension (6.25 mL/2.5 mL if <2 y, 125 mg/5 mL if >2 y) or amoxicillin syrup (125 mg/5 mL) three times daily. Clinical cure or improvement occurred in 95% (258/271) of evaluable infections treated with cefuroxime axetil, and in 97% (267/275) treated with amoxicillin. One hundred and ninety-one patients (30%) were bacteriologically evaluable, with GABHS being the predominant pathogen, followed by other *Streptococcus* spp., *staphylococci* and *H. influenzae*. Clearance of the primary pathogen was slightly higher in the cefuroxime axetil group (95% vs. 87%), but neither this difference, nor the difference in clinical outcome between treatments, was statistically significant (p>0.05). Cefuroxime axetil suspension and amoxicillin syrup were therefore equally effective in this study.

Having reviewed the data submitted by the MAH, the CHMP considered that the data supported the proposed indication and adopted the following harmonised indication:

"Acute streptococcal tonsillitis and pharyngitis"

1b) Acute bacterial sinusitis (ABS)

The MAH provided data to support the indication "*acute bacterial sinusitis*" and acknowledged that ABS (i.e. broadly defined without attribution of infecting agent) is in the majority of cases viral in aetiology; however, a bacterial infection occurs in about 0.5% to 2% of all cases, most often preceded by a viral upper respiratory tract infection (URTI). Although the proportion of patients that actually progress to acute bacterial sinusitis is small, bacterial infection nonetheless leads to millions of cases of ABS each year in Europe (Desrosiers, 2006).

A particularly challenging task is to distinguish viral from bacterial sinusitis. In most patients, rhinoviral illness improves in 7 to 10 days; therefore, a diagnosis of acute bacterial sinusitis requires the persistence of symptoms for longer than 10 days or a worsening of symptoms after 5 to 7 days (Piccirillo, 2004; Sinus and Allergy Health Partnership, 2004). There may be some or all of the following signs and symptoms: nasal drainage, nasal congestion, facial pressure/pain (especially when unilateral and focussed in the region of a particular sinus), post-nasal drainage, hyposmia/anosmia, fever, cough, fatigue, maxillary dental pain, and ear pressure/fullness. Failure to treat ABS risks serious complications such as meningitis, peri-orbital abscess, osteitis of the sinus bones, orbital cellutitis and mastoiditis (Sinus and Allergy Health Partnership, 2004). Today, because of the general use of antibiotics in ABS, the prevalence of these complications is very rare (estimated 1/10000 cases of sinusitis, (Balk, 2001)). Additionally, an evidence based report by Benninger, 2000, concluded that compared with no treatment, antibiotic use reduced the incidence of clinical failures in patients with ABS by 50%. Furthermore, when antibiotics were used in conjunction with a clinical criteria-based diagnosis, antibiotic treatment was a cost-effective strategy. The most common bacteria recovered from paediatric and adult patients who have community-acquired ABS, using sinus aspiration by puncture or surgery, include *S. pneumoniae*, *H. influenzae, M. catarrhalis*, group A beta-haemolytic streptococci, and *S. aureus* (Brook, 2007). A review of sinus aspiration studies performed in adults with ABS suggests that *S. pneumoniae* is isolated in approximately 20% to 43%, *H. influenzae* in 22% to 35%, and *M. catarrhalis* in 2% to 10% of aspirates (Anon, 2006; Berg, 1988; Brook, 1996; Gwaltney, 1996). In children with ABS, *S. pneumoniae* is isolated in approximately 35% to 42%, while *H. influenzae* and *M. catarrhalis* each are recovered from about 21% to 28% of aspirates (Brook, 2007; Gwaltney, 1996). ABS can also be polymicrobial in about one third of the cases. Enteric bacteria are recovered less commonly, and anaerobes are recovered from only a few cases of ABS.

With regard to the pharmacokinetics and pharmacodynamics (PK/PD) of cefuroxime axetil, the MAH stated that the bacteriological and clinical efficacy observed for cefuroxime in a wide range of bacterial infections is supported by its favourable PK/PD profile and broad spectrum activity. PK/PD principles indicate that for cefuroxime axetil, 250 mg and 500 mg BID, the T>MIC (minimum inhibitory concentration) exceeds 40% for *S. pneumoniae* (both susceptible and penicillin intermediate isolates), *H. influenzae* and *M. catarrhalis* and is expected to provide efficacy for organisms with MICs up to and including 1 µg/m.

The MAH stated many clinical trials have been conducted evaluating the efficacy of cefuroxime axetil 250 mg and 500 mg BID in comparison to various antibiotic comparators routinely used for the treatment of ABS. In many studies cefuroxime axetil has been used as a standard comparator as part of first registration for many antibiotics, including the quinolones, macrolides and newer generation cephalosporins The most common bacterial pathogens isolated in patients were *S. pneumoniae*, *H. influenzae, M. catarrhalis* and *S. aureus*. ABS patients were enrolled in the trials if they had symptoms of sinusitis for more than 7 days for mild/moderate infection or for more than 3 days (but less than 28 days) for severe disease. Signs and symptoms of ABS were defined by purulent nasal discharge or purulence in the nasal cavity on examination. All ABS cases had to be supported by radiological evidence, i.e. sinus opacification and/or air-fluid level, provided by Waters view sinus x-ray or a computed axial tomography scan of the affected maxillary sinus or sinuses within the 72 hours before study enrolment. In all comparative studies, cefuroxime axetil was shown to be equivalent to the comparator antibiotic for the primary endpoint studied.

In a randomised, double-blind placebo-controlled study by Kristo, 2005, which evaluated the efficacy of cefuroxime versus placebo in 82 children aged 4–10 years, who presented in medical care with acute respiratory symptoms and ultrasonography findings suggestive of acute rhinosinusitis followed by diagnosis of sinusitis based on the presence of persistent symptoms and imaging. Patients received cefuroxime axetil (125 mg tablets, twice a day) or placebo for 10 days. Main outcome measures were complete cure after 2 weeks and absence of prolonged symptoms or complications. A total of 72 children (88%) completed follow-up. The sinusitis findings in the ultrasound could be confirmed with plain radiographs in 65 of the 72 patients (90%). The proportion of children completely cured by week 2 was similar 63% for the cefuroxime groups vs. 57% for the placebo group, and there were no significant differences in the incidence of complications (i.e. otitis media, pneumonia, severe clinical deterioration) in the two groups, which lead the authors to conclude that cefuroxime axetil provided no clear benefit in the treatment of acute sinusitis in children. However, it should be considered that failure of cefuroxime axetil to show a difference from placebo may have been explained, in part, by the relatively low dose of cefuroxime axetil used in this trial. All children received a fixed dose of cefuroxime axetil rather than dosing by weight. Therefore, many children, especially those at the older end of the age range, may have been significantly under-dosed on a per weight basis. Additionally, the majority of children had symptoms of ABS for less than 10 days with only 26% and 38% of children in the treatment and placebo groups, respectively, having had at least 10 days of symptoms. Therefore it is likely that many patients may have had sinusitis of viral aetiology rather than a bacterial infection.

Falagas, 2008, conducted a meta-analysis of randomised controlled trials (RCTs) to assess the therapeutic role of antibiotics for acute sinusitis compared with placebo. Seventeen double-blind RCTs were included (three involving children). Acute sinusitis was diagnosed with clinical criteria in nine RCTs, imaging studies in six RCTs, and microbiological or laboratory methods in two RCTs. To account for potential statistical heterogeneity between studies, a random-effects model was used for all analyses. Compared with placebo, antibiotics were associated with a higher rate of cure or improvement (2648 patients, odds ratio (OR) 1·64 (95% CI 1·35–2·00), data from 16 RCTs), or cure alone (1813 patients, OR 1·82(1·34–2·46), 12 RCTs). Furthermore, the rate of symptom resolution was faster with antibiotics in most RCTs. The authors concluded that antibiotics are of therapeutic benefit over placebo and should be reserved for carefully selected patients with a higher probability for bacterial disease.

A Cochrane systematic review was conducted by Ahovuo-Saloranta, 2008, compared the effect of antibiotics versus placebo on clinical failure rates for acute maxillary sinusitis and compared the different classes of antibiotics for treatment of acute maxillary sinusitis. Fifty-nine studies were included in the review; six placebo controlled studies (five of them conducted in primary care) and 53 studies comparing different classes of antibiotics. Five of the placebo-controlled studies (involving 631 participants) reported clinical failure rates (lack of cure or improvement) at seven to 15 days follow up. For participants with symptoms lasting at least seven days, antibiotics decreased the risk of clinical failure (pooled RR of 0.66, 95% confidence interval (CI); 0.44 to 0.98. In the head to head comparison with antibiotics, no antibiotic class was found to be superior in efficacy.

Young, 2008, undertook an individual patient meta-analysis of randomised trials to assess whether common signs, symptoms, or specific patient characteristics can be used to identify a subgroup that would benefit from antibiotic treatment. Ten double blind clinical trials were selected that compared an antibiotic with placebo and included 2640 patients. The estimated odds ratio (OR) for the overall treatment effect of antibiotics relative to placebo was 1·35 (95% CI 1·15–1·59) indicating that antibiotics are of some benefit over placebo. However, common clinical signs and symptoms could not

identify a subgroup of patients for whom treatment was clearly justified. But the meta-analysis did suggest that patients with purulent sputum and a high temperature benefited from antibiotic treatment.

A systematic review was conducted by Ip, 2005, which included 5 trials (7 comparisons, total of 780 enrolled patients) comparing antibiotics to placebo. All of these trials recruited patients from a primary care setting. Overall, antibiotics were found to be more effective than placebo, reducing the risk of clinical failure by about 25% to 30%, 7 to 14 days after treatment initiation (risk ratio (RR) 0.69, 95% confidence interval (CI); 0.53-0.89. It was noted that, symptoms improved or were cured in 65% of patients without any antibiotic treatment at all (95% CI 40- 91%).

The MAH also provided a review of the existing guidelines, stating that there are no consensus European guidelines for the treatment of ABS, although many countries have their own official or unofficial guidelines for the treatment of ABS which are broadly similar in recommending cefuroxime axetil as first or second line treatment. The guidelines generally concur that there is a role for anti-bacterial therapy for ABS and that the main aims of treatment are to shorten the duration of symptoms, to eradicate the causative pathogen, to reduce the danger of transmitting the infection to family members and to prevent the development of permanent mucosal damage, chronic sinusitis or other serious complications.

The MAH stated that the clinical success rates reported in more recent studies (Zervos, 2003) are generally comparable to those obtained in similar studies conducted 15 to 20 years earlier when cefuroxime axetil was introduced to the market (Brodie, 1989; Hebblethwaite, Sydnor, 1989). Comparative studies with other oral antibiotics indicate that clinically, a 10 day course of cefuroxime axetil twice daily is statistically equivalent to the same course of treatment with clarithromycin at 250mg twice daily (Stefannson, 1998), ciprofloxacin at 500 mg twice daily (Weis, 1998; Johnson, 1999), moxifloxacin (Burke, 1999; Siegert, 2000), faropenem medoxomil (Upchurch, 2006; Siegert, 2002), sparfloxacin (Gehanno, 1996), cefopodoxime proxetil (Pessey, 1994), ceprozil (Brankston, 1998), telithromycin (Buchanan, 2003), pristinamycin (Gehanno, 2004; Pessey, 2001) and amoxicillin or amoxicillin/clavulanic acid at 500mg three times daily (Brodie, 1989; Camacho, 1992, Henry, 1999). In general practice studies, clinical success rates have ranged from 86-96%, (Griffiths, 1987; Hebblethwaite, 1987; Alvart, 1992; Seppey, 1997). Paediatric patients with sinusitis have also been shown to benefit from cefuroxime axetil therapy (Gürses, 1996). Additionally, a study by Dubreuil, 2001, demonstrated that, 5 days of therapy with 250 mg cefuroxime axetil BID was as effective as the same regimen given for 10 days. Cefuroxime axetil was also shown to be an effective treatment in patients with acute exacerbations of chronic sinusitis when compared to amoxicillin/clavulanate (Namysłowski, 1998).

The CHMP noted that acute bacterial sinusitis is difficult to differentiate from the much more common viral sinusitis and that antibacterial treatment is often not warranted. However, having reviewed the data submitted by the MAH, the CHMP agreed that the proposed indication was acceptable. In conclusion, the CHMP adopted the following harmonised indication:

"Acute bacterial sinusitis"

1c) Acute otitis media (AOM)

The MAH provided data to support the indication "*acute otitis media*" and stated that the pathogenesis of AOM is directly related to a preceding viral infection (Heikkinen, 2003) and that AOM is primarily caused by bacteria such as *S. pneumonia*, non-typeable *H. influenza*e and *M. catarrahlis*. *S. pneumoniae* is considered the most important, as it is the least likely to resolve spontaneously, particularly in young children less than 2 years of age (Dowell, 1999; Rovers, 2006). AOM is usually a self-limiting disease but rare complications associated with AOM can occur including meningitis, bacteraemia, mastoiditis, pneumococcal pneumonia, spontaneous perforation of the tympanic membrane, chronic suppurative otitis media, labyrinthitis, facial palsy, intracranial abscess and hearing loss (Bluestone, 2000; Jackson, 1996; Reid, 1995).

The MAH stated that two very recent randomised, blinded trials have conclusively shown that antibiotics are beneficial over placebo in treating AOM (Hoberman, 2011; Tähtinen, 2011). The AOM in the children (aged 36 months or less) who were enrolled in the respective studies was defined by the acute onset of the condition and the presence of middle-ear effusion, a bulging tympanic membrane, and otalgia or erythema of the tympanic membrane. In these two studies, AOM was meticulously assessed by experienced otoscopists, and only children with a clear, certain diagnosis of AOM were

enrolled. The results of each study showed a significant benefit among children who received antibiotic with respect to the duration of acute signs of illness. Among children with moderate disease and children with severe disease, the rates of clinical failure were higher in the placebo group than in the amoxicillin–clavulanate group. As expected, the condition of many children in the placebo group improved without antibiotics, and more children in the antibiotic groups had associated side effects. Both these recent studies with a well-defined patients population, clearly demonstrated that children benefited from antibiotic treatment with improvement in signs and symptoms of AOM. Given the recent positive data indicating antibiotics are more effective in comparison to placebo in well conducted controlled trials and the fact that meta-analyses indicate that antibiotics are beneficial in treating children with AOM particularly younger children aged 2 or less, the MAH considered that cefuroxime axetil remains an appropriate treatment choice for AOM. The MAH also stated that cefuroxime axetil is an appropriate antibiotic in patients who are considered to be allergic to penicillin and its use in such patients is recommended by several national guidelines and the American Academy of Paediatrics guidelines (AAP, 2004).

With regard to the PK/PD of cefuroxime axetil, the MAH considered that the bacteriological and clinical efficacy observed for cefuroxime in a wide range of bacterial infections is supported by its favourable PK/PD profile and broad spectrum activity. PK/PD principles indicate that for cefuroxime axetil, 30 mg/kg/day given BID the T>MIC exceeds 40% for *S. pneumoniae* (both susceptible and penicillin intermediate isolates), *H. influenzae* and *M. catarrhalis* and is expected to provide efficacy for organisms with MICs up to and including 1 µg/mL (Dagan, 2003).

