EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2015
EMA/499802/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pursuant to Article 30 of Directive 2001/83/EC

Amoxil and associated names

INN of the active substance: amoxicillin

Marketing authorisation holder: GlaxoSmithKline group of companies and associated companies

Procedure no: EMEA/H/A-30/1372

Note

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 22 July 2013 the European Commission presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, in order to harmonise the national summary of product characteristics (SmPC), labelling and package leaflet (PL) of the medicinal products:

Amoxil 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 July 2013 meeting. The marketing authorisation holder was informed of the start of the procedure.

The Committee for Medicinal Products for Human Use (CHMP) appointed Robert James Hemmings (UK) as rapporteur and Concepcion Prieto Yerro (ES) as co-rapporteur.

Amoxil medicinal products are registered in the following European Union (EU) Members States (MS): Belgium, Cyprus, France, Greece, Ireland, Latvia, Lithuania, Luxembourg, Malta, Portugal, Spain and the United Kingdom.

2. Scientific discussion during the referral procedure

2.1. Introduction

Amoxil contains amoxicillin (as amoxicillin sodium or amoxicillin trihydrate), a moderate-spectrum, bacteriolytic, β-lactam antibiotic used to treat bacterial infections caused by susceptible microorganisms. Amoxicillin exerts its effect through inhibition of penicillin-binding transpeptidase proteins, disrupting peptidoglycan cross-linking in the cell-wall synthesis of both Gram-negative and Gram-positive organisms. Peptidoglycan is an integral structural component of the bacterial cell wall and serves to maintain the shape and integrity of the cell. Inhibition of peptidoglycan synthesis leads to weakening of the structure, usually followed by cell lysis and bacterial death.

Amoxil is indicated in both adults and children for the oral and parenteral treatment of many common infections, including bone/joint, skin/soft tissue and those of the urinary, respiratory, gastrointestinal and genital tracts.

The first amoxicillin-containing product was authorised in 1972 and Amoxil has been since authorised in the EU through national procedures. It is currently authorised in 12 EU Member States. Amoxil is approved for marketing in Europe in 17 different formulations: two strengths of capsules (250 mg and 500 mg), two strengths of dispersible tablets (750 mg and 1 g), four strengths of powder for oral suspension (125 mg/1.25 ml, 125 mg/5 ml, 250 mg/5 ml, 500 mg/5 ml), four strengths of powder for oral suspension in sachets (250 mg, 500 mg, 1g and 3g) and four strengths of 125 mg/1.25 ml powder for solution for injection or infusion via intravenous or intramuscular route (IV/IM) or both (250 mg (intravenous or intramuscular, IV/IM), 500 mg (IV/IM), 1g (IV/IM and IM) and 2g (IV)).

Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned products (and its associated names), the European Commission notified the European Medicines Agency of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised product information (PI) and thus to harmonise its divergent product information across the EU.

The harmonisation of the Quality documentation (Module 3) has been also included in this procedure at the request of the Marketing Authorisation Holder.

2.2. Critical Evaluation

2.2.1. Quality aspects

2.2.1.1. Introduction

The harmonised dossier was provided for the active substance (amoxicillin) and for products containing this substance: Amoxil capsules 250mg and 500mg, Amoxil dispersible tablets 750mg and 1g, Amoxil powder for Oral suspension 125 mg/1.25 ml, 125 mg/5 ml, 250 mg/5 ml and 500 mg/5 ml, Amoxil Sachets 250mg, 500mg , 1g and 3g, Amoxil powder for injection or infusion via intravenous or intramuscular route (IV/IM) 250mg, 500mg , 1g and 2g.

Module 3 was also harmonised and updated to reflect additional data collected by the MAH since the first marketing authorisation of Amoxil, and to upgrade the dossier in general.

2.2.1.2. Active substance

Information on the active substances was submitted via the respective CEPs, CEPs R1-CEP-2000-010-Rev 01 and R1-CEP 1996-013-Rev 05 for amoxicillin sodium including annexes for sterile grade and R1-CEP-2001-367 for amoxicillin trihydrate.

The active substances in Amoxil (amoxicillin sodium and amoxicillin trihydrate) were part of a Worksharing procedure (DE/H/XXXX/WS/20) to harmonise the Module 3 for the combination product Augmentin (amoxicillin and clavulanic acid) which concluded in December 2012. Those active substances are identical in Amoxil and Augmentin products. The MAH reference to the amoxicillin information from the combination product was accepted by the CHMP.

European monographs for amoxicillin trihydrate and amoxicillin sodium are currently being updated. The MAH has committed to modify the limits for specified and any unknown impurities in the specification of the active substances in line with the respective monographs within 6 months of their publication by the European Directorate for the Quality of Medicines (EDQM).

The description of the manufacturing process of amoxicillin trihydrate has been updated in line with a clarification regarding the two alternative routes for obtaining compacted amoxicillin trihydrate (amoxicillin trihydrate may be supplied compacted or may be compacted as a part of manufacture of capsule filling mix). Specification issued by the finished product manufacturer has been also updated to include the corresponding requirements for compacted grade.

2.2.1.3. Finished product

More data were provided during the procedure for all Amoxil pharmaceutical forms and more detailed description of the analytical methods was introduced in the dossier.

For all oral products, analytical method summaries and validation summaries have been updated to include reference for analytical methods and corresponding validation data. The MAH has also updated the pharmaceutical development section to indicate that suitability of the microbiological method has been demonstrated and a discussion on microbiological quality and compatibility has been included in the dossier. The assay limits for Amoxil suspensions have also been revised.

Excipients and flavouring agents in the oral formulations were also discussed and it was concluded that they are being adequately controlled.

For the capsules, testing for “tapped bulk density” will be performed on a routine basis on the active substance or on the capsule filling mix. The MAH committed to undertake studies to establish the correlation between “tapped bulk density” on active substance and “tapped bulk density” in the capsule fill mix. The results will be submitted in a variation to introduce a common limit for the capsule filling mix regardless of the source of active substance.

For parenteral formulations, details on the description of manufacturing process, process controls and process validation of the methods used for the determination of sterility and bacterial endotoxins were provided to allow harmonisation and to include information on the sterilisation of vials and rubber closures. The dossier was updated to include compatibility studies with various types of diluents, PVC bags and syringes.

The MAH has conducted in-use shelf life stability studies for the reconstituted parenteral formulations in order to investigate microbiological purity and to demonstrate the physicochemical compatibility of the finished product after dilution with the solvents (water for injection and lidocaine hydrochloride solution). Once the report is available, the MAH will submit a variation to provide the results of these studies along with any consequential changes to SmPC and PL. In this respect, during the procedure the MAH informed the committee of their intention to stop using benzyl alcohol as solvent for dilution of parenteral products and to withdraw the corresponding intramuscular presentation authorised in two MSs. This had not been implemented at time of opinion and will be handled at national level.

For all formulations, during the procedure the finished product specification was extensively discussed and revised specification limits for some of the impurities were set. The MAH has committed to modify the limits for specified and any unknown degradation product in all presentations of the finished product through the appropriate variations in line with the updated monographs for the actives substances amoxicillin sodium and amoxicillin trihydrate within 6 months of their publication by EDQM. A limit of NMT 0.2% for any unspecified degradation product would be deemed suitable.

2.2.1.4. Discussion and Conclusions on quality

As a result of this harmonisation procedure, the Module 3 was substantially updated and revised to include data which has become available during the years since the first marketing authorisation. The manufacture and control of both the active substance and the finished product comply with CHMP and International Conference on Harmonisation (ICH) guidelines. At the time of the CHMP opinion, there were five minor unresolved quality issues which have no impact on the benefit/risk ratio of the products. The MAH committed to address these through the appropriate post-referral variations. The quality of the product is considered satisfactory.

2.2.2. Clinical aspects

The initial clinical development of oral and parenteral amoxicillin occurred almost 50 years ago and the regulatory approval of some of the indications was based on clinical trials conducted in a small number of patients in comparison to current standards. The conduct of these clinical trials was considered appropriate at that time. Since then, amoxicillin has been the subject of numerous clinical studies, many of them by independent research groups and individuals. Studies published in the literature in peer-reviewed journals were also presented and although they do not represent a defined clinical programme for amoxicillin per se, they do collectively illustrate the efficacy and safety and tolerability of the drug in the indications claimed. Additionally, amoxicillin has been evaluated as a comparator in

many more recent antibacterial drug development programmes, and data from these studies are also included in this overview as supporting evidence of the continuing efficacy of amoxicillin in the claimed indications. The MAH has proposed a harmonised PI taking into consideration the current dataset, recommendations from recent evidence based and consensus European or national clinical prescribing guidelines in support of the use of amoxicillin in the claimed indications as well as the CHMP guideline on the evaluation of medicinal products indicated for treatment of bacterial infections and its addendum (CPMP/EWP/558/95 rev 2 and EMA/CHMP/351889/2013). The MAH also considered the SmPC guideline and implemented the current QRD template. The CHMP reviewed the totality of the data and consulted its Infectious Diseases Working Party on the proposed harmonised PI. It is hereafter summarised the main points discussed for the harmonisation of the different sections of the SmPC.

2.2.2.1. Section 4.1 - Therapeutic indications

The MAH proposed a harmonised set of indications on the different indications authorised in the MSs, however when single broad indications (e.g. infections caused by amoxicillin-sensitive organisms) were approved these were not taken into account. Early in the procedure, the MAH proposed to remove indications in which amoxicillin is no longer considered suitable and therefore are not discussed in the report. These included bronchitis, acute lung disease, urethritis, gonococcal infection, male genital infections, gonorrhoea, enteritis with bacteraemia and intra-abdominal infections such as peritonitis, cholecystitis and acute cholangitis, serious infections caused by haemophilus influenzae. In line with the CHMP guidelines, indications should describe the specific types of clinical infections for which the risk-benefit relationship is considered to be favourable, therefore indications such as upper or lower respiratory tract infections are no longer acceptable and the MAH has further specified those. For all indications, to encourage the responsible use of antibacterial agents and to direct prescribers to take note of any existing national or local guidance and opinions on how antibacterial agents should be used the following sentence will be included in this section: "*Consideration should be given to official guidance on the appropriate use of antibacterial agents*". In addition a cross reference to section 4.2, 4.4 and 5.1 is included at the beginning of the section, in particular to highlight that "*amoxicillin is not suitable for the treatment of some types of infection unless the pathogen is already documented and known to be susceptible or there is a very high likelihood that the pathogen would be suitable for treatment with amoxicillin*".

Upper respiratory tract infections

The indication "*upper respiratory tract infections*" is approved in all countries where Amoxil has a marketing authorisation, however such general indication is no longer acceptable and the MAH proposed to replace it by specific terms, "*acute bacterial sinusitis (adequately diagnosed)*", "*acute otitis media*" and *acute streptococcal tonsillitis and pharyngitis*" for oral formulations and "*severe infections of the ear, nose and throat (such as mastoiditis, peritonsillar infections, epiglottitis, and sinusitis when accompanied by severe systemic signs and symptoms)*" for parenteral formulations.

<u>Acute bacterial sinusitis - oral formulations</u>

Acute rhinosinusitis (ARS) is a symptomatic inflammation of the nasal cavity and paranasal sinuses lasting less than four weeks. The most common aetiology of ARS is a viral infection associated with the common cold. Uncomplicated acute viral rhinosinusitis (AVRS) typically resolves in 7 to 10 days. Acute bacterial rhinosinusitis (ABRS) may also be a self-limited disease; however on rare occasions patients with untreated bacterial disease may develop serious complications. The indication "*sinusitis*" is approved in 9 out of the 12 MSs where Amoxil has a marketing authorisation, however the MAH proposed a more specific wording "*acute bacterial sinusitis (adequately diagnosed)*". The MAH

presented a number of clinical studies conducted in adults and children between 1986 and 1999 comparing amoxicillin to placebo or other antibiotics as well as recommendations from guideline groups and meta-analysis that support the use of amoxicillin in adults and children with sinusitis.

Table 1. Summary of clinical trials comparing amoxicillin with other antibacterial agents in sinusitis (adults and paediatrics)

Reference	Trial Design	Number of patients	Treatment regimen (Duration)	Response rate[1] Clinical	Bacteriological
Adult Studies					
Nord, 1988□	Double blind, randomised	132 138	AMX 500mg TID BAC 899mg BID (10 days)	92% 91%	Not evaluated
Brodie, 1989[2]□	Single blind, randomised	80 80	AMX 250mg TID CEX 250mg BID (10 days)	87% 91%	83% 100%
Marchi, 1990□	Non-blinded, randomised	59 61	AMX 500mg BID CLA 250mg BID (10 days)	84% 91%	Not evaluated
Casiano, 1991□	Single blind, randomised	37 41	AMX 500mg TID (10 days) AZT 500mg OD for one day, then 250mg OD for 2-5 days	100% 100%	100% 100%
Felstead, 1991□	randomised[3]	127 131	AMX 500mg TID (10 days) AZT 250mg BID for one day, then OD for 2-5 days	98% 97%%	87% 94%
Karma, 1991□	Single blind, randomised	50 50	AMX 500mg TID CLA – 500mg BID (10 days)	89% 91%	91% 88%
Edelstein, 1993	Single blind, randomised	51 63	AMX 500mg TID CEF 400mg OD (10 days)	96% 94%	100% 95%
Calhoun, 1993[4]	Single blind, randomised	72 70	AMX 500mg TID CLA 500mg BID (7 to 10 days)	89% 91%	Not evaluated
Huck, 1993[5]	Double blind randomised	54 54	AMX - 500mg TID CEL – 500mg BID (10 days)	87% 91%	Not reported
Lindbaek, 1996[6]	Double blind randomised	39 44 44	AMX 500mg TID PEN 1320mg TID PLB TID (7 to 10 days)	89% 82% 56%	Not evaluated
Von Sydow, 1995□	Double blind randomised	143 143	AMX 750mg BID CEP- 200mg BID	91% 96%	90% 97%
D'Andrea Marcolino, 1999	Non-blinded, randomised	63 63	AMX 500mg TID (14 days) AZT 500mg OD (3 days)	96% 96%	Similar bacteriological efficacy
Paediatric studies					
Wald, 1986	Single blind, randomised	30 28 35	AMX 40mg/kg/day TID AMC 40mg/kg/day TID PLB TID (10 DAYS)	83% 75% 60%	Not evaluated

1. Clinical and bacteriological response rates were usually evaluated at the end of therapy.
2. Study included acute and acute on chronic sinusitis patients.
3. Blinding of study not stated.
4. Paediatric patients were also enrolled aged from 14 years.
5. Study included acute, recurrent and chronic sinusitis patients.
6. Clinical success rate – patient evaluation of efficacy.