In a randomised, multicentre study by Pessey (1999) in children with acute otitis media with effusion, diagnosed by tympanocentesis and microbiological culture, a 5-day course of cefuroxime axetil suspension (CXM, 30 mg/kg/day in two divided doses, n = 252) was shown to be equally efficacious compared with 8-10 days treatment with amoxicillin/clavulanate (AMX/CL) given three times daily. The normal dose of AMX/CL was 40 mg/kg/day in three divided doses for 10 days (n=255), but in French centres, AMX/CL was given at 80 mg/kg/day (in three divided doses) for eight days (AMX/CL-8; n=209). There were 153 withdrawals, with a similar proportion of patients withdrawing from CXM and AMX/CL-10, but less than half this rate withdrawing from AMX/CL-8. No reason was given for the difference. In the clinically evaluable population, the proportions of patients with a clinical cure at one to four days post-treatment were 175/203 (86%), 181/205 (88%) and 145/154 (88%) in the CXM, AMX/CL-10 and AMX/CL-8 groups respectively. After 21-28 days the clinical response rates were 74%, 70% and 79%, respectively. Similar results were obtained in a subset of patients aged <18 months. A total of 837 pre-treatment pathogens were isolated from middle ear fluid from 73% of the patients, the majority of isolates being *S. pneumoniae* and *H. influenza.*

Gooch, 1996 describes two independent, investigator-blinded, multicentre clinical trials, in which five and 10-day periods of treatment with cefuroxime axetil suspension and amoxicillin/clavulanate (AMX/CL) suspension were compared. One study included microbiological evaluation of middle ear fluid obtained by tympanocentesis at the start of treatment, and where possible, post-treatment in patients with an unsatisfactory clinical outcome. Seven hundred and nineteen patients aged 3 months to 12 years were randomly assigned to receive one of three treatments: cefuroxime axetil suspension at 15 mg/kg twice daily (maximum 1 g/day) for five days plus the same dose of placebo for a further five days (n=242); cefuroxime axetil suspension as before for 10 days (n=242), or AMX/CL suspension 13.3 mg/kg three times daily for 10 days (maximum 1.5 g/day) (n=235). A satisfactory clinical response (cure or improvement) was obtained in 69%, 70% and 74% of the 497 clinically evaluable patients in the three treatment groups, respectively. There were no statistically significant differences between paired treatments, nor was the outcome affected by whether the patient had undergone tympanocentesis. Bacteriologically, 177/244 patients had positive cultures from middle ear fluid, 102 of which were evaluable. The primary pathogens isolated were *S. pneumoniae* (42%), *H. influenzae* (41%) and *M. catarrhalis* (14%), with 49% of the *H. influenzae* and 93% of the *M. catarrhalis* strains being β-lactamase-producers. Eradication rates for the three treatments 92% (CXM for five days), 84% (CXM for 10 days) and 95% (AMX/CL 10 days) respectively, again with no statistically significant differences between paired treatments. Only one clinical failure in the cefuroxime axetil 10-day group was attributable to the pathogen being cefuroxime-resistant, the majority of failures in this group resulting from superinfection.

A randomised, investigator-blind multicentre study by McLinn, 1994, enrolled 263 paediatric patients (aged 3 months to 11 years), comparing the efficacy of cefuroxime axetil suspension (15 mg/kg twice daily for 10 days, n=165) with that of AMX/CL suspension (13.3 mg/kg three times daily for 10 days, n=98) for the treatment of acute otitis media with effusion (OME). A satisfactory outcome (cure or improvement) was obtained in 113/146 (77%) of evaluable patients treated with cefuroxime axetil and 66/89 (74%) of those treated with AMX/CL. Two hundred pathogens were isolated from pre-treatment middle ear fluid samples obtained by tympanocentesis, of which 39% were *H. influenzae*, 34% *S. pneumoniae* and 16% *M. catarrhalis*. Over 1/3 of the *H. influenzae* strains, and over 3/4 of *M. catarrhalis* strains were β-lactamase-producers. Bacteriological data from 184 patients was included in efficacy analyses. A satisfactory bacteriological response (cure, presumed cure, cure with re-infection) was achieved in 81% of evaluable patients treated with cefuroxime axetil and 76% who received AMX/CL ($p>0.05$). Clinical failure or recurrence of infection within two weeks of completing treatment occurred in 22% and 26% of cefuroxime axetil and AMX/CL-treated patients respectively.

A study by McLinn, 1990, enrolled 400 paediatric patients aged three months to 12 years, comparing ten days of treatment with cefuroxime axetil suspension (15 mg/kg twice daily, n=261) and AMX/CL (13.3 mg/kg three times daily, n=139)). Over 60% had experienced a previous episode of otitis media, and 46% had recurrent infection. Clinical evaluations were carried out after 3-5 days of treatment, at 1-4 days post-treatment, and at 12-16 days post-treatment. Resolution of all signs and symptoms throughout the post-treatment evaluation period was defined as a clinical cure, improvement being classified similarly but with persistence of middle ear effusion. A patient was considered to be a clinical failure if no improvement was evident after at least 3 days of treatment, or if treatment was discontinued for an adverse event. Clinical success rates were 77.4% and 76.3% for cefuroxime axetil and AMX/CL, respectively. Only 3.4% and 5.8% of patients failed to respond, with approximately 13% in each group suffering a recurrence. There were no statistically significant differences between the two treatments. Assessment of bacteriological efficacy was possible in 202 patients. A total of 93.3% of patients in the cefuroxime axetil group and 95.3% of patients in the AMX/CL group achieved bacteriological cure or presumed cure after treatment. The predominant pathogens encountered pre-treatment were *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*, with 25% of *H. influenzae* and 75% of *M. catarrhalis* being β-lactamase producers.

In a multicentre study by Schwarz, 1991, involving 475 children, the efficacy of cefuroxime axetil (30 mg/kg/day in two divided doses) was compared with that of amoxicillin/clavulanate (40 mg/kg/day in three divided doses) for the treatment of AOM Patients were randomised to the respective drugs in a 2:1 ratio, and 460 received a 10-day course of treatment. Positive bacterial cultures were obtained from 66% of the children, yielding mainly *H. influenzae* (39%), *S. pneumoniae* (39%), and *M. catarrhalis* (13%), with 20% of isolates being β-lactamase producers. Rates of cure (eradication of pain, fussiness, fever and contour of the freely mobile tympanic membrane, with no recurrence within two weeks) and improvement (evidence of secretory OM in the absence of symptoms) were almost identical in the two treatment groups at 83.1% and 80.7% respectively.

In an open, randomised, multi-centre general practice study by Brodie, 1990, 660 children (aged three months to 12 years) with otitis media were randomised to receive a 10-day course of cefuroxime axetil suspension or amoxicillin syrup. Diagnosis was based on clinical examination. Some specimens for bacteriological culture were obtained by tympanocentesis, but most consisted of swabs from discharging ears. Ninety-six bacterial isolates were obtained, with *H. influenzae* accounting for 29%, *S. pneumoniae* for 22% and *M. catarrhalis* for 6%. *S. aureus* and *P. aeruginosa* were also identified. All isolates, except four *Pseudomonas* spp., were susceptible to cefuroxime axetil. However, some strains of *H. influenzae* (7.1%), *M. catarrhalis* (50%) and *S. aureus* (75%) produced β -lactamase and were resistant to amoxicillin. Patients under two years of age received 125 mg cefuroxime axetil twice daily after food (n=144), or amoxicillin 125 mg three times daily (n=140). Older children were given 250 mg of cefuroxime axetil (n=188) or amoxicillin (n=188) at the same dosage intervals. The overall cure or improvement rate at one to four days after treatment was 94.3% for those treated with cefuroxime axetil and 94.5% for those treated with amoxicillin.

A randomised, blinded, multi-centre study by Pichichero, 1990, enrolling 377 infants and children (aged up to the age of 12 years) with signs or symptoms of acute otitis media compared the efficacy of 10-day courses of cefuroxime axetil suspension (125 mg/5 mL; 15 mg/kg twice daily, n=99), cefaclor (13.3 mg/kg three times daily, n=121) or AMX/CL (13.3 mg/kg three times daily, n=103). Clinical success was defined as resolution of signs and symptoms of otitis media during the 10-day treatment period, with continued resolution through to the two week post-treatment follow-up. Children with persistence of middle-ear effusion were classified as improved. Using these strict criteria, a statistically significant difference between treatment groups was identified with respect to clinical outcome. Clinical success or improvement was achieved in 77%, 74%, and 68% of the cefuroxime axetil, cefaclor and AMX/CL groups respectively, with 62%, 46% and 52% of patients from these groups having complete resolution of symptoms including effusion. The greatest failure rate occurred in the AMX/CL group (33% vs. 23% with cefuroxime axetil), and the most cases of residual middle ear effusion in the cefaclor group (28% vs. 15% with cefuroxime axetil).

The MAH concluded that the efficacy of cefuroxime axetil suspension 15 mg/kg twice daily for 7-10 days has been clinically evaluated in substantial numbers of paediatric patients with AOM, with or without effusion, including those who have failed amoxicillin therapy, and comparative studies have been conducted with other first-line antibacterial agents used in to treat AOM. Cefuroxime axetil has achieved comparable efficacy to the commonly used antibiotics for AOM such as; amoxicillin syrup, clarithromycin suspension, amoxicillin/clavulanate suspension, cefotiam hexetil and cefaclor. Cefuroxime axetil was effective in eradicating the key respiratory tract pathogens *S. pneumonia* (including penicillin intermediate strains)*, H. influenzae* and *M. catarrhalis*. Cefuroxime axetil was equally effective against both β-lactamase-producing and non-β-lactamase-producing strains. Cefuroxime axetil was also effective in patients who had previously failed to respond to amoxicillin. Furthermore, short-course (5-day) therapy with cefuroxime axetil suspension twice daily was equivalent to that obtained with eight or 10-day courses of amoxicillin/clavulanate three times daily. This factor, particularly if combined with a shorter treatment period, is likely to enhance patient compliance with cefuroxime axetil relative to other agents

Several review articles on AOM also support the use of cefuroxime axetil in treating AOM. Leibovitz, 2004 reviewing *H. influenza* and AOM, considered that cefuroxime axetil is an appropriate treatment choice for patients with infection due to nontypeable *H. influenzae*. Dagan, 2003, using PK/PD predictions, considered that of all the oral antibiotics to treat AOM, Augmentin was the most appropriate choice for AOM, followed by cefuroxime axetil. Using, clinical, bacteriological and PK/PD data, Brook, 2004, reviewed all the available cephalosporins for therapy in AOM. It was concluded that cefuroxime remains one of the most appropriate cephalosporin antibiotics for the treatment of AOM due to penicillin susceptible and penicillin intermediate *S. pneumoniae, H. influenza* and *M. catarrhalis.*

Finally, the MAH provided a summary of European national consensus or evidence based guidelines which recommend cephalosporin group 2 / cefuroxime axetil as treatment options for AOM and recommending cefuroxime axetil as second-line treatment in patients or for those patients allergic to penicillin.

Based on the submitted data, the CHMP considered the proposed indication to be acceptable. In conclusion, the CHMP adopted the following harmonised indication:

"Acute otitis media"

2) Lower respiratory tract infections (LRTI)

The MAH proposed the indication "*Lower respiratory tract infections (e.g., pneumonia, acute bronchitis, and acute exacerbations of chronic bronchitis)*" and presented a summary of LRTI studies reviewed by Scott, 2001 and Perry, 1996, including both MAH sponsored and published studies, which were mixed studies including the indications pneumonia, acute bronchitis, acute exacerbation of chronic bronchitis (AECB) and/or bronchieactasis. Clinical and bacteriological success rates from these studies for both adults and paediatric patients with LRTI were provided.

However the CHMP 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 CHMP

also noted that acute bronchitis is primarily of viral aetiology, and therefore not an appropriate indication for antibacterial agents. The MAH agreed and provided a sub-categorisation of the submitted studies, presenting how many patients were investigated in each study for each of the sought indications, and the clinical and bacteriological cure rates obtained. The MAH also acknowledged that acute bronchitis is principally viral in aetiology and that the role of antibacterials in treating acute bronchitis is questionable. The MAH therefore withdrew the proposed indication "*acute bronchitis*" and instead proposed the indications "*community acquired pneumonia" and* "*acute exacerbations of chronic bronchitis".*

2a) Community acquired pneumonia (CAP)

With regard to pneumonia, the MAH stated that several clinical trials have been conducted evaluating the efficacy of cefuroxime axetil BID (either as monotherapy or as sequential therapy) in comparison to various antibiotic comparators routinely used for the treatment of CAP. The MAH presented the clinical and bacteriological success rates from these studies for both adults and paediatric patients. Although one study (Siegel, 1999) was double-blinded, the majority of these studies were open, comparative studies. The most common bacterial pathogens isolated in patients 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. The MAH also submitted three studies evaluating the oral administration of cefuroxime.

In a multi-centre trial by Yanco, 1990, the clinical success rate (cure or improvement) was similar for each of the treatment groups. If the cure rate alone was considered, patients treated with 250 mg cefuroxime axetil had a lower cure rate in comparison to cefuroxime axetil 500 mg and cefaclor (58% vs. 94% and 88%; $p<0.05$). Although the severity of illness was comparable, the mean age of this group was significantly older (mean age 61 years) than that of the other two groups (mean age 40 and 42 years, respectively; $p<0.001$). This difference may have contributed to the lower clinical cure rate. However, there was no significant difference in bacteriological outcome between treatments. The most frequently encountered pathogens (*H. influenzae*, *S. pneumoniae* and *K. pneumoniae*) were successfully eradicated from the majority of patients by all three regimens.

In a multicentre, randomised, investigator blinded, comparative trial (Higuera 1996) 162 patients with CAP were randomly assigned to receive 10 days treatment with cefuroxime axetil 500 mg twice daily or amoxicillin/clavulanic acid (500 mg/125mg three times daily. *S. pneumoniae* and *H. influenzae* were the most common pathogens isolated from the 97 patients who had positive pre-treatment sputum cultures. All 55 patients treated with cefuroxime axetil were successfully treated with similar efficacy to amoxicillin/clavulanic acid, 96%. The bacteriological efficacy rate was ≥93% for both treatment groups.

Pettersson, 1999, evaluated the efficacy of trovafloxacin vs. cefuroxime axetil with or without erythromycin in the treatment of 327 patients with CAP. Efficacy rates were similar for patients hospitalised with CAP, 71% for cefuroxime axetil treated patients vs. 82% for trovafloxacin treated patients. In outpatients, clinical success occurred in ≥ 93% of patients in each group. Additionally, there were no differences in clinical success rates between the two treatment groups in those patients aged ≤ 65 and those ≥ 65 years of age. The most common pathogens isolated were *S. pneumonia*, *H influenza*, *M. catarrhalis*, *C. pneumonia* and *M. pneumonia*. Clinical success rates and bacteriological eradication rates for each baseline pathogen were comparable between groups.

Sequential therapy with cefuroxime i.v. followed by oral cefuroxime axetil was studied in 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% to 94% of cefuroxime axetil recipients achieved a satisfactory clinical response versus 74% to 94% of patients treated with comparator agents. In the studies that reported bacteriological eradication rates ranged, eradication occurred in a similar percentage of patients in the cefuroxime axetil (ranging from 70% to 82%) and the comparators, clarithromycin (67%) and azithromycin (75%) sequential therapy groups (table 8). Lode, 2002, 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. In one large open study 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 -10.7 to -1.3) (File, 1997). The bacteriological efficacy was also considered superior for the comparator group (85% vs. 98%) however as the sample size is small for the microbiological population hence no firm conclusions can be made with regard to microbiological efficacy. Of note is that the eradication rate for patients with CAP due to *S. pneumoniae*, *S. aureus* and *M. catarrhalis* was 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 to 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 as shown to be of similar efficacy in veterans with moderately severe CAP, (Siegel, 1999).

The MAH also stated that several studies have evaluated sequential therapy in children. An open non-comparative study was carried out to evaluate the efficacy of cefuroxime axetil suspension as sequential therapy to parenteral cefuroxime in 87 paediatric patients with CAP (Shalit, 1994). Patients were initially treated with intravenous cefuroxime for 48-72 hours (5 9 doses) followed by cefuroxime axetil suspension to complete a 7-10 day course of treatment. Out of 84 evaluable patients, 79 (94%) were cured and 3 (3.6%) were improved within 24 hours after completing oral therapy, giving a clinical response rate of 97.6%. Only one relapse occurred amongst 74 patients who returned for follow-up14-28 days later. At this time, chest X-rays had returned to normal in 94% of patients (75/79) and improved in 3.8% (3/79).

An open-label, multicentre study has been conducted comparing the efficacy of cefuroxime axetil suspension and cefpodoxime proxetil for the treatment of CAP in 121 paediatric patients (Boulesteix, 2000). Sputum or nasopharyngeal cultures, obtained from 37.2% of patients, yielded *S. pneumoniae*, *H. influenza* and *M. catarrhalis*. The clinical success rates obtained were 93% for Cefuroxime axetil and 80% for cefpodoxime proxetil.

In a randomised, multi-centre study in 140 patients with CAP, cefuroxime axetil was shown to be significantly more effective than ceftibutin, (93% vs. 80%, respectively), (Nogeova, 1997). Additionally cefuroxime was more effective in eradicating the key respiratory pathogens *S. pneumoniae* and *H. influenzae*. The bacteriological eradication rate for typical pathogens was also higher for cefuroxime treated patients in comparison to ceftibuten treated patients, 76% vs.67%, respectively.

Cefuroxime axetil was also shown to be effective treatment with comparable efficacy to ampicillin sulbactam in children with CAP who had failed previous antibacterial therapy with amoxicillin, ampicillin, penicillin, cephalexin, cotrimoxazole and roxithromycin (Damisovicova-Nogeova, 1998). This study included 149 patients (aged 3 months to 15 years), and the clinical success rates obtained were 97% for cefuroxime axetil and 96% for ampicillin sulbactam.

A paediatric study of sequential cefuroxime/cefuroxime axetil therapy for the treatment of CAP was conducted by Barlinski, 1994. Fifty-one children aged three months to seven years were treated with cefuroxime 75 mg/kg/day by the intramuscular or intravenous route, in three divided doses within 48

72 hours, with possible extension of treatment for a further 24 hours. If subsequent oral therapy was not possible, the case was classified as a failure. In those patients in whom oral therapy was possible, cefuroxime axetil was given at 30 mg/kg/day (maximum 500 mg/day; suspension n=41, tablets n=10) in two doses at twelve-hourly intervals for 10 14 days. Transfer from parenteral to oral therapy was achieved in all 51 children after two to four days of treatment. By the end of the study, 43 children were cured; a further six had sufficiently improved and required no further antibiotic therapy. The overall clinical success rate was thus 96% (49/51).

The MAH also discussed the variability in cefuroxime *in vitro* activity against *S. pneumonia.* In 6 recently published studies, cefuroxime MICs were relatively low (MIC50/90 of 0.016/0.125 mg/L) among 426 strains from Germany (Jacobs, 2009). Slightly higher MICs were reported in a study of 97 strains from Turkey (MIC90 = 1 mg/L) and in a study of 398 strains from Poland (MIC50/90 ≤0.015/4 mg/L) (Gonullu, 2009; Skoczynska, 2007). Among more than 3,400 strains collected worldwide, the MIC50/90 was 2/4 mg/L (Blasi, 2009). In another global study, penicillin susceptible - intermediate - resistant rates were 67.7% – 14.2% – 18.1% for 2,655 *S. pneumoniae* and the cefuroxime MIC50/90 were ≤0.06/0.12 – 0.5/4 – 8/8 mg/L, respectively (Biedenbach, 2009). In a recent study from Spain, the variability in cefuroxime resistance was noted among different serotypes. For example, all serotype 11A organisms were resistant and in contrast 100% of serotypes 23B organisms were susceptible (Fenoll, 2010). Viberg, 2008 has evaluated the optimal cefuroxime IV dosing strategies based on databased models and decision-based risk functions. The authors found that for infections caused by *S. pneumoniae*, the results indicated that a dosing strategy comprising only 2 dosing categories with lower dose rates than 1500 mg TID, 750 mg TID or BID would be sufficient.

The MAH provided the available epidemiology and susceptibility surveillance data from the last 5 years from European countries, including the key respiratory pathogens *S. pneumoniae, M. catarrhalis,* and *H. influenzae*. With regard to resistance trends among CAP pathogens, the MAH considered that susceptibility rates remain high for *H. influenzae* and *M. catarrhalis* and therefore focused on *S. pneumoniae* as the primary organism of interest. Nonetheless, information on the susceptibly of *H. influenzae* and *M. catarrhalis* was also provided. The MAH referenced studies by Ambrose, 2007; Craig 2003; Dagan, 1996; Klein, 1993; Auckenthaler, 2002; Stein, 1997; Dubois, 2000 to conclude that the PK/PD principles indicate that for 500 mg BID cefuroxime axetil and the 15 mg/kg dose BID for children, the T>MIC in fact exceeds 55 % of the dosing interval for *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* and is therefore expected to provide the appropriate coverage of key pathogens up to an MIC of 1µg/mL.

The MAH also presented an overview of a number of European and American guidelines which recommend cefuroxime axetil for the treatment of CAP, but acknowledged that the recently revised European Respiratory Society (ERS) consensus guideline for the antibiotic treatment of LRTI (Woodhead 2011) makes no reference with regard to the suitability of cefuroxime axetil for the treatment of CAP.

The CHMP raised concerns that the highest daily dose of Zinnat (500 mg BID) is not sufficient to provide adequate coverage against common respiratory pathogens such as penicillin-intermediate *S. pneumoniae, H. influenzae* and *M. catarrhalis* (Bulitta et al, 2009). Although the submitted clinical trials provide some level of support for the indication CAP, the CHMP considered that the change in MIC distributions for relevant respiratory pathogens over the last decades impacts the suitability of cefuroxime axetil in this indication. There is no safety data to support three times daily treatment. As a result, the CHMP considered the empirical use of cefuroxime axetil in CAP to be inappropriate. The CHMP considered this to be confirmed by the MIC distributions for the three organisms.

Regarding *H. influenza*e, the CHMP was of the opinion that there has been a change in prevalence of chromosomal mediated resistance (change in PBP-3) which has resulted in an increase in MIC values. EUCAST breakpoints for *H. infuenzae* are as follows: S≤0.125 mg/L and R>1 mg/L. According to the EUCAST MIC distribution data, only 1248 isolates of a total of approximately 96750 isolates have a MIC ≤0.125 mg/L, which shows that only about 1% of isolates are fully sensitive while the majority of the population have MIC values from 0.25 to 4 mg/L and are therefore considered less-susceptible. These MIC values are much higher than serum concentrations which can be achieved with oral cefuroxime.

Regarding *M. catarrhalis,* the CHMP noted the surveillance data from the 2009 NethMap report, which states that “cefuroxime resistance was 0-5% over the years, apparently without a clear trend, but when looking at the MIC distribution, a clear shift was observed from 2004. In 2002 and 2003 the MIC distributions were unimodal over a broad range from < 0.03-0.5 mg/l; thereafter the whole population

moved to the right with most MICs 0.5-4 mg/l and a clear peak of strains with MIC = 2 mg/l. This is the breakpoint of intermediate resistance when using EUCAST breakpoints". Current EUCAST breakpoints for *M. catarrhalis* are as follows: S≤0.125 mg/L and R>2 mg/L. According to the EUCAST MIC distribution data, only 189 (1.2%) isolates of a total of approximately 14540 isolates have a MIC ≤0.125 mg/L and are therefore sensitive. The majority of the population seems to have MIC values up to 4 mg/L, which shows that most of these isolates are less-susceptible to cefuroxime and will fall in the intermediate category. These MIC values are far higher than serum concentrations which can be achieved with oral cefuroxime.

Due to the small number of sensitive isolates and/or that almost all population consists of less susceptible isolates with high MIC values up to 4 mg/L for both *H. influenzae* and *M. catarrhalis*, and considering the poor PK of cefuroxime axetil, the CHMP considered these bacteria to be poor targets for therapy with cefuroxime axetil.

Regarding *S. pneumonia*e, the EUCAST breakpoints are as follows: S≤0.25 mg/L and R>0.5 mg/L. According to the EUCAST MIC distribution data, 24076 isolates of a total of approximately 32676 isolates have a MIC ≤0.25 mg/L, which shows that 75-80% of isolates are sensitive while the rest (20-25%) is less-susceptible or resistant.

The CHMP considered that when the MIC distributions for relevant causative pathogens for CAP indicate reduced susceptibility to cefuroxime (except for *penicillin-sensitive S. pneumoniae* as described above), the key consideration is whether high enough plasma concentrations of cefuroxime axetil can be achieved, following administration of 500 mg BID to be able to eradicate these pathogens. According to Auckenthaler (2002); "Dosing schedules for β-lactam antibiotics should maintain serum concentrations above the MIC for the bacterial pathogen for at least 50% of the dosing interval to achieve therapeutic efficacy and prevent development of resistance. This is a basic criterion for the clinical efficacy of β-lactams". This is supported by a number of scientific articles (Ludwig et al 2006, Eagye et al 2007, Cars et al 2008, Ambrose et al 2004, Auckenthaler et al 2002) and endorsed by the CHMP. It is considered especially important to choose the PK/PD target of T>MIC: 50% for less susceptible Gram-negative bacteria such as *H. influenza* and *M. catarrhalis.*

Cefuroxime axetil is administered 12 hourly based on available clinical data. Bioavailability is about 50% when administered with food and the drug is 50% protein-bound in plasma. In order to show adequate antibacterial activity, the plasma concentration of cefuroxime should be higher than MIC values at least 50% of the dose interval (i.e. 6 hours). Following administration of 500 mg cefuroxime axetil, peak plasma concentration (Cmax) is approximately 8 µg/mL and mean elimination half-life is 1.2 hrs. The CHMP therefore inferred that the plasma concentration of cefuroxime after 5 half-lives (6 hours) would be 0.25 µg/mL. This concentration seems to provide adequate coverage for Penicillin-sensitive *S. pneumoniae* isolates. However, 500 mg BID is not likely provide an adequate coverage for most *H. influenzae* and *M. catarrhalis* isolates considering high MIC values as discussed above.

Regarding the PK modelling carried out by Bulitta et al (2009), the CHMP noted the MAH argument that only the 250 mg BID dosing regimen was evaluated, not the 500 mg BID regimen. However, the CHMP was of the opinion that when 500 mg TID was used in the model, the PTA expectation values were approximately 65% for PISP, 81-99% for *H. influenzae,* and 77-93% for *M. catarrhalis* (for the PK/PD target of T>MIC 40%). The PTAs for T>MIC 65% (near maximal killing) target were much lower, i.e. approximately 55% for PISP, 52-93% for *H. influenzae,* and 43-69% for *M. catarrhalis*. A PTA of at least ≥90% can be considered robust in order to reassure an adequate bacteriostasis or bactericidal activity. According to the above PK modelling with Monte Carlo (MC) simulations, robust high PTAs (>90%) were achieved by 250 mg cefuroxime axetil BID or TID for MICs of ≤0.375 mg/L or ≤0.5 mg/L, respectively for bacteriostasis target (%T>MIC: 40%) and for MICs of ≤0.094 mg/L or ≤0.375 mg/L, respectively, for the near maximal killing target (%T>MIC: 65%). Oral cefuroxime (250 mg q12 h or q8h) achieved high PTA expectation values (≥91.4%). for penicillin-susceptible *S. pneumoniae*.

According to PK/PD calculations (for the target of T>MIC 50%) by Auckenthaler 2002, cefuroxime 500 mg BID showed borderline values by providing 43% coverage at MIC90: 2 mg/L for *H. influenzae* and *M. catarrhalis*. For *S. pneumoniae* at MIC90: 0.25 mg/L the calculated coverage was 73%. The CHMP also considered that the PK/PD data submitted did not support the MAH claim that cefuroxime axetil 500 mg BID would cover isolates with MIC up to 1 µg/mL would be covered.

Regarding clinical data, the CHMP noted that no randomized, active controlled and double-blind pivotal studies were submitted to support the indication CAP. The available clinical data included open, randomized, controlled or non-controlled small or large size clinical studies in which cefuroxime axetil was used for 7 days following 1-4 days i.v. treatment with cefuroxime or another antibiotic in the

treatment of CAP. Although the majority of the studies are quite old, there are five studies performed between 2000 and 2005 in hospitalized CAP patients. In these studies cefuroxime axetil was used alone or with erythromycin following i.v. treatment with cefuroxime or ceftriaxone. Without discussing the appropriateness of the comparators, cure rates were ranging from 74% to 93% and seem to be comparable to cure rates with the comparator treatment. Bacteriological eradication rate for relevant RTI pathogens (not investigated in all studies) ranged from 74-100%.

The CHMP concluded that based on the EUCAST MIC distributions, the vast majority of *M. catarrhalis* and *H. influenzae* isolates seem to have high MIC values (i.e. up to 4mg/L) and the number of susceptible isolates are very low (<1%). Considering the poor PK of the drug, these bacteria are not considered to be a good target for therapy with cefuroxime axetil. However, 75% of *S. pneumoniae* isolates have MIC ≤0.25 mg/L, which are susceptible to cefuroxime. The CHMP also considered that the available PK/PD data is sparse and does not confirm that a 500 mg BID dosing regimen provides an adequate coverage for less susceptible pathogens which have MIC up to 1 mg/L. The PK/PD data seem however to support that cefuroxime axetil 500 mg BID can provide adequate coverage for penicillin-susceptible *S. pneumoniae* (S≤0.25 mg/L, R>0.5 mg/L). The CHMP also considered that managing less susceptible pathogens by using higher doses of cefuroxime axetil than the maximum daily dose of 500 mg BID is not an option, and the lack of efficacy and safety data regarding TID treatment. The CHMP therefore concluded that based on the MIC distributions for relevant causative pathogens in CAP and the PK/PD data and the lack of convincing clinical documentation, cefuroxime axetil is not an appropriate agent for empirical treatment of CAP.