Abbreviations: AMX – amoxicillin, BAC - Bactrim , CEX - Cefroxadine , CLA - clarithromycin , AZT - azithromycin, CEF - Cefuroxime, PEN-Penicillin, PLB - polymyxin B sulfate, AMC - amoxicillin-clavulanic acid

Treatment with amoxicillin at a dose of 250mg TID, 500mg TID, 750mg BID for adults or 40mg/kg/day for paediatric patients for 7 to 10 days, generally produced high clinical and bacteriological response rates (around 90%), with efficacy similar to the antibiotic comparators, (penicillin, bacampicillin, cefixime, cefpodoxine, azithromycin, clarithromycin, cefuroxime and cefaclor). In a study by Wald,

1986, which investigated the effects of 40mg/kg/day amoxicillin vs amoxicillin/clavulanate or placebo for 10 days in children, aged between 2-16 years, suffering with acute paranasal sinus infections, 83% of patients who had taken amoxicillin were cured or improved compared with 75% of amoxicillin-clavulanate-treated patients and 60% who had taken the placebo.

More recent reviews of antibiotic clinical trials for the treatment of sinusitis in paediatrics (Temple, 2000 and Zacharisen, 2005) concluded that amoxicillin remains the drug of first choice for the treatment of acute sinusitis in paediatrics with efficacy similar to that of other broad spectrum antibiotics. Furthermore, a systematic Cochrane review of forty-nine clinical trials, involving 13,660 participants, evaluated antibiotic treatment for acute maxillary sinusitis, and concluded that amoxicillin is a suitable antibiotic for treating sinusitis (Williams, 2003).

The CHMP was of the view that amoxicillin remains an effective treatment for acute bacterial sinusitis. The wording "*adequately diagnosed*" was however not accepted as it was considered misleading regarding the need for an adequate diagnostic in the other indications.

Acute otitis media (AOM) - oral formulations

AOM is an inflammation of media ear caused by bacterial and/or viral respiratory tract pathogens. Overall, AOM resolves in 24 h in 60% of cases without antibiotics. The indication "*otitis media*" is approved in all countries where Amoxil has a marketing authorisation, however and the MAH proposed a more specific wording in line with the population studied in clinical trials "*acute otitis media*". The MAH presented clinical studies in paediatrics conducted between 1986 and 2005 including comparative trials with macrolides and cephalosporins as well as recommendations from various treatment guideline groups based in the US and in the EU that support the use of amoxicillin in AOM. The use of varying dose regimens ranging from 40 mg/kg/day to 90 mg/kg/day showed efficacy rates of around 90% in majority of the trials. Similar results were observed with a short course (2 day) 750 mg BID regimen. Amoxil was found to be as efficacious as macrolides and cephalosporins in children in the 10 clinical trials presented. A search in the literature retrieved only one study in 61 adults in which amoxicillin was found to be slightly less efficacious than clarithromycin at 7 days but as efficacious at 14 days. Although there is a paucity of clinical studies in adult AOM patients, the aetiology appears to be very similar to that in children, with *H. Influenzae*, *S. pneumoniae* and *M. catarrhalis* being the predominant pathogens implicated in adult AOM. In addition taking in to account the similarity in bacteriological aetiology and pathogenesis of adult ABS and AOM, it was considered that the clinical data demonstrating that amoxicillin is an effective treatment in ABS can be extrapolated to support efficacy of amoxicillin in the treatment of adult AOM. This is further supported by appropriate pharmacokinetic/pharmacodynamic (PK/PD) studies and data demonstrating that amoxicillin effectively penetrates the upper respiratory tract in adults. The CHMP was of the view that amoxicillin is a suitable treatment option for AOM in both adults and children.

Acute streptococcal tonsillitis and pharyngitis – oral formulations

Viral agents are the most common infectious cause of tonsillitis/pharyngitis in children and recover within 3-5 days without antimicrobial therapy. Nevertheless, some of them can be of bacterial origin, *Streptococcus pyogenes* (group A beta-hemolytic streptococcus) being the most common agent. In case of bacterial pharyngitis and important symptoms, contact with a documented case of group A streptococcal pharyngitis, clinical signs of scarlet fever, history of acute rheumatic fever or pharyngitis complications, antibiotic therapy is recommended. The indication "*tonsillitis*" is approved in 7 out of the 12 MS where Amoxil has a marketing authorisation, however the MAH proposed to further qualify as follows "*acute streptococcal tonsillitis and pharyngitis*". The MAH presented clinical studies conducted in adults and children between 1993 and 2008 as well as recommendations from various treatment

guideline groups that support the use of amoxicillin in tonsillitis and pharyngitis particularly that due to group A beta-haemolytic streptococcal infections (GABHS).

Table 2. Summary of clinical trials with amoxicillin for the treatment of streptococcal tonsillopharyngitis (adults and paediatrics)

Reference	Trial Design	Number of patients	Treatment regimen (Duration)	Response Rate[1] Clinical	Bacteriological
Adult Studies					
Nyffenegger, 1993	Randomised[2]	233 231	AMX 750mg TID BPD 400mg loading dose, then 200mg OD (8-12 days)	95% 98%	88% 88%
Peyramond 1996[3]	Non-blinded, randomised	165 173	AMX 1000mg BID PEN V 1MU TID (10 days)	96% 96%	92% 93%
Paediatric Studies					
Cohen, 1996 (aged 2 -12yrs)	Non-blinded, randomised	161 160	AMX 50mg/kg/day given BID (6 days) PEN V 45mg/kg/day given TID (10 days)	91% 89%	84% 85%
Feder, 1999 (Aged 3-18yrs)	Randomised[2]	84 77	AMX 750mg OD PEN 250mg TID (10 days)	90% 90%	95% 89%
Aguilar, 2000 (Aged 2 -12yrs)	Single blind, randomised	258 249	AMX 45mg/kg/day BID AMX 40mg/kg/day TID (7 days)	95% 96%	95% 96%
Berezin, 2003 (aged 2-16yrs)	Double-blind, randomised	74 74	AMX 40mg/kg/day BID CEL 40mg/kg/day BID (10 days0	92%[4] 90%	81% 90%
Clegg, 2006 (aged 3-18yrs)	Single blind, randomised	296 294	AMX BID[5] AMX OD[6] (10 days)	93% 91%	84% 80%
Sakata, 2008 (aged 6mths-12yrs)	Non-blinded, randomised	80 82 88	AMX 30-40mg/kg/day TID (10 days) CFN 9-10mg/kg/day TID 9 (5 days) CFN 9-10mg/kg/day TID 9 (10 days)	100% 100% 100%	92% 94% 96%
Lennon, 2008□	Randomised[2],	177 176	AMX 1500mg OD or 750mg if body weight ≤30kg PEN V- 500mg BID or 250mg if body weight ≤30kg (10 days)	Similar between groups	84% 86%

1. Clinical and bacteriological response rates were usually evaluated at the end of therapy.
2. Blinding of study not stated.
3. Children were included >15 years.
4. Clinical response included evaluation of key signs and symptoms (pharyngeal ache, difficulty swallowing pharyngeal erythema, pharyngeal exudates, and painful cervical adenopathy).
5. Amoxicillin BID dosing regimen: for children <40kg, dose was 375mg BID and children ≥40kg, 500mg BID.
6. Amoxiciillin OD dosing regimen; for children <40kg, dose was 750mg and children ≥40kg, 1000mg.

Abbreviations: BID – twice daily, OD – once daily, TID- trice daily, AMX – amoxicillin, BPD- Brodimoprim, PEN – Penicillin, CEL - Cefaclor, CFN- ciprofloxacin

Treatment with amoxicillin at a dose of 1500mg OD, 1000mg BID and 750mg TID for adults or 375mg BID, 750mg OD, 30 to 50mg/kg/ day for paediatric patients for 8 to 12 days, generally produced high clinical (around 90%) and bacteriological response rates, with efficacy comparable to the comparators.

The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) Sore Throat Group Guidelines recommend amoxicillin as an alternative to penicillin V. Several national guidelines and international societies including the World Health Organization recommend amoxicillin either as first or second line treatment for streptococcal pharyngitis. The CHMP was therefore of the view that amoxicillin remains a valid therapeutic option in this indication.

Severe infections of the ear, nose and throat (such as mastoiditis, peritonsillar infections, epiglottitis, and sinusitis when accompanied by severe systemic signs and symptoms) - Parenteral formulation

As mentioned above, this wording was proposed in replacement for the too broad "*upper respiratory tract infection*" wording which is authorised in all member states with some variations in the exact wording.

Mastoiditis is a rare bacterial infection and inflammation of the mastoid air cells in the ear, spreading to the mastoid bone, which in rare cases can lead to destruction of the mastoid process. It can occur in an acute form, as a direct complication of AOM, or in a chronic form resulting from incomplete treatment of AOM. The bacterial species most often implicated in acute mastoiditis are *Streptococcus pneumoniae* (including multiply resistant *S. pneumoniae*, particularly serotype 19A), *Streptococcus pyogenes*, and *Staphylococcus aureus* (including methicillin-resistant *S. aureus*). The treatment of acute mastoiditis depends on the stage and presence or absence and type of complications. Nevertheless, in all cases antimicrobial therapy and drainage of the middle ear and mastoid are the cornerstones of therapy for acute mastoiditis.

Peritonsillar abscess is the most common deep infection of the head and neck that occurs in adults. This infection begins as a superficial infection and progresses into tonsillar cellulitis. A peritonsillar abscess forms at the most advanced stage. Evidence shows that chronic tonsillitis or multiple courses of oral antibiotics for acute tonsillitis may predispose persons to the development of a peritonsillar abscess. The most common aerobic organisms associated with peritonsillar abcesses are Group A *streptococcus (S. pyogenes), S. aureus, and H. influenza* and the most common anaerobic organism is *Fusobacterium*. The treatment of peritonsillar abscess requires both the selection of appropriate antibiotics and aspiration or drainage of the abscess and in some cases tonsillectomy.

Acute epiglottitis is a cellulitis of the epiglottis and adjacent structures that has the potential for causing abrupt complete airway obstruction. Epiglottitis was originally considered a childhood disease but has been increasingly diagnosed in adults. In addition to *H. influenzae* type b, the major bacterial organisms responsible for epiglottitis include *S. pneumonia*, Group A *Streptococci* and *S. aureus*. Management focuses on two important aspects: close monitoring of the airway with intubation if necessary and treatment with intravenous antibiotics.

The treatment of severe infections of the ear, nose and throat requires parenteral antimicrobial therapy. Empiric antimicrobial therapy should provide coverage for the most frequent bacterial pathogens: *S. pneumoniae* (including multiply resistant *S. pneumoniae*), *S. pyogenes*, *S. aureus* (including methicillin-resistant *S. aureus*) and *H. influenzae*. The growing resistance to amoxicillin of *H. influenzae* and *M. catarrhalis* (through β-lactamase production) and *S. pneumoniae* and *H. influenzae* (through changes in protein binding site) increased the risk of treatment failure, therefore amoxicillin should not be used as empirical treatment in these infections. The CHMP was of the view that the susceptibility of the organism to amoxicillin should be confirmed by laboratory results prior to initiating treatment with amoxicillin and requested that a warning to that effect be included in section 4.4 (and cross referred in section 4.1). The CHMP considered that the parenteral route was adequate for the more severe infections of the ear nose and throat.

Lower respiratory tract infections

The indication "*lower respiratory tract infections*" is approved in all countries where Amoxil has a marketing authorisation, however such general indication is no longer acceptable and the MAH

proposed to replace it by specific terms, "*Acute exacerbations of chronic bronchitis (adequately diagnosed)*" and "c*ommunity acquired pneumonia"* for oral and parenteral formulations.

Acute exacerbations of chronic bronchitis (AECB) – all formulations

Amoxil is authorised in all countries where it is marketed in lower respiratory tract infections and more specifically in severe respiratory infections in 2 MSs, the MAH proposed to replace these general wordings by "a*cute exacerbations of chronic bronchitis (adequately diagnosed)"*. The MAH presented seven clinical studies conducted between 1989 and 2001 as well as recommendations from various treatment guideline groups that support the use of amoxicillin in AECB.

Table 3. Summary of Clinical Trials comparing Amoxicillin with other Antibacterial Agents in Acute Exacerbations of Chronic Bronchitis

Reference	Trial Design	Number of patients	Treatment regimen (Duration)	Response Rate[1]	
				Clinical	Bacteriological
Bint, 1989☐	Single-blind randomised	56 55	AMX 500mg TID CFD 1000mg BID	81% 85%	Not evaluated
Klietmann, 1992☐	Double-blind randomised	65 64 63	AMX 500 mg BID RUX 200mg OD RUX 150mg OD (10 days)	98% 94% 95%	91% 93% 95%
Saenz Aguirre, 1992[3]☐	Single-blind randomised	81 82	AMX 500mg TID LOM 400mg OD	82% 93%	75% 82%
Langan, 1997☐	Double-blind randomised	218 219 219	AMX 500mg TID GRP 400mg OD GRP 600mg OD (7 to 10 days)	85% 82% 85%	86% 86% 92%
O'Doherty, 1998☐	Double-blind randomised	132 145 134	AMX 500mg TID TRV- 100mg OD TRV-200mg OD (5 Days)	89% 91% 88%	85%-100%[2] 96%-100%[2] 86%-98%[2]
Georgopoulos, 2001	Double-blind randomised	197 198	AMX 500mg TID AMX 1000mg BID (10 days)	93% 89%	90% 82%

1. Clinical and bacteriological response rates usually determined at the end of therapy
2. Bacterial response rate is for pathogens *H.influenzae*, *M.catarrhalis* and *S.pneumoniae*
3. Most of the clinical and bacteriological failures were associated with *Pseudomonas aeruginosa*, which is not included in the spectrum of activity for amoxicillin

Abbreviations: BID – twice daily, OD – once daily, TID- twice daily, AMX – amoxicillin, CFD- cefadroxil, GRP- Grepafloxacin, LOM- lomefloxacin, TRV - Trovafloxacin, RUX - Rufloxacin

In clinical trials amoxicillin given either at a dose of 1000mg BID or at a dose of 500mg BID or TID was found to have similar response rates to the comparators (successful clinical and microbiological outcomes in ≥81% and ≥ 85% of patients, respectively).

Many national and European guidelines recommend amoxicillin as one of several treatment options for AECB in adults patients with increased dyspnoea, sputum volume and sputum purulence or in case of exacerbations in patients with severe chronic obstructive pulmonary disease (COPD). In these cases, Amoxicillin is recommended as one of first choice antibiotics based on the wide experience in clinical practice. Therefore, the CHMP considered this indication adequate. The wording "*adequately diagnosed*" as proposed by the MAH was removed as it was considered misleading regarding the need to diagnose adequately for the other indications.