The CHMP therefore recommended the removal of the proposed indication from the harmonised SmPC.

2b) Acute exacerbations of chronic bronchitis (AECB)

The MAH stated that acute exacerbations of chronic bronchitis (AECB), which are a characteristic of chronic obstructive pulmonary disease (COPD), contribute to morbidity and decreased quality of life for patients with COPD. COPD is estimated to affect between 3.7% and 6.8% of the population in Europe (Blasi, 2006), Most patients with COPD will experience recurrent episodes of AECB. The clinical definition of AECB is an acute change, beyond day-today variability, in a patient's baseline characteristics such as increased cough, worsening dyspnoea and changes in sputum purulence and volume. Infectious agents are estimated to account for around 80% of these episodes, with the remaining 20% attributed to non-infectious causes such as inadequate medical treatment, congestive heart failure and pulmonary embolism (Sethi, 2000a). A significant proportion of acute exacerbations are due to bacterial infections. Studies using bronchoscopic sampling have been more informative, and have consistently shown that in AECB approximately 50% of patients have a significant bacterial infection (Fagon, 1990; Monso, 1995; Pela, 1998; Soler, 1998; Wilson, 2001). The most common bacterial pathogens isolated in AECB patients are *H. influenzae*, *S. pneumoniae* and *M. catarrhalis* (Ball, 1995; Sethi, 2000b; Sethi, 2000c; Soler, 1998). The presence of these bacteria can depend on the severity of airway disease. Pathogens such as *S. aureus* and *P. aeruginosa* are usually isolated in patients with more severe AECB (Sethi, 2000b). The MAH stated that several clinical trials evaluating the efficacy of cefuroxime axetil BID in comparison to various antibiotic comparators routinely used for the treatment of AECB have been conducted. The MAH presented the clinical and bacteriological success rates from these studies for both adults and paediatric patients. The majority of the studies were comparative studies and several studies were double blind studies. The most common bacterial pathogens isolated in patients were *S. pneumoniae, H. influenzae* and *S. aureus*. An exacerbation was defined as having at least two of the following symptoms: increased frequency and severity of cough, an increase in volume and/or purulence of sputum, increased dysponea, and auscultatory findings consistent with chronic obstructive pulmonary disease (COPD).

The MAH presented the PK/PD profile of cefuroxime axetil, considering that cefuroxime showed bacteriological and clinical efficacy in a wide range of bacterial infections, as supported by its favourable PK/PD profile and broad spectrum activity. The MAH stated that the understanding of the pharmacodynamics of antibiotics has evolved significantly since the initial approval of cefuroxime axetil in the late 1980s, and has complemented the interpretation of traditional measures of antibiotic activity, such as the minimum inhibitory concentration (MIC). Maximising bacterial eradication is a key goal in the selection of an appropriate antibacterial. Bacteriological eradication is important not only to improve clinical success but also to reduce the potential for the development of resistance (Dagan, 2001; Dagan, 2002). The bacteriological efficacy of antimicrobials can, to some extent, be predicted on their pharmacokinetic/ pharmacodynamic (PK/PD) properties. For β-lactams agents, the bacteriological efficacy is dependent on the time for which free serum concentrations of the drug exceed the MIC for the target pathogen (i.e., T>MIC). The percentage of the dosing interval for which the circulating

antibiotic concentrations remain above the MIC of the infecting organism has emerged as a predictor of the efficacy of β-lactam antibiotics. An effective target T>MIC for cefuroxime is considered to be 40% or more of the dosing interval for most bacterial species, except for staphylococcal infections where a T>MIC of 15 to 25% predicts efficacy (Craig, 1997; Craig, 2003; MacGowan, 2004; Bulitta, 2009).

In a comparison of 8 oral cephalosporins (cefuroxime axetil (500 mg twice daily), cefpodoxime proxetil (400 mg twice daily), cefetamet pivoxil (500 mg twice daily), cefixime (400 mg once daily), cefaclor (500 mg 3 times daily) cefprozil (500 mg twice daily), ceftibuten (400 mg once daily) and cefdinir (400 mg twice daily)), Stoeckel, 1995, calculated the length of time that unbound plasma concentrations were above the MIC90 values for *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Only cefuroxime axetil, cefetamet pivoxil and cefpodoxime proxetil were associated with plasma concentrations above the MIC90 for >90% of the time for *S. pneumoniae* and *H. influenzae*. However, against *M. catarrhalis*, the plasma concentration of cefuroxime axetil was above the MIC90 for only <25% of the time.

In healthy volunteers, serum concentrations of cefuroxime axetil (single dose 500 mg) remained above the MIC90 of β-lactamase positive and β-lactamase negative strains of *H. influenzae* for 60% of the recommended dosage interval (Stein, 1997), In an *in vitro* study of cephalosporins, predicted plasma concentrations for cefuroxime axetil was above the mean MIC values for at least 40% of the dosage interval for penicillin-susceptible *S. pneumoniae* (Mason, 2000). Notably in the same study, only cefuroxime (64% of the dosage interval; dosage 15 mg/kg twice daily), cefpodoxime (63%; dosage 5 mg/kg twice daily) and cefprozil (56%; dosage 15 mg/kg twice daily) exceeded the T>MIC of 40% threshold value against *S. pneumoniae* isolates that were intermediately susceptible to penicillin.

In a recent study with healthy volunteers, Bulitta, 2009, evaluated the pharmacodynamics for cefuroxime axetil (250 mg). Robust (>90%) high probabilities of target attainment (PTAs) were achieved by 250 mg cefuroxime given BID for MICs of <0.375 mg/litre or <0.5 mg/litre, respectively, for the bacteriostasis target fT>MIC of >40% and for MICs of <0.094 mg/litre or <0.375 mg/litre, respectively, for the near-maximal-killing target fT>MIC of >65%. High PTA expectation values (>90% for a fT>MIC of 40%) was achieved by oral dosing of 250 mg BID for *S. pyogenes* and penicillin susceptible *S. pneumonia* (Bulitta, 2009). Cefuroxime at 250 mg BID achieved PTAs below 73% or 92%, respectively, for *H. influenzae, M. catarrhalis*, and penicillin-intermediate *S. pneumoniae* for susceptibility data from various countries. The 500 mg BID regimen is expected to provide higher PTA values against penicillin-intermediate *S. pneumonia*, *H. influenza*, 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.

Auckenthaler, 2002, using a combination of microbiological activity and pharmacokinetic characteristics of β-lactam antibiotics calculated the time that serum antibiotic concentrations exceeded the MIC for the major respiratory tract pathogens. The PK/PD modeling in this study indicated that cefuroxime 500 mg BID, exceeded the T>MIC of 40% for *S. pneumoniae* (both susceptible and penicillin-intermediate isolates), *H. influenzae* and *M. catarrhalis.* This data therefore confirms that cefuroxime would be a suitable antibiotic for respiratory tract infections.

The serum bactericidal test is another approach used to estimate antibacterial efficacy through the integration of pharmacodynamic and pharmacokinetic parameters (Stein, 1997). Of 5 oral cephalosporins (cefuroxime, cefpodoxime, cefaclor, cefprozil and loracarbef) evaluated in 10 healthy volunteers, only cefuroxime (single 500 mg dose) and cefpodoxime (single 200 mg dose) achieved serum bactericidal activity for at least 6 hours against β-lactamase positive strains of *H. influenzae*. In contrast, with the exception of cefaclor which showed little bactericidal activity, all cephalosporins showed good bactericidal activity against β-lactamase negative strains of *H. influenzae*. In another study, cefuroxime axetil (single 250 mg dose) demonstrated excellent serum bactericidal activity against *S. pneumoniae* and *S. pyogenes*, but limited activity against *H. influenzae* and *K. pneumoniae* (Dan, 1998). In a further study, cefuroxime achieved serum bactericidal activity for 50% of the dosing interval against penicillin-sensitive *S. pneumoniae*, whereas bactericidal activity was only maintained for 17% of the time against intermediately-susceptible strains of *S. pneumoniae* (Lacy, 1998). *In vitro*, cefuroxime demonstrated serum bactericidal activity against methicillin susceptible *S. aureus* and β-lactamase positive strains of *H. influenzae* for 24 hours, *S. pyogenes* for 6 hours and β-lactamase positive strains of *M. catarrhalis* for 12 hours (Dubois, 2000).

While PK/PD principles are helpful in predicting efficacy, particularly for respiratory tract pathogens such as *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, evidence of clinical and bacteriologic efficacy in clinical trials is the key parameter for assessing efficacy. The pharmacodynamic and pharmacokinetic properties of cefuroxime axetil therefore provide a rationale for activity against target

pathogens, and evidence for the potential activity in the clinical setting has been confirmed in clinical studies.

The MAH presented the clinical and bacteriological success rates from a number of studies using cefuroxime axetil as a standard comparator as part of first registration for many antibiotics, including the quinolones, macrolides and newer generation cephalosporins. The majority of these studies were comparative and many were double blinded. The most common bacterial pathogens isolated were *S. pneumoniae*, *H. influenzae, M. catarrhalis* and *S. aureus*.

Langan, 1998, conducted a large double-blind, randomised multi-national study involving 684 patients, to compare the efficacy of a five day course of cefuroxime axetil (250 mg twice daily, n=340) with a seven day course of clarithromycin (250 mg twice daily, n=344) for the treatment of AECB. A large proportion of patients had co-morbidities, mostly cardiovascular, musculoskeletal or respiratory. By intent-to-treat analysis, post-treatment response to both antibiotics was equivalent with 82% of patients in each group either cured or improved. Similar reductions in symptom severity and increases in peak expiratory flow rate (PEFR) were noted. Of the patients who had a satisfactory clinical response, this improvement was maintained in 77% from each group at follow-up assessment 3 4 weeks post-treatment. Eradication of the pre-treatment pathogen occurred in 73% of evaluable patients treated with cefuroxime axetil (74/102) and 82% of evaluable patients treated with clarithromycin (74/90) at 1-3 days post-treatment. A conclusion of non-inferiority could not be reached. Clinical failure or relapse, with persistence of the original pathogen, was noted in 11% of the cefuroxime axetil group and 9% of the clarithromycin group during the later follow-up assessment.

Vogel, 1997, evaluated sequential therapy with cefuroxime 750 mg i.v. twice or three times daily for 48-72 hours followed by cefuroxime axetil 500 mg twice daily for 5-7 days. 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 three times daily, and 225/255 (88%) of those on the twice daily dosing regimen. In both groups, cure was maintained in approximately 85% of patients at 14-28 days post-treatment. Bacteriologically, 73% of patients were cleared of infection by cefuroxime three times daily and 87% by cefuroxime twice daily. Superinfection occurred in 3% and 1% of patients, respectively, while the original pathogen persisted (treatment failure) in 10% and 7%, respectively.

Alvarez-Sala, 2006, performed a randomised, double-blind, double-dummy trial comparing 200 mg of cefditoren-pivoxil twice daily for 5 days versus standard cefuroxime-axetil treatment (250 mg twice daily for 10 days) of Anthonisen type I or II acute exacerbations of chronic bronchitis. The modified intention-to-treat population included 541 patients. Clinical success was obtained in 80% of the 264 patients included in the cefditoren-pivoxil group and in 83% of the 277 patients in the cefuroxime-axetil group (treatment difference, 95% confidence interval (CI): –2.8, –9.7 to 3.6%). At the end of treatment, exploratory analysis of the per-pathogen bacteriological response showed 72.8% (of 103 isolates) eradication in the cefditoren-pivoxil arm versus 67.0% (of 94 isolates) in the cefuroxime-axetil group (treatment difference; 95% CI: 5.8, –7.0 to 18.6%). Clinical success in patients infected with *Haemophilus influenzae*, the most frequent isolate, was 84% (of 50) and 82.5% (of 40) (treatment difference; 95% CI: 1.5, –14 to 17%) in the cefditoren-pivoxil versus the cefuroxime-axetil group.

Zervos, 2003, conducted a randomised, double-blind, multicentre study evaluating the efficacy and tolerability of telithromycin 800 mg once daily for 5 days vs. cefuroxime axetil 500mg twice daily in the outpatient treatment for acute exacerbations of chronic bronchitis. The study included 376 patients. The per-protocol clinical cure rates at post-therapy/test of cure (days 17–24) were 86.4 and 83.1% for telithromycin and cefuroxime axetil respectively, and 78.6 and 76.5%, respectively, at late post-therapy (days 31–36). Clinical cure rates were comparable for patients at increased risk, including those of ≥ 65 years and those with severe infection or significant airway obstruction. Rates of

bacteriological eradication were similar for the treatment groups 76% for telithromycin vs. 79% for cefuroxime axetil.

Weiss, 2002, conducted a prospective, open-label, randomised study evaluating clarithromycin 500 mg twice daily, levofloxacin 500 mg once daily, and cefuroxime axetil 250 mg twice daily, each administered for 10 days with food, in patients with AECB. A total of 283 patients (150 men, 133 women) with a mean age of 55 years (range, 29 to 86 years) were randomised to receive clarithromycin (n = 97), levofloxacin (n = 94), or cefuroxime axetil (n = 92). The clinical success rate was 88% (80/91) for patients treated with clarithromycin, 87.4% (76/87) for patients treated with levofloxacin, and 79.8% (67/84) for those treated with cefuroxime axetil. Eight (8.8%) clarithromycin-treated patients, 6 (6.9%) levofloxacin-treated patients, and 12 (14.3%) cefuroxime axetil-treated patients required a change in antimicrobial therapy to achieve clinical cure/improvement. No patients treated with clarithromycin required hospitalisation for further antimicrobial treatment, compared with 3.4% (3/87) of levofloxacin-treated and 3.6% (3/84) of cefuroxime axetil-treated patients.

Shah, 1999, performed a randomised, double-blind, double-dummy, three-arm parallel design, multicentre study among adult patients with AECB in order to compare the efficacy and safety of two different doses of levofloxacin with cefuroxime axetil. A total of 832 patients were randomized to receive oral levofloxacin (250 mg OD or 500 mg OD) or oral cefuroxime axetil (250 mg BID) for 7- 10 days. The primary efficacy analysis was based on the clinical response in patients with bacteriologically confirmed AECB, determined 5- 14 days after the end of therapy (per-protocol population). Of 839 patients, 281 received levofloxacin 250 mg, 280 levofloxacin 500 mg and 271 cefuroxime axetil. The cure rates in the intent to treat population were: levofloxacin 250 mg, 70% (196/281); levofloxacin 500 mg, 70% (195/280); cefuroxime axetil, 61% (166/271); those in the per-protocol population were: 78% (121/156), 79% (108/137) and 66% (88/134), respectively.