Community acquired pneumonia (CAP) – all formulations

CAP are most often cause by bacterial infections but can also be of viral, fungal or parasitic aetiology. It causes the alveoli to fill with fluids which in turn inhibits lung function and can lead to sepsis respiratory failure, pleural effusion and death. *S. pneumoniae* accounts for most cases of CAP in all

groups of patients, whether treated on an outpatient basis or admitted to the hospital, including the subset admitted to the intensive care unit while *H. influenzae* and *M. catarrhalis* are more common in elderly patients with COPD and in smokers, accounting for 3–10% of CAP episodes. The indication "*pneumonia*" and "*bronchopneumonia*" are approved respectively in 2 and 9 MSs out of the 12 where Amoxil has a marketing authorisation; the MAH proposed to replace it by the current terminology "c*ommunity acquired pneumonia*". The MAH presented clinical studies in adults and paediatrics conducted between 1992 and 2008, as well as recommendations from various treatment guideline groups that support the use of amoxicillin in CAP.

Table 4. Summary of clinical trials in adults of amoxicillin for the treatment of CAP

Reference	Trial Design	Number of patients	Treatment regimen (Duration)	Response Rate[1]	
				Clinical	Bacteriological
Carbon, 1992□	Double-blind randomised	121 125	AMX 500mg TID TEM 600mg BID (7 days)	86% 89%	97% 99%
Tremolieres, 1998	Double-blind randomised	169 173	AMX 1000mg TID TRV 1000mg OD (7-10 days)	89% 93%	90% 94%
Aubier, 1998□	Double-blind randomised	170 159	AMX 1000mg TID SPR 200mg OD (10 days)	87% 92%	89% 93%
Petitpretz, 2001□	Double-blind randomised	208 200	AMX 1000mg TID MXF 400mg OD (10 days)	90% 92%	82% 90%
Hagberg, 2002 □	Double-blind randomised	205 199	AMX 1000mg TID TEL 800mg OD (10 days)	90% 95%	87% 88%
Jardim, 2003□	Double-blind randomised	39 45	AMX 1000mg TID MOX 400mg OD (10 days)	92% 94%	88% 88%
Tremolieres, 2005	Double-blind randomised	182 189	AMX 1000mg TID PTN 1000mg OD (6-10 days)	88% 88%	88% 82%

1. Clinical and bacteriological response rates usually determined immediately at the end of therapy
Abbreviations: BID – twice daily, OD – once daily, TID – three times daily, AMX – amoxicillin, GRP- grepafloxacin, MXF- moxifloxacin, PTN – Pristinamycin, SPR- Sparfloxacin TEL- Telithromycin, , TEM-Temofloxacin, TRV-trovafloxacin

Treatment with oral amoxicillin at a dose 1000mg TID or 500mg TID for 7 to 10 days produced clinical response rates ranging from 86% to 90% and bacteriological response rates ranging from 82% to 92%. These results are similar to that of other antibiotics for the treatment of CAP in adults. Additionally a recent review of clinical trials evaluating the antibiotic treatment of community-acquired pneumonia (CAP) in adults published between 1999 and 2005 (Chidiac, 2006), concluded that high-dosage amoxicillin (1 g TID) remains the drug of choice for the treatment of CAP.

Table 5. Summary of clinical trials in children and adolescents comparing amoxicillin with other antibacterial agents in severe and non-severe CAP.

Reference	Trial Design	Number of patients	Treatment regimen (Duration)	Response Rate[1]	
				Clinical	Bacteriological
Awasthi, 2008	Open labelled, randomised	993 1016	AMX 125mg TID (3 days) TMP/SMZ 25mg BID (5 days)	86% 90%	Not evaluated
Hazir, 2007[2□]	Double-blind randomised	437 439	AMX 45/mg/kg days AMX 80-90mg/kg/day (3 days)	94% 92%	Not evaluated

Reference	Trial Design	Number of patients	Treatment regimen (Duration)	Response Rate[1] Clinical	Bacteriological
ISCAP, 2004[2]☐	Double-blind randomised	1095 1093	AMX 125mg TID (3 days) AMX 125mg TID (5 days)	90% 90%	Not evaluated
Addo yobo[3], 2004	Open labelled, randomised	857 845	AMX 45mg/kg/day in three divided doses (7 days) PEN G IV 200, 000 IU/kg per day QID (2 days) followed by oral AMX 5 days	81% 81%	Not evaluated
MASCOT, 2002[2]	Double blind randomised	1000 1000	AMX 15mg/kg TID (3 days) AMX 15mg/kg TID (5 days)	79% 80%	Not evaluated
Catchup, 2002[2]	Double blind randomised	730 741	AMX 25mg/kg BID TMP/SMZ 24mg/kg BID (5 days)	84% 81%	Not evaluated
Hazir, 2002[3]☐	Open labelled, randomised	1052[4] 1048[4]	AMX 40-45mg/kg BID (5 days) AMP 25mg/kg QID (2 days) followed by AMX 40-45mg/kg BID (3 days)	93 91%	Not evaluated
Straus, 1998[5]☐	Double blind randomised	197 308	AMX15mg/kg TID TMP/SMZ 24mg/kg BID (5 days)	85% 77%	85%[6] 68%[6]

1.Clinical and bacteriological response rates usually determined immediately at the end of therapy
2.Patients were treated for non-severe pneumonia according to WHO defined criteria: patients with no lower chest in drawing but have fast breath(≥50 breaths per min in infants aged 2-11 months, ≥40 breaths per min in those aged 12-59 months)
3.Patients were treated for severe pneumonia according to WHO defined criteria: patients with lower chest in drawing and have fast breath(≥50 breaths per min in infants aged 2-11 months, ≥40 breaths per min in those aged 12-59 months
4.Patients randomised to the amoxicillin arm were treated as outpatients at home and those randomised to ampicillin were treated in hospital.
5.Patients with non-severe and severe pneumonia were enrolled in the study
6.Microbiological response was only evaluated in bacteraemic patients
Abbreviations: OD – once daily, BID – twice daily, TID – three times daily, QID – four times daily, AMX – amoxicillin, PEN – penicillin, TMP/SMZ - Trimethoprim/sulfamethoxazole

In the paediatric studies submitted, amoxicillin showed comparable efficacy to that of the comparators and comparable responses rates to that seen in adults, greater efficacy was seen with the higher doses. A recent Cochrane review evaluated the most effective antibiotic treatment for pneumonia in children. The review concluded that for the treatment of ambulatory paediatric patients with CAP, amoxicillin was better than co-trimoxazole and no different to azithromycin, erythromycin, cefpodoxime and amoxicillin/clavulanic acid (Kabra, 2006).

The use of parenteral formulation showed similar results to the oral formulation.

The use of amoxicillin in treating respiratory infections is further reflected in many national and European guidelines which recommend amoxicillin empiric treatment of community acquired pneumonia in adults and children. The CHMP considered that these studies demonstrated that amoxicillin continues to be an efficacious treatment for CAP.

Genitourinary tract infections

The indication *"genitourinary tract infections"* is approved in all countries where Amoxil has a marketing authorisation, however only 7 used this general indication. Such general indication is no longer acceptable. The MAH proposed to replace it by several terms of different levels of specificity regarding the infection site.