Van Herwaarden, 2000, conducted a double-blind, randomized, multicentre, parallel- group study in patients with AECB comparing once-daily cefdinir 600 mg, to twice-daily cefdinir 300 mg, to twice-daily cefuroxime axetil 250 mg for 10 days. Of 1045 patients enrolled in the study, 589 were evaluable for efficacy. The microbiological eradication rates by pathogen were 90% with once-daily cefdinir, 85% with twice-daily cefdinir, and 88% with twice-daily cefuroxime. The corresponding values for microbiological eradication rate by patient were 90% (once-daily cefdinir), 85% (twice-daily cefdinir), and 86% (twice-daily cefuroxime). The respective clinical response rates by patient were 81%, 74%, and 80%.

Chodosh, 1998 evaluated 208 patients with microbiologically confirmed acute bacterial exacerbations of chronic bronchitis, randomised to receive either ciprofloxacin or cefuroxime axetil (500 mg twice daily for 14 days). Clinical resolution was achieved at the end of therapy in 90% of the cefuroxime axetil group and 93% of the ciprofloxacin group, a difference which was not statistically significant ($p=0.47$). Bacterial eradication rates were significantly higher for ciprofloxacin (96% vs. 82%, $p<0.01$). The mean infection-free interval was 146 days and 179 days for ciprofloxacin and cefuroxime axetil, respectively. ($p=0.37$), with 51% of ciprofloxacin recipients and 61% of cefuroxime axetil recipients avoiding a relapse during the 36 week follow-up period.

DeAbate, 1996, evaluated cefuroxime axetil (250 mg twice daily for 10 days) and levofloxacin (500 mg four times daily for 5 7 days) in 492 subjects with AECB. The reported clinical success was 92.6% in patients treated with cefuroxime axetil compared with 94.6% treated with levofloxacin. Cefuroxime axetil eradicated 93.5% of *H. influenzae* (29/31), 90.6% of *M. catarrhalis* (29/32) and 100% of *S. pneumoniae* (10/10). The corresponding eradication rates for levofloxacin were 95.5% (42/44), 100% (25/25), and 87.5% (14/16), respectively.

Wilson, 2003 conducted a randomised, open-label, controlled, multicentre study, comparing the clinical and bacteriological efficacy, safety and tolerability of oral gemifloxacin (320 mg once daily,5 days) with sequential iv ceftriaxone (1 g once daily, maximum 3 days) followed by oral cefuroxime axetil (500 mg twice daily, maximum 7 days) in 274 adults who required hospital treatment for AECB. The clinical

success rates at follow-up in the clinical per-protocol population (the primary endpoint) were 86.8% (105/121) for gemifloxacin vs. 81.3% (91/112) for ceftriaxone/cefuroxime. The median time to discharge was 9 days in the gemifloxacin group vs.11days in the ceftriaxone/cefuroxime group. The bacteriological success in the intent to treat population was 81.3% for gemifloxacin compared to 82.4% to the ceftriaxone/cefuroxime group.

The MAH also submitted several smaller, open or single-blinded studies (Gaillat 2001, Camus 1994, Bonnet 1992 and Kleckow 1991) as well as one small double-blinded (Zuck 1999).

Regarding guidelines, the MAH stated that the global initiative for the management of chronic obstructive lung disease (GOLD) had recently updated their consensus guidelines with regards to managing patients with COPD. Reference is made with regard to treating patients with an acute exacerbation of COPD and second generation cephalosporins are recommended as one of the alternative treatment choices in patients classed as having a mild exacerbation requiring antibacterial therapy (group A) (GOLD, 2009). The MAH also provided an overview of the current European national consensus or evidence based guidelines which continue to recommend cefuroxime axetil for the treatment of AECB. The MAH noted that beta-lactam antibiotics such as cefuroxime axetil are generally recommended across many European guidelines as a first-line or second line treatment option for patients with mild to moderate AECB.

The CHMP reviewed the clinical documentation submitted by the MAH, which consisted of four relatively large (>300 patients) double-blinded, comparative studies. The CHMP also noted that the most dominant pathogens in AECB, *H. influenza*, *S. pneumonia*, *S. aureus* and *M. catarrhalis* are susceptible to cefuroxime axetil in vitro. The CHMP was therefore of the opinion that the proposed indication is supported by several adequately designed studies, including comparative studies. In conclusion, the CHMP adopted the following harmonised indication:

"Acute exacerbations of chronic bronchitis"

3) Urinary tract infections (UTI)

The MAH proposed the indication "*Genito-urinary tract infections (e.g., pyelonephritis, cystitis and urethritis)*" and submitted data from eight studies, as well as three studies in paediatric patients. In most of the studies, only patients with cefuroxime-susceptible pathogens were included in clinical and bacteriological analyses, the primary measures of efficacy. Clinical success was generally defined as resolution or improvement in symptoms, during or by the end of treatment. Bacteriological cures included patients in whom the original pathogen was eliminated from the urine, or those who had eliminated the infecting pathogen but who subsequently became re-infected with another organism in the urine, while recurrence of the original pathogen in a urine sample taken after treatment was classified as treatment failure. The MAH acknowledged that the cefuroxime axetil clinical programme was largely conducted in the 1980s but that the comparators used as part of the evaluation of efficacy were considered appropriate at that time.

In a study by Williams, 1987, patients received five days treatment with either cefuroxime axetil (250 mg twice daily, n=152), amoxicillin/clavulanic acid (375 mg three times daily, n=92), or cefaclor (250 mg three times daily, n=39). Two studies were conducted; one in general practice and one in hospital. In the general practice study, clinical signs and symptoms were evaluated prior to treatment and on days 7 and 14. In the hospital study, signs and symptoms were assessed prior to, two to four days after the start of, and five to nine days after the end of treatment. The results of the two studies were pooled for analysis as there were no significant differences between them. Of 140 evaluable patients treated with cefuroxime axetil, 108 were considered clinically "cured" and 28 clinically "improved" (overall 97% success rate), compared to 75/89 (99%) treated with amoxicillin/clavulanic acid and 38/39 (97%) treated with cefaclor. Bacteriological clearance occurred in 73/101 (72%) patients treated with cefuroxime axetil , 43/61 treated with amoxicillin/clavulanic acid (70%) and 27/28 given cefaclor (96%). *E. coli* and other Enterobacteriaceae accounted for 88% of the isolates in the cefuroxime and amoxicillin/clavulanate groups and 90% in the cefaclor group. Seventy-eight out of 105 (74%) *E. coli* and other Enterobacteriaceae were cleared by cefuroxime axetil compared to 48/67 (70%) with amoxicillin/clavulanic acid, and 25/26 (96%) with cefaclor. Superinfections occurred in two

patients treated with cefuroxime axetil (one case of *Candida* spp. and one of *E. coli*) and in four given cefaclor (*P. aeruginosa, Candida* spp*., E. coli*)*.* The authors concluded that five days of cefuroxime axetil was effective therapy for urinary tract infections.

Cox, 1987, compared the efficacy of 10 days treatment with cefuroxime axetil (125 mg twice daily, n=73), cefaclor (250 mg three times daily, n=22) and cephalexin (250 mg four times daily, n=31) in 126 patients, 87 with acute uncomplicated UTIs and 39 with complicated infections. Out of the total patient group, there was one treatment failure, which occurred after discontinuation of cefuroxime axetil due to an adverse event (mouth ulcers and nausea). There was little difference in cure rate between treatment groups with respect to uncomplicated infections (73-79%), but the cure rate for cefuroxime axetil in complicated infections 20/25; 80%) was higher than that obtained with cefaclor 3/7; 43%) or cephalexin (4/7; 57%), though the patient numbers in the latter groups were very small. Amongst the patients with complicated infections, cefuroxime axetil eradicated all 24 pathogens isolated, whereas 1/7 organisms persisted in both the cefaclor and cephalexin groups. Longer-term monitoring at four to six weeks post-treatment indicated a higher recurrence rate in the cephalexin group (30%) compared to cefuroxime axetil and cefaclor (21%).

In a double-blind randomised, multi-centre trial by Vieiralves, 1993, 353 adult patients (age 26-90 years, 254 male, 99 female) with complicated urinary tract infections or acute pyelonephritis and proven bacteruria (105 cfu/mL), were treated with either cefuroxime axetil (250 mg, n=177) or the third generation cephalosporin cefetamet pivoxil (500 mg, n=176 patients) twice daily for five days. Complicating factors included calculi, stricture, prostatectomy, prostatic obstruction, indwelling catheters, neurogenic bladder and diabetes. The most common infecting organisms were *E. coli* (212 isolates), *Klebsiella* spp. (39 isolates) and *Proteus* spp. (.22 isolates). A successful clinical outcome was achieved in 129/154 evaluable patients (83.8%) treated with cefuroxime axetil and in 137/156 evaluable patients (87.8%) treated with cefetamet pivoxil, with a prompt response observed to both treatments. The bacteriological outcome seven to ten days post-therapy was assessable in 310 patients. Bacteriological success, as determined by eradication (<104 cfu/mL at days 2-4 and at the end of treatment) of the initial pathogen and any reinfection, was achieved in 139/154 assessable patients (97.4%) treated with cefetamet pivoxil and in 152/156 (90.3%) treated with cefuroxime axetil.

In a study by Cooper, 1992, 113 male and female patients with dysuria and/or frequency of micturition were treated with a seven-day course of antibiotics, 54 with cefuroxime axetil (125 mg twice daily) and 59 with cephradine (500 mg twice daily). The overall clinical cure rates were 44/54 (81%) for patients treated with cefuroxime axetil and 31/59 (56%) for patients treated with cephradine ($p<0.05$). The bacteriological cure rate (which included reinfections but not relapses, i.e. eradication of original infection), was 97% for both antibiotics at one week post-treatment and 96% at five weeks post-treatment. 89% of infecting organisms were *E. coli*, 7% were *S. saprophyticus*, and there was a single isolate each of *S. epidermidis*, *P. mirabilis* and *K. pneumoniae*. All were susceptible to cefuroxime. Although cefuroxime axetil resolved symptoms better than cephradine, the authors considered both agents to be of equal value in the treatment of simple acute urinary infections in general practice.

In a study by Naber, 1993, 163 patients with typical symptoms of acute uncomplicated lower urinary tract infections such as frequency of micturition, urgency and pain on micturation, and with pyuria, were treated with either cefuroxime axetil, 125 mg twice daily for three days (85 patients, mean age 41 years) or ofloxacin, 100 mg twice daily for three days (78 patients, mean age 37 years). Clinical cure or improvement, was achieved in 56 of 66 (84.8%) and 59 of 62 (95.2%) of evaluable patients treated with cefuroxime axetil and ofloxacin, respectively, at the follow-up visit nine days post-treatment ($p>0.1$). Cure was defined as elimination of clinical symptoms and bacteriuria; improvement was defined as either improvement of clinical symptoms and elimination of bacteriuria or elimination of clinical symptoms and reduction of bacteriuria). Seven to nine days after therapy, bacteriuria had been eliminated (<103 cfu/mL) in 53 of 66 (80.3%) and 57 of 64 (89.1%) of evaluable patients receiving cefuroxime axetil and ofloxacin, respectively ($p>0.1$). There was therefore no statistically significant difference in efficacy between the two treatments. Pathogens with MICs of up to 16 g/mL were successfully eradicated by cefuroxime axetil.

The MAH also submitted non-comparative studies. Bulpitt, 1991, conducted three trials involving 672 female patients with symptoms of cystitis recruited from general practices throughout the UK. 637 patients were clinically evaluable, and 605 completed the seven day course of treatment. Of these, 510 were given cefuroxime axetil 125 mg twice daily (Studies 1 and 2) and 95 were treated with 250 mg twice daily (Study 3). No statistically significant differences in clinical, demographic or adverse event data were found between the three studies. A complete cure was obtained in 466/637 patients, with a further 129 being clinically improved, giving an overall response rate of 93.4%. The condition was unchanged in 5.5% (35/637), worsened in four and was unknown in three (0.5%). Statistical analysis of changes in symptom scores showed a highly significant improvement ($p<0.001$) in all symptoms (fever, dysuria, frequency of micturition, urgency) post-treatment compared with pre-treatment. There was no significant difference in clinical outcome between patients reporting first episode or recurrent infection ($p=0.076$).

In a two-centre study conducted by Adams, 1985, the efficacy of cefuroxime axetil was evaluated in a group of mainly elderly patients (only two <60 years old) with symptomatic urinary tract infections, four of whom were catheterised. In the first centre, 21 patients aged 70-93 years old (mean 80 years), were given oral cefuroxime axetil, either 500 mg twice daily (n=10) or 500 mg three times daily (n=11) five days. In the second centre, a further 13 patients aged 15-91 years old (mean 73 years) were treated similarly, with eight receiving twice daily dosing and 11 receiving treatment three times daily. Patients were stratified into catheterised and non-catheterised categories before randomisation to a treatment regimen. Three patients with cefuroxime-resistant organisms (*P. aeruginosa, K. oxytoca*) or inadequately confirmed bacteriuria were excluded from the efficacy analysis. Of the 31 patients evaluated, 16 (52%) were assessed as clinically cured (resolution of symptoms during the treatment period) and 12 (39%) as clinically improved (incomplete resolution of symptoms during the treatment period), giving an overall clinical response rate of 90%. There was no significant difference between the two treatment regimens. The bacteriological isolates from the 3 patients were *E. coli* (22), *K. aerogenes* (5), *P. mirabilis* (3), and mixed *E. coli/P. mirabilis* (1). MIC determinations indicated that 30 isolates were inhibited by <8 µg/mL of cefuroxime, with only one strain of *K. aerogenes* being relatively resistant (MIC=64 µg/mL). The infecting organisms were eradicated in 27 /31 infections (87%) either during or by the end of therapy. By the one week follow-up (range 5-12 days) the overall short term bacteriological cure rate was 17/31 (55%) with 10 relapses. Two further relapses and two reinfections occurred before the three to six weeks follow-up, leaving 13/31 patients (42%) free of bacteriuria, and 15/31 (48%) cured of their original infection. All the catheterised patients were amongst those who failed to respond, or relapsed. The authors considered that this long-term cure rate was comparable to that obtained with other agents in this age group. The development formulation of cefuroxime axetil used in this study was found to give variable and inconsistent absorption.

The MAH further submitted three studies in paediatric patients. An open, comparative randomised study by Contardi, 1992, evaluated the efficacy cefuroxime axetil in comparison to amoxicillin clavulanate in 50 children with acute non-complicated UTI. Children were treated with cefuroxime axetil 30 mg/kg/day or amoxicillin/clavulanic acid 50 mg/kg/day twice daily for seven days. In the cefuroxime axetil group, 23/25 (92%) children had the infecting organism eradicated, with one treatment failure and one relapse. By comparison, amoxicillin/clavulanic acid eradicated the infection in 24/25 (96%) children, with one treatment failure.

A study by Graham, 1993, Included 15 paediatric patients (aged four to 14 years old) with signs and symptoms of urinary tract infection who were treated with a seven day course of cefuroxime axetil suspension (20 mg/kg twice daily up to 12.5 kg body weight, 125 mg twice daily above 12.5 kg body weight). Each dose was administered after food or a glass of milk. Patients were assessed pre-treatment and at 5-9 days and 4-6 weeks post-treatment. Mid-stream urine specimens were collected for bacteriological analysis on each occasion. At the first post-treatment assessment, 10 patients were cured and four improved (93% clinical success), and there was one clinical failure. Nine patients were available at the later follow-up assessment at which time four remained clinically cured (44%) and five had experienced a recurrence. Before treatment the predominant pathogen was *E. coli* (12 cases), all of which were susceptible to cefuroxime but included four strains resistant to ampicillin. At first follow-up, 13 patients with 15 organisms were evaluable. Eleven out of fifteen (73%) of organisms were cleared, including one *K pneumoniae* and one of *P. mirabilis*. Two patients had become superinfected

with *E. faecalis*. At the second follow-up, only eight patients were evaluated. Seven remained clear of the original infection although two had superinfection/reinfection with *E. faecalis,* and one had relapsed. Re-infection/relapse was not unexpected in this group of patients, as the majority had concurrent conditions or medical history which made them susceptible to UTIs. Pharmacokinetic analysis indicated that urinary concentrations of cefuroxime averaged 19.6-221.2 g/mL over the 12 hour dosage interval, and remained well above the MIC90 of *E. coli* (5 g/mL) for a median of 8.6 hours after dosing.

Finally, a randomised, prospective study by Kornberg, 1994, enrolled 50 children, aged two to 11 years old to compare the efficacy of oral cefuroxime axetil, 125 mg twice daily, given as either a short two day course or a conventional ten-day course, for the treatment of symptomatic bacterial urinary tract infections. Twenty-five patients were clinically evaluable, and 26 bacteriologically evaluable. The remainder were withdrawn from analysis on the basis of the study exclusion criteria, which included: deviation from the protocol, failure to complete post-treatment visits, lack of significant bacteriuria (>105 cfu/mL of urine from clean void or >104 cfu/mL of urine obtained by urethral catheterisation), and urogenital abnormality. Of the 37 pathogens initially isolated, all were sensitive to cefuroxime *in vitro*. *E. coli* predominated, accounting for 32/37 isolates. All patients in the ten-day treatment group (13/13, 100%) became symptom-free compared with 9/12 (75%) in the two-day group, a result that approached statistical significance (p=0.06). Bacteriologically, 12/14 (86%) were successfully treated in the ten-day group (exhibiting a ten-fold or greater reduction in colony count), and 8/12 (67%) were considered a bacteriological success in the two-day treatment group (p=0.26). Two patients in the ten-day group and one in the two-day group were defined as bacteriological successes, were cures with superinfection. Three of the six patients who were bacteriological failures were subsequently found to have previously unsuspected urogenital abnormalities. Overall, in this small sample of patients, both two-day and ten-day courses of cefuroxime axetil were generally effective at eradicating uropathogens in children, but the clinical response rate favoured the longer treatment course with the difference approaching statistical significance.

The MAH also discussed the PK and clinical data supporting the use of cefuroxime axetil in children and pregnant women, stating that several review articles on the management of UTI for children recommend oral cephalosporins as either first or second-line treatment options for acute pyelonephritis in children (Malhotra, 2004; Montini, 2011; Chang, 2006; Wald, 2004). The MAH stated that cephalosporins such as cefuroxime attain good concentrations in the renal parenchyma and urine, and are active against common uropathogens (Scott, 2001). Additionally, cephalosporins such as cefuroxime are considered to have good safety when used in pregnancy. Second generation cephalosporins are recommended in several published review articles as a suitable treatment for acute pyelonephritis in pregnant women (Jolley, 2011; Lane, 2011; Fiadjoea, 2010; Macejko, 2007; Schnarr, 2008). Given the limited availability of safe and effective antibiotics to treat pregnant women with pyelonephritis, the MAH considered that both oral and parenteral cefuroxime would therefore be an appropriate antibiotic treatment choice in geographical areas where the target organisms remain susceptible to cefuroxime.

The CHMP noted that no studies were provided by the MAH regarding urethritis, other than those caused by *N. gonorrhoeae*. The CHMP therefore recommended the removal of the proposed indication "*urethritis*".

The CHMP further noted that most of the studies submitted by the MAH were open label studies conducted in patients with uncomplicated UTI, for which there are more narrow-spectrum antibiotic treatment options. The CHMP also raised concerns that most studies were conducted in the 1980's or early 1990's, as cefuroxime resistance to *E. Coli* and other relevant urinary tract pathogens has emerged in the last decades, which leads to potential therapeutic failure. Nevertheless, the CHMP reviewed the data in support of the indication, noting that the wording in section 5.1 of the SmPC adequately covers the need for regional considerations on the probability of resistant species as pathological agents in patients with UTI. Second generation cephalosporins are included in many European national guidelines for the treatment of urinary tract infections, which reflects current clinical practice based on medical community experience, rather than on old clinical trials data. Although cefuroxime axetil is not the drug of choice, the CHMP agreed that it can be a valuable treatment option for pyelonephritis and cystitis, including in children and pregnant women. In conclusion, based on the

data submitted by the MAH, the CHMP agreed that cystitis and pyelonephritis are acceptable indications and adopted the following harmonised indications:

"Cystitis"
"Pyelonephritis"

4) Gonorrhoea

The MAH proposed the following indication "*Gonorrhoea, acute uncomplicated gonococcal urethritis, and cervicitis*" and stated that several clinical trials have assessed the efficacy of single doses of cefuroxime axetil, both alone and in combination with probenecid, for the treatment of uncomplicated gonorrhoea in substantial numbers of both men and women patients. The MAH provided a summary of these studies (Reichman, 1985, Fong, 1985, Gottileb, 1986, Schift, 1986, Wanas 1986, Das, 1988, Baddour, 1989, Kinghorn, 1990 and Thorpe, 1996). The MAH also discussed a MAH-sponsored study and four published studies comparing cefuroxime axetil with amoxicillin or amoxicillin/clavulanate.

The 1985 study by Baddour included 295 women (18-52 years old) with culture-positive gonococcal infections in a randomised trial comparing the efficacies of single oral doses of cefuroxime axetil (1 g), with the combination of amoxicillin (3 g) plus probenecid (1 g). Microbiological cure rates at four to seven days post-treatment were 136/153 (89.5%) for the cefuroxime axetil group and 132/143 (92.3%) for the amoxicillin/probenicid group. The sites of infection were the cervix, urethra, rectum, pharynx and any combination of genital and/or rectal infections. When examined by site of infection, the data indicated that both regimens were efficacious in clearing gonococcal infections in over 95% of cervical, urethral and rectal sites. In contrast only 15/25 (60.0%) of cefuroxime axetil-treated and 14/22 (63.6%) of amoxicillin with probenecid-treated patients were cured of pharyngeal gonococcal infections. Almost all the strains of *N. gonorrhoeae* isolated were penicillin-susceptible. Three penicillinase-producing strains were obtained from patients who were cured by treatment (cefuroxime axetil 2 cases, amoxicillin/probenecid 1 case) and no treatment failures were associated with penicillinase production.

The 1986 study by Gottileb enrolled 129 homosexual males (age 18 65 years) with culture-positive urethral and/or rectal gonorrhoea, which were treated with single oral doses of cefuroxime axetil (1 g) with or without probenecid (1 g), or amoxicillin (3 g) with probenecid (1 g). One-hundred patients returned for re-examination within four and eight days of treatment. The study suggested that the addition of probenecid increased the efficacy of cefuroxime axetil in the treatment of rectal gonococcal infection.

The 1986 study by Fong enrolled patients with uncomplicated infections of the urethra or cervix, who were randomised to receive single oral doses of cefuroxime axetil (1.5 g) with probenecid (1 g) or amoxicillin (3 g) with probenecid (1 g). Seventy-four patients received cefuroxime axetil and 76 received amoxicillin. Although a single 1 g dose of cefuroxime axetil is recommended for the treatment of gonococcal infections, a 1.5 g dose was used successfully in this trial with acceptable patient tolerance.

The efficacies of cefuroxime axetil and amoxicillin plus clavulanic acid in uncomplicated urogenital and rectal gonorrhoea were compared by Schift, 1986. Cefuroxime axetil (1.5 g) and amoxicillin/clavulanic acid (3 g/0.25 g) were given as single doses with probenecid (1 g). Five-hundred patients were enrolled in the trial, of which 376 were clinically evaluable. Persistent gonorrhoea was found in only 1/107 (0.9%) men and none of 78 (0%) women treated with cefuroxime axetil, compared to 5/108 (4.6%) men and 1/83 (1.2%) women treated with amoxicillin/clavulanic acid (differences not statistically significant).

The 1985 randomised study by Reichman enrolled 184 patients to evaluate the efficacy and safety of a single oral dose of cefuroxime axetil compared with amoxicillin in the treatment of men and women with uncomplicated anogenital gonorrhoea. Sixty-two patients received cefuroxime axetil 1 g alone, 62

received cefuroxime axetil 1 g plus probenecid and 60 received amoxicillin (3 g) plus probenecid. There were seven patients who had pharyngeal gonorrhoea. A total of two patients in the cefuroxime axetil plus probenecid group and three patients in the amoxicillin plus probenecid group were successfully treated. However, in the cefuroxime axetil group alone one of the two patients with pharyngeal gonorrhoea failed to eradicate *N. gonorrhoeae*.

The MAH also submitted data comparing the efficacy and safety of single-dose oral treatments with cefuroxime axetil and ciprofloxacin in a total of 832 male and female patients with uncomplicated gonorrhoea or a history of exposure to infection (Thorpe 1996). Four hundred and seventeen were treated with cefuroxime axetil (1 g), and 415 with ciprofloxacin (500 mg). Specimens for the isolation of *N. gonorrhoeae* were obtained from the urethra, pharynx and when possible the rectum for male patients, and from the endocervix, pharynx and rectum of female patients. Follow-up cultures were carried out four to eight days post-treatment, with the primary bacteriological efficacy endpoint being eradication of gonococci from the urethra and cervix, in males and females respectively. Two hundred and thirty seven out of 434 female patients and 337 out of 398 male patients were considered bacteriologically evaluable. Most of the remainder either failed to return for follow-up, or initial cultures proved negative. Fifteen per cent of cervical infections and 20% of urethral infections in males were caused by penicillinase-producing *N. gonorrhoeae* (PPNG). The authors concluded that single oral doses of cefuroxime axetil and ciprofloxacin were equally effective at eradicating PPNG from males and females with uncomplicated cervical or urethral gonorrhoea and in eradicating all stains of *N. gonorrhoeae* from the cervix. Cefuroxime axetil was, however, significantly less effective than ciprofloxacin in treating urethral and pharyngeal infections in male patients, although the number with pharyngeal infection was small.

The MAH submitted further data comparing cefuroxime axetil with other antibiotics, including two studies sponsored by the MAH. In the first, a study by Wanas, 1986, 110 men and 30 women with gonococcal infections were treated with either a single oral dose of cefuroxime axetil (1.5 g) and probenecid (1 g) or ampicillin (3 g) and probenecid (1 g). Gonorrhoea was cured in 66/67 (98.5%) evaluable patients given cefuroxime axetil. In the second, by Kinghorn, 1990, the efficacy of single dose cefuroxime axetil was compared with that of single dose intramuscular procaine penicillin (PP) in a randomised, open-label study of 311 patients presenting with uncomplicated gonococcal infection, confirmed microscopically or by culture. A total of 174 men and 137 women were enrolled in the study, and were randomised sequentially to cefuroxime axetil (1 g orally) or PP (2.4 Mu intramuscularly in two injections). At follow-up, 2-15 days after treatment, cure rates with cefuroxime axetil were 98.7% (77/78) for males and 98.1% (52/53) for females (overall cure rate 98.5%), compared to 97.3% (72/74) for males and 100% (55/55) for females (overall cure rate 98.4%) treated with PP. Of the two patients who appeared to fail cefuroxime therapy, re-infection was considered likely in one case, while in the other, gonococci were successfully eradicated from the urethra and cervix but persisted in the pharynx.

The study by Das, 1988, compared the efficacy of cefuroxime axetil alone with ampicillin plus probenecid for the treatment of uncomplicated gonococcal infections in 81 men and women. Patients with acute gonococcal infections were randomised in a ratio of 2:1 to receive either a single dose cefuroxime axetil of 1 g or ampicillin 3 g plus probenecid 1 g. Clinical and bacteriological assessment were conducted before treatment and a week after treatment. 54 patients were treated with cefuroxime and 27 patients were treated with ampicillin plus probenecid. Of the patients with urethral gonorrhoea, 96% of patients in both treatment groups were successfully treated. All patients with anogenital gonorrhoea were successfully treated with both regimens. Five patients in the study had pharyngeal gonorrhoea, two in the cefuroxime group and three in the ampicillin probenecid group. Of these patients one and two patients in the cefuroxime and ampicillin plus probenecid treatment groups were treatment failures. Four patients in the study had gonorrhoea caused by PPNG strains, all were in the cefuroxime group and all were successfully treated.

The CHMP considered the efficacy of cefuroxime axetil in gonorrhoea to be highly questionable and consequently, treatment with cefuroxime axetil might not curtail further transmission of the infection. Based on the data submitted by the MAH, the CHMP was of the view that uncomplicated gonorrhoea

(urethritis and cervicitis) is not a suitable indication for this product. The CHMP also noted that the recent European guidelines (2009 European (IUSTI/WHO) Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults) do not include cefuroxime on the list of antibiotics recommended in this indication. There is specific statement in the guidelines that the pharmacokinetics of cefuroxime axetil (1 g oral) is suboptimal as a single dose treatment The main concern about cefuroxime are its inferior (as compared to ceftriaxone and cefixime) PK/PD characteristics which may lead to worse effectiveness and to the selection of the resistant bacteria strains (Aison et al, 2004).

In conclusion, the CHMP recommended the removal of the proposed indication "*gonorrhoea, acute uncomplicated gonococcal urethritis, and cervicitis*" from the harmonised SmPC.

5) Skin and soft tissue infections

The MAH proposed the following indication "*Skin soft tissue infections (e.g., furunculosis, pyoderma and impetigo)*" and submitted data from one double blind and several randomised, comparative and open labelled studies.

Bucko, 2002, conducted a double blind comparative, multicentre study comparing the efficacy and tolerability of cefditorin 200 mg or 400 mg BID and cefuroxime 250 mg BID for 10 days in patients (aged ≥12 years) with uncomplicated SSTI. The test-of-cure visit was 7-14 days after treatment completion. A total of 857 patients were enrolled in the study (291 and 283 patients received cefditorin 200 mg and 400 mg, respectively, and 283 patients received cefuroxime 250 mg). Cellulitis (28%), wound infection (25%) and simple abscess (17%) were the most common skin infections. Approximately 50% of patients had a pre-treatment pathogen isolated. The most common pathogen isolated was *S. aureus*. Clinical cure rates at the test-of-cure visit were 84% for cefditoren 200 mg group, 84% for cefditorin 400 mg group and 88% for the cefuroxime axetil treatment group. The corresponding microbiological eradication rates were 81%, 85% and 89%, respectively. The eradication rates for *S. aureus* and *S. pyogenes*, respectively, were 83% and 90% for the cefditoren 200 mg group, 87% and 90% for the cefditoren 400 mg group, and 88% and 100% for the cefuroxime group.