Acute cystitis, asymptomatic bacteriuria in pregnancy and acute pyelonephritis – all formulations

Urinary tract infections are mainly caused by *Escherichia coli* and often involve only the lower urinary tract, in which case it is known as acute cystitis. Acute pyelonephritis may occur as a progression of urinary infection from the lower to the upper tract or from a bacterial infection that has travelled through the bloodstream to the kidneys. Alternatively if significant levels of bacteria are found in the urine but no symptoms are reported, the condition is known as asymptomatic bacteriuria. The indications "*cystitis*" and "*bacteriuria*" are approved respectively in 10 and 8 MS out of the 12 MS where Amoxil has a marketing authorisation, the CHMP requested to replace it by the current terminology, in line with the population studied, "*acute cystitis", "asymptomatic bacteriuria in pregnancy"*. The indication "*pyelonephritis*" and "*acute pyelonephritis"* are approved respectively in 8 and 2 out of the 12 MS where Amoxil has a marketing authorisation, the MAH proposed to keep the general indication, however in line with the population studied, the CHMP requested to keep the more specific terminology "*acute pyelonephritis".* The MAH presented clinical studies in children and adults, including pregnant women, conducted between 1973 and 1993 with oral and parenteral amoxicillin as well as recommendations from various treatment guideline groups that support the use of amoxicillin in these indications.

Table 6. Summary of clinical trials in children and adults comparing amoxicillin with other antibacterial agents or different regimens of amoxicillin in acute cystitis

Reference	Trial Design	Number of patients	Treatment regimen (Duration)	Response Rate[1]	
				Clinical	Bacteriological
Nicolle, 1993[2]	randomised, double-blind multicentre study	199 400	AMX 250mg TID (3 days) CD 300mg BID (3 days)	71% 69%	77% 77%
Sigurdsson, 1983	randomized, double-blind study	70 76	AMX 1000mg BID (3 days) CT 500 MG BID (3 days)	88% 100%	Not evaluated
Davies, 1991	Double-blind randomised	196 205	AMX 250mg TID (7 days) (LEX 1g BID (7 days)	79% 81%	Not evaluated
Richard, 1981	Open labelled, randomised	74 72	AMX (250 mg TID for 10 days) BAPC 400mg BID (10 days)	99% 99%	97% 95%
Mannisto, 1978	clinical study[3]	38 43	AMX 375mg TID (10 days) TMP-SDZ 160/500 mg BID (10 days)	Not evaluated	84% 100%
Vogel, 1975□	clinical study[3]	54 54	AMX 250 mg TID NOR 400 mg BID for 7 days	Not evaluated	74% 83%
Hill, 1985	randomised study	18 19	AMX 250 mg TID NOR 400 mg BID for 10 days	Not evaluated	85% 88%
Fang, 1978	randomised study	61	AMX 3g once AMX 250 mg QID	70%[4] 70%	Not evaluated
Bailey, 1985	clinical study[3]	37 37 37 39	AMX 3 g (1) TMP 600 mg (1) CT 1.92 g (1) TMP 300 mg (5 days)	80% 65% 80% 86%	Not evaluated
Bailey, 1977	Open study	25 6	AMX 3g (1) AMX 100 mg/kg	74%	Not evaluated
Bailey, 1977	Randomised study	20	AMX 3g (1) AMX 250 mg TID (for 5 days)	75% 54%	Not evaluated

Reference	Trial Design	Number of patients	Treatment regimen (Duration)	Response Rate[1] Clinical	Bacteriological
		16	AMX 100 mg/kg (>5yo) AMX 25 mg/kg (<5yo) AMX 250 mg TID for 7 days	54% 54% 54%	
Abbas, 1983	clinical study[3]	60 47	AMX 3 g BID AMX 250 mg TID (for 5 days)	88% 98%	83% 93%

1. Clinical and bacteriological response rates usually determined at one week, relapses not accounted for. evaluable
2. only 309 patients were assessable
3. design not specified
4. All 43 patients without antibody coated bacteria in the urine were cured

Abbreviations: AMX – amoxicillin, CD - cefcanel daloxate, CT - cotrimazine, LEX - cephalexin, BAPC - bacampicillin, TMP-SDZ - sulfadiazine-trimethoprim, NOR - norfloxacin, TMP - trimethoprim

Table 7. Summary of clinical trials in children and adults of amoxicillin in treatment of pyelonephritis (oral and parenteral)

Reference	Trial Design	Number of patients	Treatment regimen (Duration)	Response Rate[1] Clinical	Bacteriological
Piekkala, 1985	Clinical study[2]	14 20	AMX IV 60 mg/kg/day (7 to 9 days) of CXM IV 60 mg/kg/day 300mg BID (7 to 9 days)	64% 65%	64% 80%
Kienitz, 19742	Open study	64[3]	AMX 33mg/kg/day TID (14 days)	72%	Not evaluated
Price, 1973[4]	Open study	318	AMX 250mg TID (7 days)	97%	83%
Roland, 1977	Open study	19	AMX 500 mg for 14 days)	90%	Not evaluated
Lohrman, 1979	Open study	24[5]	AMX 1 g TID or 5 g IV for 7 to 14 days depending on the severity of infection	85%	84% 100%

1. Clinical and bacteriological response rates usually determined at one week, relapses not accounted for
2. design not specified
3. Children with chronic pyelonephritis
4. 39 patients with pyelonephritis
5. 40 patients included but 40% had non microbial infections and are not reported here

Abbreviations: AMX – amoxicillin, CXM = cefuroxime

Table 8. Summary of clinical trials in children and adults of amoxicillin in treatment of bacteriuria in pregnant women (oral and parenteral)

Reference	Trial Design	Number of patients	Treatment regimen (Duration)	Response Rate[1] Clinical		Bacteriological
Leigh, 1972	Open study	257[2]	amoxicillin 500 mg TID for 7 days	88%		Not evaluated
Tan, 1973	Clinical study[5]	34[3]	AMX 375 mg TID or AMX 500 mg BID or QID (for 7-14 days)	Not evaluated		83%
Brumfitt, 1982	Randomised study	93[4]	AMX 250 mg TID (7 days) AMX 3g (1) followed 3 g (1) 12 h later	Gp1 68% 65%	Gp2 70% 79%	Not evaluated
Gerstner, 1989	Randomized clinical trial	38 53	AMX 750 mg TID (4 days) AMX 3g (1)	62% 77%		Not evaluated
Masterton, 1985	Randomized clinical trial	90	AMX “conventional” (7 days) AMX 3g (1)	84% 88%		Not evaluated
Cefal, 1989	Clinical study[5]	50 70	AMX 750 mg TID (7 days) NTF 100 mg QID (7 days)	Not evaluated		67% 79%

1. Clinical and bacteriological response rates usually determined at one week, relapses not accounted for
2. including 28 pregnant patients with bacteriuria (cure rate 68% at 2 weeks and 100% at 6 weeks)
3. including 7 pregnant women
4. split into 2 groups; group 1 of women with bacteriuria (cure rate 68%) and; group 2 of 39 patients with a history of recurrent

Reference	Trial Design	Number of patients	Treatment regimen (Duration)	Response Rate[1] Clinical	Bacteriological

UTIs
5. design not specified
Abbreviations: AMX – amoxicillin , NTF = nitrofurantoin

Wise, 1974, has reviewed the clinical trials conducted in the United States with amoxicillin in the early 1970's which included patients treated with urinary tract infections. Six hundred and thirty one patients were treated with different doses of oral amoxicillin which included 423 patients with cystitis, 155 with pyelonephritis and 53 with asymptomatic bacteruria. The success rate for patients treated with 250 mg TID was 74% in 465 patients and for the 500 mg dose TID it was 60% in 92 patients.

A Cochrane data base review of antibacterials in symptomatic UTIs in pregnancy concluded that the antibacterials studied, including amoxicillin, were equally effective at treating infection and reducing complications (Vazquez, 2003).