In a multi-centre study by Gooch, 1991, a total of 330 patients with mild to moderate infections of the skin or skin structure (furunculosis, cellulitis, impetigo, folliculitis, carbunculosis, injury-induced wound) were randomised to receive cefuroxime axetil (250 mg, n=107), cephalexin (500 mg, n=111), or cefadroxil (500 mg, n=112), twice daily for 10 days. In the 64% of patients who were bacteriologically evaluable, the primary pathogens were identified as *S. aureus*, coagulase-negative *staphylococci* and *S. pyogenes*. A satisfactory clinical response (defined as resolution of clinical symptoms and healed lesions at one to three days after treatment or resolution of clinical symptoms, but incomplete healing of lesions at one to three days after treatment) was achieved in 97% (89/92) of evaluable patients treated with cefuroxime axetil, 89% (80/90) treated with cephalexin and 94% (82/87) treated with cefadroxil. The difference between cefuroxime axetil and cephalexin was statistically significant (p=0.047). Out of 211 bacteriologically evaluable patients, cefuroxime axetil produced a significantly higher satisfactory response rate (cure or presumed cure) than cephalexin (95.8% vs. 84.5%, p=0.026). The difference between cefuroxime axetil and cefadroxil (95.8% vs. 92.6%) was not statistically significant.

In another randomised, open-label, multi-centre trial (Parish, 1987) the efficacy of cefuroxime axetil (250 mg or 500 mg twice daily) and cefaclor (250 mg three times daily) were compared in 125 adolescent and adult out-patients. Conditions treated included pyoderma, impetigo, cellulitis, carbuncle, folliculitis and infected wounds, with 80% being confirmed bacteriologically. 82% of infections were attributed to Gram-positive cocci, including penicillin-resistant *S. aureus*. Both drugs were administered for 10 days, with the final assessment being carried out within three days of completing treatment. The clinical cure in the cefuroxime 250 mg group was 81% (30/37). Comparative figures for the higher dose of cefuroxime axetil were 90% cure, 5% improvement and 5%, failure, while in the cefaclor group these were cure in 81%, improvement in 16% and failure in 3%, respectively. There was no significant difference between treatments with respect to clinical outcome. Bacterial eradication was achieved with 93% of Gram-positive isolates in each cefuroxime axetil group, and 97% in the

cefaclor group. The difference was not significant, and no patients became superinfected in any group. Nineteen patients with mixed infections all responded to their allocated therapy.

Jacobs, 1992, conducted a randomised, single-blind, multi-centre study to compare the efficacy of cefuroxime axetil suspension and cefadroxil for the treatment of SSTIs in paediatric patients. Children aged 3 months to 12 years presenting with impetigo, cellulitis, paronychia, pyoderma, wound infection or other skin/skin structure infections were randomised in a 2:1 distribution to receive 10 days treatment with either cefuroxime axetil suspension (125 mg/5 mL) at 30 mg/kg/day in two divided doses (n=189), or cefadroxil suspension at the same dose (n=98). *S. aureus* and *S. pyogenes*, or a mixture of both organisms, were the primary pathogens isolated from infected skin lesions. Patients were withdrawn if no pathogen was isolated, if the infecting organism proved resistant to study medication, or for protocol violations. One hundred and fifty-six patients in the cefuroxime axetil group and 82 in the cefadroxil group were clinically and bacteriologically evaluable. In these patients, a clinical cure rate of 95.7% was obtained with cefuroxime axetil and 90.3% with cefadroxil, the difference was not statistically significant. The rate of recurrence was higher in the cefadroxil group (8.3% vs. 2.2%). There was no statistically significant difference in satisfactory bacteriological response rate (cure or presumed cure) between the two treatments (97.8% and 94.3% for cefuroxime axetil and cefadroxil respectively; p=0.242). This study extends the data presented in an earlier publication by the same group (Jacobs, 1990).

In a pilot study, a five day course of cefuroxime axetil (250 mg or 500 mg twice daily) was administered to 195 adult patients with mild to moderate skin and soft tissue infections presenting to general practitioners, in the UK, and compared with the standard dose of amoxicillin/clavulanate (375 mg three times daily) (Watts, 1987). A positive clinical response (cure or improvement) was obtained in 96% (56/58) of patients treated with cefuroxime axetil at the 250 mg dose, 96% (55/57) at the 500 mg dose, and 98% (55/66) of those treated with amoxicillin/clavulanate. The remaining patients were unassessable. Positive bacteriology was obtained from 63/80 (79%) of pre-treatment swabs, but only 35 patients were bacteriologically assessable. Of the evaluable patients, 7/11 (63%) treated with cefuroxime axetil 250mg, 8/12 (67%) treated with cefuroxime axetil 500 mg, and 10/12 (83%) treated with amoxicillin/clavulanate were bacteriologically cured. The differences in bacteriological cure rates observed amongst the small sample of patients evaluated (<20%) were not considered significant.

Two non-comparative studies were also submitted (Gudgeon, 1989; Perry, 1996), where cefuroxime axetil was given as 250 mg BID, for seven days.

The CHMP agreed that the bacterial species most frequently involved in SSTIs (i.e. staphylococci and streptococci) are sensitive to cefuroxime. However, cefuroxime has no activity against MRSA. The comparators in the clinical studies submitted were, with one exception (Watts, 1987), other cephalosporins, and not beta-lactamase stable penicillins, which is a limitation. First generation cephalosporins are frequently used in the treatment of uncomplicated SSTIs. Based on the results from one double blind study and several supporting studies, the CHMP concluded that there is sufficient data in support of this indication. However, as all studies were conducted in uncomplicated skin and soft tissue infections, and the primary pathogens were Gram-positive, the CHMP considered the proposed indication to be acceptable. In conclusion, the CHMP adopted the following harmonised indication:

"*Uncomplicated skin and soft tissue infections"*

6) Lyme disease

The MAH proposed the following indication "*Treatment of early Lyme disease and subsequent prevention of late Lyme disease in adults and children over 12 years old* and provided data from five randomized studies to support the indication.

In a study by Nadelman, 1992, a total of 123 patients with physician-documented erythema migrans participated in a randomised, single blind, multicentre comparison of 20 days treatment with cefuroxime axetil (500 mg twice daily, n=63) or doxycycline (100 mg three times daily, n=60) (Nadelman 1992). One failure and three recurrences occurred with cefuroxime axetil, compared to four failures and two recurrences with doxycycline. Eighty-six of the 96 patients with successful clinical outcomes were available for evaluation one year after treatment. At this time point, 90% of those from the cefuroxime axetil group and 92% from the doxycycline group had maintained satisfactory clinical outcomes and did not develop symptoms of late Lyme disease. The incidence of Janisch-Hexheimer reactions (a transient immunological reaction resulting from the bacteriocidal activity of antibiotics against *B. burgdorferi*) was approximately three times higher in the cefuroxime axetil group (28.6% vs. 8.3%; p=0.005), but these reactions were transient, usually lasting one to two days, and did not lead to any withdrawals from the study.

In order to confirm results from the study by Nadelman, Luger conducted a second randomised, single blind, which used the same methodology as the Nadelman study, but involved more study centres with a larger number of patient (Luger 1995). Two hundred and thirty two patients were treated with either cefuroxime axetil (n=119) or doxycycline (n=113). Of the 194 patients who were clinically evaluable, 90/100 (100%; 95% CI 84 -96%) and 89/94 (95%; 95% CI 90-99%) of those treated with cefuroxime axetil and doxycycline respectively, had a satisfactory outcome (success or improvement) at one month post treatment. Seven patients in the cefuroxime axetil group (four clinical recurrences) and four in the doxycycline group (one clinical recurrence) failed to respond. One hundred and eighteen of the 189 responders were evaluable after 1 year. At this time point, 62/65 (95%) of cefuroxime axetil-treated patients and 53/53 (100%) doxycycline-treated patients had a satisfactory outcome. The three cefuroxime axetil patients who became clinical failures during the one year follow-up period experienced a variety of late Lyme disease symptoms including arthritis, arthralgia, cognitive dysfunction and headache. Significantly fewer patients treated with cefuroxime axetil reported adverse effects (17% vs. 28%; p=0.041). Transient (lasting 1-2 days) Janisch-Hexheimer reactions occurred in 12% of patients in each treatment group.

Arnez, 1995 conducted a randomised trial compared the efficacy of cefuroxime axetil with that of phenoxymethylpenicillin in the treatment of 90 children (<15 years of age) with erythema migrans. Cefuroxime axetil 30 mg/kg/day (administered as a divided daily dose; maximum dose 1000 mg/day) for 14 days was as effective as 14 days treatment with phenoxymethylpenicillin 100 000 IU/kg/day (administered as 3 divided doses; maximum dose 3 million IU/day) in children with erythema migrans associated with early stage Lyme disease. The respective duration of erythema migrans in these 2 treatment groups was 7.1 and 10.6 days, with all patients in both treatment groups remaining free of symptoms at 12 months follow-up. Although more cefuroxime axetil recipients had Jarisch-Herxheimer's reactions than patients receiving phenoxymethylpenicillin (11 vs. 5 patients), this difference was not statistically different.

Eppes (2002) conducted a randomised, open study comparing 2 dosage regimens of cefuroxime axetil (20 mg/kg/d and 30 mg/kg/d) with amoxicillin (50 mg/kg/ each given for 20 days in 43 children (6 months to 12 years of age) with early Lyme disease (erythema migrans). Follow-up evaluations for safety, tolerability, and efficacy occurred at 10 and 20 days, 6 months, and 1 year. At the completion of treatment, there was total resolution of erythema migrans in 92% of the low-dose cefuroxime group, and 87% of the high-dose cefuroxime group compared with 67% in the amoxicillin group. Resolution of constitutional symptoms occurred in, 69%, 87% and 100%, of the treatment groups, respectively. All patients had a good outcome, with no long-term problems associated with Lyme disease. Janisch-Hexheimer reactions were suspected by study physicians for one amoxicillin and one low-dose cefuroxime recipient, although neither had a skin eruption.

Cerar (201) conducted a European, randomised, open, prospective clinical trial comparing cefuroxime axetil and doxycycline in 295 adult patients with erythema migrans. The study also included a control group. Patients were assessed at baseline, 14 days, and 2, 6, and 12 months after enrolment. Control subjects were evaluated at baseline and at 6 and 12 months. Subjective symptoms that newly

developed or intensified since the onset of erythema migrans or the date of enrolment for controls were referred to as “new or increased symptoms”. Cefuroxime axetil and doxycycline had comparable efficacy. At both 6 and 12 months, the frequency of new or increased symptoms in patients with erythema migrans did not exceed the frequency of such symptoms in a control group of individuals of similar gender and age without a clinical history of Lyme disease. At 12 months after enrolment, 95% patients in both treatment groups had no symptoms. Additionally, there were only two patients that were considered treatment failures both in the doxycycline group.

The MAH concluded that a 15 to 21 day course of treatment with cefuroxime axetil at 500 mg twice daily in adults and 30 mg/kg/day (given as two divided doses) in children has proved successful therapy for early Lyme disease and for the prevention the development of late Lyme disease in adults and children. The clinical data have demonstrated that in early Lyme disease, cefuroxime axetil is of similar efficacy to doxycycline and amoxicillin, with a high proportion (88-95%) of patients having a positive response at one month post-treatment, and between 90% and 100% of these remaining clinical symptom-free over the one-year follow-up period. Additionally, cefuroxime axetil is effective in that less than 10% fail treatment which is of importance in the management of Lyme disease (Corapi, 2008). Cefuroxime axetil has advantages over amoxicillin and doxycycline in that it can be given twice daily. The MAH noted that the efficacy of cefuroxime axetil as a treatment for early and late Lyme disease is recognised in the published literature. Cefuroxime axetil is also recommended by The European Union Concerted Action on Lyme Borreliosis, as one of the preferred treatment choices for Lyme disease in adult and paediatric patients (EUCALB, 2010). Furthermore, many European Societies also recommend cefuroxime axetil for the treatment of Lyme disease in adults and children.

The CHMP reviewed the data from five randomised controlled studies submitted by the MAH, two of which included patients aged >12 years(Nadelman 1995; Lugar 1995), one which included patients aged >15 years (Cerar 2010), one study including children aged < 15 years (Arnez 1995) and one study including children aged between 6 months - 12 years. The efficacy of cefuroxime for the treatment of Lyme disease was compared with amoxicillin, doxycycline and penicillin V and was shown to be comparable with all these comparators, which are considered as drugs of choice for treatment of Lyme diseases in many countries. Based on the submitted study data, the CHMP considered the indication for Lyme disease to be acceptable. However, the CHMP considered the claim for “subsequent prevention of late Lyme disease” to be redundant. In conclusion, the CHMP adopted the following harmonised indication:

“Treatment of early Lyme disease”

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

“Zinnat is indicated for the treatment of the infections listed below in adults and children from the age of 3 months (see sections 4.4 and 5.1).

- *Acute streptococcal tonsillitis and pharyngitis.*
- *Acute bacterial sinusitis.*
- *Acute otitis media.*
- *Acute exacerbations of chronic bronchitis.*
- *Cystitis.*
- *Pyelonephritis.*
- *Uncomplicated skin and soft tissue infections.*
- *Treatment of early Lyme disease.*

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

Section 4.2 - Posology and method of administration

The MAH presented a proposed harmonised posology, based on a review of the available data. The MAH stated that in healthy volunteers, serum concentrations of cefuroxime axetil (single dose 500 mg)

remained above the MIC90 of β-lactamase positive and β-lactamase negative strains of *H. influenzae* for 60% of the recommended dosage interval (Stein, 1997). In an in vitro study of cephalosporins, predicted plasma concentrations for cefuroxime axetil was above the mean MIC values for at least 40% of the dosage interval for penicillin-susceptible *S. pneumoniae* (Mason, 2000). Notably in the same study, only cefuroxime (64% of the dosage interval; dosage 15 mg/kg twice daily), cefpodoxime (63%; dosage 5 mg/kg twice daily) and cefprozil (56%; dosage 15 mg/kg twice daily) exceeded the T>MIC of 40% threshold value against *S. pneumoniae* isolates that were intermediately susceptible to penicillin. The MAH considered that the PK/PD principles indicate that for the paediatric dose of cefuroxime axetil, 30 mg/kg/day in children given BID the T>MIC exceeds 40% for *S. pneumoniae* (both susceptible and penicillin intermediate isolates), *H. influenzae* and *M. catarrhalis* and is expected to provide efficacy for organisms with MICs up to and including 1 µg/mL (Dagan, 2003). Cefuroxime axetil is principally used for community acquired infections. The likely indications where Enterobacteriacae such as *E. coli* will be isolated are in uncomplicated urinary tract infections. For this indication high urinary concentrations are achieved and these are usually above MICs of the infecting uropathogens (Scott, 2001). The current susceptibility breakpoint from EUCAST, for cefuroxime axetil (for uncomplicated urinary tract infections) is 8 µg/mL. The commonly used dosing regimen of cefuroxime axetil for the treatment of urinary tract infections given BID is therefore expected to provide efficacy for organisms with MICs up to and including 8 µg/mL. The MAH acknowledges that PK/PD principles are helpful in predicting efficacy; however, evidence of clinical and bacteriologic efficacy in clinical trials is the key parameter for assessing efficacy.

The CHMP noted the MAH proposal and agreed that the clinical and PK/PD data confirm that a twice daily regimen of cefuroxime axetil is an effective dosage and that the use of cefuroxime axetil given three times daily is unsupported by the clinical and safety data. 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 CHMP noted that according to the population PK modelling using Monte Carlo (MC) simulations developed by Bullitta et al (2009), robust high PTAs (>90%) were achieved by 250 mg cefuroxime given every 12 h or every 8 h for MICs of ≤0.375 mg/L or ≤0.5 mg/L, respectively for bacteriostasis target (%T>MIC: 40%), and for MICs of ≤0.094 mg/L or ≤0.375 mg/L, respectively, for the near maximal killing target (%T>MIC: 65%). Oral cefuroxime (250 mg q12 h or q8h) achieved high PTAs for *S. pyogenes* (≥96.7%) and penicillin-susceptible bacteria (≥91.4%). However, cefuroxime axetil at 250 mg q12h and q8h achieved PTAs below 73% and 92%, respectively, for penicillin-intermediate *S. pneumonia* (PISP), *M. catarrhalis* and *H. influenza* for most studied MIC distributions for various countries. MC simulations showed that administering cefuroxime axetil 250 mg or 500 mg q8h yielded notably higher PTAs for some but not all MIC distributions of *H. influenzae* and *M. catarrhalis* while still very low PTAs (i.e. far below the PK/PD targets) were achieved for PISP. The CHMP therefore concluded that the 250 mg q12h dosing regimen would cover most infections caused by *S. pyogenes* and penicillin-susceptible *S. pneumonia*. However, much higher doses (i.e. 500 mg q12h or q8h) seem to be necessary to treat less susceptible species. Increasing the dose of cefuroxime axetil to 500 mg q8h is not be recommended due to the lack of safety data and concerns on the potentially toxic degradation products of axetil. However, for the treatment of severe infections such as AECB, the CHMP considered that it would be most appropriate to administer larger parenteral doses of cefuroxime and therefore agreed that infections suspected or proven to be due to less susceptible bacterial species (such as penicillin intermediate *S. pneumonia*, *M. catarrhalis* and *H. influenzae*) should be treated with 500 mg administered every 12 hours.

For cystitis, the MAH proposed a posology of 125 mg BID for adults and paediatric patients ≥ 40 kg and 10 mg/kg BID up to 125 mg BID for paediatric patients < 40 kg, based on PK/PD and clinical data for UTI in adults and children. For more severe infections, the proposed posology was 15 mg/kg BID (250 mg daily up to 500 mg twice daily). For pyelonephritis, the MAH proposed a dosage of 250 mg BID in adults and 15 mg/kg BID (250 mg daily up to 500 mg twice daily) for children. According to Scott et al (2001), high urinary concentrations of cefuroxime are achieved since it is excreted unchanged approximately 50% in urine. However, there is no data estimating or simulating the actual cefuroxime concentrations achieved in urine at any time, following oral administration. The clinical trials in uncomplicated UTIs, in which the dose of 125 mg q12h was used, were performed in 1990s or earlier. The CHMP therefore raised concerns, based on the available data and on the PK/PD profile of cefuroxime axetil, on the adequacy of the proposed dosing regimen, especially considering the reduced susceptibility to Enterobacteriaceae which concern the most relevant pathogens in UTIs. In 2008 the EUCAST increased the MIC breakpoint for Enterobacteriaceae from 4 ug/mL to 8 ug/mL. Consequently, the CHMP recommended an adult dosing regimen for cystitis of 250 mg BID, as this dose will ensure

that adequate urinary concentrations of cefuroxime are achieved, which in turn will ensure key uropathogens implicated in urinary tract infections are appropriately eradicated. Similarly, the CHMP recommended a dosage in children of 15 mg/kg BID (250 mg twice daily up to 500 mg daily).

For Lyme disease, the CHMP noted that the proposed dosage in adults and children over 12 years is 500 mg twice daily for 20 days but also noted that the existing clinical data shows that treating early Lyme disease for 12 and up to 21 days was an effective treatment regimen. The CHMP also noted the recommendation proposed by the European Union Concerted Action on Lyme Borreliosis (EUCALB), which recommend a cefuroxime treatment regimen of 14 days (range of 10 to 21 days) (EUCALB, 2010). The CHMP therefore agreed on a cefuroxime treatment regimen of 14 days (range of 10 to 21 days). The CHMP considered that this treatment duration was also adequate for the paediatric population. With regard to the posology in children, the CHMP noted the MAH review of the literature data, including published guidelines, supporting the proposed dosing of cefuroxime axetil in Lyme disease in children. The MAH referred to the published literature (Arnez, 1999 and Eppes, 2002) together with consensus and evidence based International, European and national guidelines recommending cefuroxime axetil at a dose of 30 mg/kg/day for 14 days. The MAH stated that it had not conducted any no clinical trials using a dosing regimen of 40 mg/kg/day in two divided doses for any indication and that this dosing regimen could therefore not be endorsed due to the lack of safety data in children. The CHMP noted the MAH proposal and reviewed the two randomized studies provided by the MAH. However, the CHMP considered that the MAH proposal was not in agreement with the recommendation by the European Union Concerted Action on Lyme Borreliosis (EUCAIB), which recommends a cefuroxime treatment regimen of 30-40 mg/kg 14 days (range of 10 to 21 days) for children (EUCALB, 2010). In conclusion, the CHMP agreed that the dosage for paediatric patients with Lyme disease should be 15 mg/kg twice daily to a maximum of 250 mg twice daily for 14 days (10-21 days).

The section on paediatric patients was revised extensively, including a revision of the table of dosing recommendations for children below 40 kg to describe dosage and duration per indication and including the dosing calculations depending the on patient's body mass. The guideline tables for simplified administration were also revised.

The CHMP agreed on a cut-off age for the product of 3 months for children, stating that there is no experience of using Zinnat in children under the age of 3 months.

In conclusion, the CHMP adopted the following harmonised posologies for adults and children:

"Posology

The usual course of therapy is seven days (may range from five to ten days).

Table 1. Adults and children (≥40 kg)

Indication	***Dosage***
Acute tonsillitis and pharyngitis, acute bacterial sinusitis	*250 mg twice daily*
Acute otitis media	*500 mg twice daily*
Acute exacerbations of chronic bronchitis	*500 mg twice daily*
Cystitis	*250 mg twice daily*
Pyelonephritis	*250 mg twice daily*
Uncomplicated skin and soft tissue infections	*250 mg twice daily*
Lyme disease	*500 mg twice daily for 14 days (range of 10 to 21 days)*

Table 2. Children (<40 kg)

Indication	*Dosage*
Acute tonsillitis and pharyngitis, acute bacterial sinusitis	*10 mg/kg twice daily to a maximum of 125 mg twice daily*
Children aged two years or older with otitis media or, where appropriate, with more severe infections	*15 mg/kg twice daily to a maximum of 250 mg twice daily*
Cystitis	*15 mg/kg twice daily to a maximum of 250 mg twice daily*
Pyelonephritis	*15 mg/kg twice daily to a maximum of 250 mg twice daily for 10 to 14 days*
Uncomplicated skin and soft tissue infections	*15 mg/kg twice daily to a maximum of 250 mg twice daily*
Lyme disease	*15 mg/kg twice daily to a maximum of 250 mg twice daily for 14 days (10 to 21 days)*

There is no experience of using Zinnat in children under the age of 3 months."

The CHMP also noted that cefuroxime axetil suspension formulation is not bioequivalent to the tablet formulation. Whereas the tablet form releases the drug into the stomach, the suspension releases cefuroxime axetil into the upper small intestine. This gives rise to differences in bioavailability and the time-concentration curve. The CHMP inserted a statement advising that the tablets and the granules for oral suspension are not bioequivalent and are not substitutable on a milligram-per-milligram basis.

Sequential therapy

The CHMP raised concerns over the MAH proposal for the use of Zinnat 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. influenza*, 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. 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

Regarding patients with renal impairment, the CHMP requested further substantiation to confirm the optimal regimen with regard to safety and efficacy in these patients. The MAH stated that the proposed dosing recommendations were based on the evaluation of cefuroxime pharmacokinetics in healthy subjects and in patients with varying degrees of renal impairment following oral dosing of cefuroxime axetil (Konishi, 1993; Höffler, 1991).

Konishi, 1993, evaluated the pharmacokinetics of cefuroxime axetil following a single oral dose of 500 mg cefuroxime axetil in 28 subjects aged between 20 and 79 years with normal and impaired renal function. The mean serum elimination half-life was 1.4, 2.4, 4.6 and 16.8 hours in subjects with creatinine clearance values of >85, 50-84, 15-49 and <15 mL/minute/1.73m2, respectively. Using the significant positive correlation (r=0.883, p<0.01) established between the elimination rate constant (Kel) and creatinine clearance (CLcr) (i.e., Kel (hr-1) = 0.0046 x CLcr +0.0108) derived in this study, a CLcr cut-off value of 30 to 50 mL/min/1.73m2 would predict cefuroxime elimination half-lives of approximately 2.9 to 4.6 hours, which would not require dose adjustment since the safety and efficacy of cefuroxime is well-established following both oral and intravenous dosing. Based on the results from this study it was concluded that dosage modification would not be required in elderly patients or in patients with mild to moderate renal impairment for whom creatinine clearance values are ≥ 30 mL/min/1.73m2. However, for patients with severe renal impairment (creatinine clearance values < 30 mL/min/1.73 m2) prolongation of the dosage interval may be required. With the dosing regimen recommended, the predicted steady-state Cmax and Cmin would be 10.2-13.6 µg/mL and 0.2-3.5 µg/mL, respectively, in subjects with CLcr between 100 and 10 mL/min/1.73m2. With a 500 mg oral dose of cefuroxime axetil given every 48 hours, the predicted steady-state Cmax and Cmin would be 10.8 µg/mL and 0.7 µg/mL, respectively, when the CLcr is 10 mL/min/1.73m2.

Höffler, 1991, performed a study in 16 adult patients with end-stage renal disease, eight on haemodialysis and eight during a dialysis free interval. Each patient received a single 250 mg tablet of cefuroxime axetil. The terminal elimination half-life increased from approximately 90 minutes in healthy subjects (Finn, 1987; Harding, 1984; Williams, 1984) to more than 20 hours in the patients with renal failure not undergoing dialysis. In those patients undergoing haemodialysis, substantial amounts of cefuroxime were removed by the dialysis process such that the half-life decreased to approximately 2 hours, the same order of magnitude as in normal subjects. Since at least 60% of the dose is removed by haemodialysis, the authors suggested that cefuroxime axetil should be administered following this treatment.

Cefuroxime is not metabolised and is eliminated primarily by the kidneys. Therefore, the elimination half-life of cefuroxime has been shown to increase progressively as renal function declines (Konishi, 1993; Höffler, 1991; Bundtzen, 1981; Kosmidis, 1977; Walstad, 1983; Davies, 1991). The pharmacokinetics of cefuroxime was evaluated following a single oral dose of 500 mg cefuroxime axetil in 28 subjects aged between 20 and 79 years with normal and impaired renal function (Konishi, 1993). The mean serum elimination half-life was 1.4, 2.4, 4.6 and 16.8 hours in subjects with creatinine clearance values of >85, 50-84, 15-49 and <15 mL/minute/1.73m2, respectively. Using the significant positive correlation (r=0.883, p<0.01) established between the elimination rate constant (Kel) and creatinine clearance (CLcr) (i.e., Kel (hr-1) = 0.0046 x CLcr +0.0108) derived in this study, a CLcr cut-off value of 20 mL/min/1.73m2 would predict a cefuroxime elimination half-life of approximately 6.7 hours which would require dose adjustment**.** Based on the results from this study the MAH concluded that dosage modification would not be required in elderly patients or in patients with mild to moderate renal impairment for whom creatinine clearance values are ≥ 30 mL/min/1.73m2. However, for patients with severe renal impairment (creatinine clearance values < 30 mL/min/1.73 m2) prolongation of the dosage interval may be required.

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 Zinnat in renal impairment

Creatinine clearance	***$T_{1/2}$ (hrs)***	***Recommended dosage***

≥30 mL/min/1.73 m²	*1.4–2.4*	*no dose adjustment necessary (standard dose of 125 mg to 500 mg given twice daily)*
10-29 mL/min/1.73 m²	*4.6*	*standard individual dose given every 24 hours*
<10 mL/min/1.73 m²	*16.8*	*standard individual dose given every 48 hours*
Patients on haemodialysis	*2–4*	*a further standard individual dose should be given at the end of each dialysis*

Hepatic Impairment

Regarding patients with hepatic impairment, the CHMP noted and agreed with the MAH proposal, which states that there is no available data: "*There are no data available for patients with hepatic impairment. Since cefuroxime is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on the pharmacokinetics of cefuroxime*."

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. 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 precaution for use

The MAH reviewed the nationally-approved SmPCs and submitted a proposal for a harmonised wording. The CHMP revised the proposal, including by rewording the statement on pseudomembraneous colitis and by including a statement concerning the potential interference with a Coomb's test. 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 submitted a proposal for a harmonised wording. The CHMP assessed the evidence submitted by the MAH to further substantiate the statement on the effect of concomitant use of antacids. The CHMP also included a statement on the risk of increased INR (international normalised ratio*)* upon concomitant use of oral anticoagulants. In conclusion, the CHMP adopted a harmonised wording for Section 4.5.

Section 4.6 – Fertility, 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 to bring the text in line with the current QRD template. In conclusion, the CHMP adopted a harmonised wording for Section 4.6.

Section 4.7 - Effects on ability to drive and use machines

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. The CHMP clarified and revised the frequency categorization, taking into account the source of the data. The CHMP also included *C. difficile* overgrowth as an undesirable effect and made changes to the categorization of certain adverse reactions, including skin reactions and dizziness and headache. The CHMP agreed that the available data shows 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 revised the proposal to include more comprehensive information concerning overdosing. 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, including a revision of the breakpoint table, to bring it line with EUCAST data. Revisions were also made to the spectrum 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 reworded the proposal, in particular based on additional data supporting the dosing recommendations in patients with impaired renal function. 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 and agreed with the MAH proposal, with the addition of a statement regarding the inhibition of gamma glutamyl transpeptidase activity. In conclusion, the CHMP adopted a harmonised wording for Section 5.3.

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 Zinnat 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 Zinnat 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 Zinnat and associated names (see Annex I).