European guidelines recommend amoxicillin as one of the treatment options for bacteruria or cystitis in pregnant women only due to the high rate of resistance (Grabe, 2013). In most countries, *E. coli* shows a high rate of resistance against amoxicillin and is therefore not recommended as empirical therapy. However several European national guidelines continue to consider amoxicillin an appropriate choice when the susceptibility of the causative pathogen is known or where guided by local surveillance data.

Generally, cure rates were lower than in other indications with a high incidence of relapse and recurrence. However higher cure rates were observed with longer treatment duration (7-10 days) and when the causative organisms were susceptible to amoxicillin. While all the clinical trials conducted in this indication are not recent, a number of recent clinical guidelines recommend the use of amoxicillin in URTI indications. Therefore the CMHP was of the view that this indication was acceptable for amoxicillin but in view of the increasingly high resistance rates, requested to cross refer to additional information in section 4.4 regarding the need for the pathogen to be known or strongly suspected as susceptible to amoxicillin before treatment initiation.

Female genital infection – parenteral formulation

Infections of the female genital tract are both aetiologically and clinically diverse and include vulvovaginitis, septic abortion, post-partum endometritis, intra-partum or post-partum bacteraemia and wound infections. The indication "*gynaecological infection including puerperal sepsis and septic abortion*" was approved in 8 out of the 12 MS where Amoxil has a marketing authorisation and "*severe gynaecological infection (salpigitis, endometritis)*" in one MS, however the MAH proposed to remove it from the oral formulation and replace it with "*female genital infections*" in the parenteral formulation. The CHMP was of the view that this indication should be further specified by site of infection. The MAH presented six clinical trials conducted between 1975 and 1986 as well as a more recent review of antibiotics in postpartum infection.

The clinical efficacy and safety of ofloxacin was compared with amoxicillin in a double-blind Japnese study for the treatment obstetric and gynaecological infections in 246 patients (Takase, 1986). Oral drugs were administered for 7 days at daily doses of ofloxacin 200 mg TID and amoxicillin 250 mg QID. Clinical success rate was 86.5% and 76.0% in the ofloxacin and amoxicillin groups, respectively. The clinical success rate of intrauterine infection and adnexitis was 85.5% and 80.7%, in the ofloxacin and amoxicillin groups, respectively. The success rate for bartholinitis and Bartholin's abscess was slightly lower for amoxicillin 68% vs 88% for ofloxacin. There was no significant difference between the two groups in terms of adverse events and abnormal changes in laboratory findings. The

authors concluded that ofloxacin was similar to efficacy to amoxicillin in the treatment of genital infections.

Onsrud, 1982, evaluated the absorption and penetration of amoxicillin in pelvic inflammatory disease (PID). Five patients had thin polyethylene catheters introduced percutaneously through the abdominal wall into the pouch of Douglas for sampling of peritoneal fluid. One-hour after the oral ingestion of 500 mg amoxicillin therapeutic levels were recorded in blood plasma; the peak level being achieved in 2 hours. The concentration of amoxicillin in the peritoneal fluid showed some delay, mainly in the cases of thick purulent exudates, but the concentrations achieved were similar to those in plasma. Therapeutic levels were maintained in blood and in the peritoneal fluid for 7 to 8 hours. Patients continued to be treated with amoxicillin 500 mg TID for 10 to 18 days and all were effectively cured.

In one Japanese study, bacteriological cure was achieved in 23 of 36 (63%) of female patients with genital infections such as adnexitis, cervicitis and myometritis treated with amoxicillin 750 mg to 1g daily for 7 to 28 days. A clinical response was obtained in 28 patients (74%).

Ceccarelli, 1977, evaluated the efficacy of Intravenous (IV) amoxicillin given at doses of 750 mg or 1500 mg per day given in three divided doses for 6 to 10 days. Patients presented with a variety of obstetric and gynaecological infections which included septic abortion, post-partum infections, urine infections in pregnant females and endometriosis. A total of 38 female patients were enrolled. After 2 days of therapy, signs and symptoms of infection had improved and 7 or 8 days after the start of therapy the majority of patients had complete resolution of all signs and symptoms. Amoxicillin was also effective in eradicating the causative pathogens implicated in these infections.

Amoxicillin was used in the treatment of 30 patients with septic abortion caused by Gram-negative and Gram-positive organisms (Soto, 1974). An oral dose of 500 mg was administered every 8 hours after removal of the contents of the uterus by suction. The average duration of therapy was six days, with an average dose of 27.8 mg/kg per day. Amoxicillin was effective in 28/30 (93%) of patients. There were no significant adverse effects directly attributable to amoxicillin, with the exception of one extensive erythematous and maculopapular cutaneous reaction.

Gaudin, 1985, evaluated the efficacy of ceftriaxone compared to a combination of intravenous antibiotics. One group of patients with endometriosis and salpingitis received ceftriaxone 2g once daily (15 patients) and a combination of 1 g amoxicillin TID and 500 mg metronidazole TID (15 patients) for 6 days. Of the 13 evaluable patients in the amoxicillin/metronidazole group all were successfully cured or improved and all 15 patients in the ceftriaxone group were also assessed as cured or improved.

A review of effective antibiotic treatments in post-partum infections, considers amoxicillin an appropriate antibiotic for the treatment of endometriosis in combination with another antibiotic such as aminoglycoside or metronidazole (Chaim, 2003).

The evidence provided, although not recent, demonstrates that amoxicillin has been used to treat a variety of genital infections in females with variable results. However, when considering the different sites of infection, insufficient data is available to support these potential indications. Furthermore, recent guidelines do not support the use of amoxicillin for genital infections such as pelvic inflammatory disease or vaginosis; other antibiotics are recommended. The CHMP therefore was of the view that this indication was no longer relevant for amoxicillin and should be removed from the product information across all member states.

Gastrointestinal infections

Typhoid and paratyphoid fever – oral formulations

"*Typhoid*" is authorised in 8 of the 12 MSs where Amoxil has a marketing authorisation. The MAH proposed to revise the term to "*Typhoid and paratyphoid fev*er", which was accepted by CHMP. The MAH presented 4 clinical trials, comparing the efficacy of oral amoxicillin to chloramphenicol or ampicillin in adults and children summarised below. In addition the MAH presented an open study in 30 adults comparing amoxicillin (1 g amoxicillin four-times daily) to chloramphenicol (1g TID until defervescence followed by 500 mg QID for one week), a study comparing the efficacy of 3 g oral amoxicillin daily to 2 g oral amoxicillin given with 1 g probenecid in 8 patients and two open label, non-comparative studies in 12 and 7 patients that further supported use in this indication.

Scragg, 1975, evaluated the efficacy of amoxicillin compared with chloramphenicol in a randomized, single blind study in 200 children aged 2 to 12 years for the treatment of typhoid fever. All typhoid cases were proved by isolation of *S. typhi* in blood cultures. Patient treated with oral amoxicillin received 2g/day for 21 days and those treated with oral chloramphenicol received 50 mg/kg/day QID for 21 days. The clinical response rate in the amoxicillin group was 82% vs. 56% for the chloramphenicol group, respectively (statistically significant difference). After 72 hours of therapy *S.typhi* was recovered in 6/95 (6%) children in the amoxicillin group and 11/93 (12%) children in the chloramphenicol group in blood cultures performed on 188 patients. Two patients in the amoxicillin group relapsed compared with 5 relapses in the chloramphenicol group. Six patients died during the study, 2 from the amoxicillin group and 4 from the chloramphenicol group. The authors concluded that amoxicillin appeared to be a superior treatment to chloramphenicol with a wider therapeutic margin and more advantageous safety profile.

A non-randomized clinical trial compared the safety and efficacy of amoxicillin and chloramphenicol in 155 children, aged between 2-11 years, with typhoid (Scragg, 1976). Patients were given either amoxicillin 100 mg/kg/day QID for 21 days (n=85), or chloramphenicol 50 mg/kg/day QID for 21 days (n=70). A satisfactory clinical response was recorded within five days in 89% (76/85) and 54% (38/70) of the amoxicillin and chloramphenicol groups, respectively, with the differences being highly significant (P<0.001). No relapses occurred in the amoxicillin group however in the chloramphenicol group one relapse occurred with reisolation of *S. typhi* from the blood 19, 20 and 22 days after the treatment stopped.

In a South African study 124 adult patients with typhoid fever, proven by blood culture, were randomised to treatment with either amoxicillin (1g six hourly) or chloramphenicol (1g eight hourly), both given orally (Pillay, 1975). There was no difference in clinical response (improvement in toxaemia, return of appetite, and general wellbeing) between the groups, although early defervescence (within 3 days) occurred in more patients on amoxicillin (15 compared to 6). The authors concluded that oral amoxicillin was an alternative to chloramphenicol in the treatment of typhoid fever and with a more advantageous safety profile.

Orally administered amoxicillin was used to treat patients with typhoid fever due to chloramphenicol-resistant *S. typhi* and was compared to ampicillin (Calderon, 1974). Twenty-five patients received 100 mg/kg/day of amoxicillin in four divided doses and ampicillin 100 mg/kg/day IV was administered to 13 patients. Of the 25 patients who received amoxicillin, all were free of fever within five days, and all cultures were negative within 72 hours. Cultures remained negative after 6 months treatment. There were no untoward effects. Orally administered amoxicillin was as effective as IV ampicillin in curing typhoid fever caused by chloramphenicol-resistant *S. typhi*.

The WHO guideline (2003) recommends amoxicillin as second-line treatment for typhoid fever especially where it is known that the pathogen is fully susceptible and there is no local evidence of resistance.

A review by Sánchez-Vargas, 2011, on salmonella epidemiology, prevention and treatment, considers that amoxicillin is an appropriate alternative for the treatment of uncomplicated enteric fever. The same review recommended amoxicillin for the treatment of severe enteric disease due to susceptible strains in addition to chloramphenicol, or trimethoprim-sulfametoxazole as well as for the treatment of the carrier state in adults or children, or ampicillin plus probenecid, trimethoprim-sulfamethoxazole, or ciprofloxacin. Other review articles on enteric fever also endorsed the use of amoxicillin as second-line treatment for non-severe enteric fever (Brusch, 2014; Ericsson, 2005).

As stated before, fluoroquinolones are widely regarded as optimal for the treatment of typhoid fever in adults. Due to the emergence of resistance to fluoroquinolones, however, their widespread and indiscriminate use in primary care settings should be restricted. In areas with high rates of fluoroquinolone resistance, cefixime, ceftriaxone or azithromycin are recommended as first options. As an alternative treatment, in infection due to a fully susceptible *S. typhi* strains, one of the alternative regimens that may be used is amoxicillin (1g divided into three or four doses in adults or 100 mg/kg per day divided every eight hours, maximum 4 g per day for 14 days in children). Although not considered the optimal therapy and only when the bacteria are fully sensitive to amoxicillin, it remains as an appropriate alternative for the treatment of typhoid fever.

The CHMP considered that while fluoroquinolones are widely regarded as optimal for the treatment of typhoid fever in adults, in areas with high rates of fluoroquinolones-resistance, amoxicillin remains an appropriate alternative for the treatment of typhoid fever. Although the MAH has submitted a limited number of studies, those demonstrate the efficacy of amoxicillin when the susceptibility of the bacterium is known. Furthermore amoxicillin is recommended as a treatment option in several recent clinical guidelines. Therefore while amoxicillin should not be used as empirical treatment in this indication, the CHMP concluded that the indication should be maintained with a cross-reference to section 4.4.

Skin and soft tissues infections (SSTI)

(Severe) dental abscess with spreading cellulitis – all formulations

"*Skin and soft tissue infections"* is authorised in 8 out of the 12 MS where Amoxil has a marketing authorisation and "*dental abscess*" and "*odontostomatological infections*" respectively in 4 and 1 MS. The MAH proposed to further specify the general indication it by adding *"in particular cellulitis, severe dental abscess with spreading cellulitis, impetigo"*, however the CHMP was of the view that the data submitted did not support all of these indications. The MAH presented five randomised double blind trials conducted between 1981 and 1989 comparing the efficacy of amoxicillin to ampicillin, amoxicillin/clavulanate, bacampicillin, lenampicillin, one open study, 9 non-comparative studies and a review in patients with various acute skin infections which are summarised below. In addition the MAH presented 4 clinical studies conducted between 1990 and 2005 in patients with dentoalveolar abscesses of different severity and an audit to determine the influence of different antibiotic therapy on treatment outcome of acute dentoalveolar infection. Several guidelines and reviews were also presented in support of these indications.

Acute skin infections

Fujita, 1985, conducted a double blind study in skin and soft tissue infections comparing amoxicillin to lenampicillin. Two hundred and thirty-five patients were enrolled, 120 received1g amoxicillin daily divided in 4 doses and 115 received lenampicillin 1g daily divided in 4 doses, both for 14 days. Skin infections were grouped in six groups according to severity and are presented in the below table.

Table 9. Distribution of the Skin and soft tissue infections

	Type of Skin Infection	**Amoxicillin Group**	**Ampicillin Group**
Group 1	Folliculitis	16	20
	Pustular acne	13	6
Group 2	Furuncle	16	15
	Furunculosis	9	7
	Carbuncle	-	5
Group 3	Impetigo	4	4
	Impetiganeous eczema	6	5
Group 4	Erysipelas	2	2
	Phlegmon	5	3
	Lymphangitis	1	1
	Whitlow	3	2
	Suppurative onchomycosis	3	4
Group 5	Subcutaneous abscess	3	3
	Suppurative hidradenitis	1	1
	Acne conglobata	2	4
	Infected atheroma	16	17
	Chronic pyoderma	3	-
	Perianal abscess	1	1
Group 6	Secondary infectious ulcer	11	8
	Infected decubitus	11	10

The predominated pathogens isolates were *S. aureus* and *S. epidermidis.* Seventy three subjects in the amoxicillin group and 84 subjects in the lenampicillin group had polymicrobial infections with a mixture of *Staphylococci* spp. and *Streptococci* spp including anaerobes. The percentage of patients cured and improved at the test of cure visit ranged from 80% to 91% for amoxicillin and from 67% to 96% for lenampicillin 67% to 96% depending on severity groups. The bacteriological response was 88.9% for amoxicillin and 81.8% for lenampicillin. The authors concluded that amoxicillin was an effective antibiotic in the treatment of a wide variety of infections.

Dagan, 1989, undertook a double-blind controlled study to compare the efficacy of amoxicillin with the efficacy of amoxicillin plus clavulanic acid combination in the treatment of non-bullous impetigo. Fifty-one culture-positive patients, aged 6 months to 9 years, were included, 26 in the amoxicillin group and 25 in the combination group. All *staphylococci* were susceptible to the combination but resistant to amoxicillin. Forty-nine patients completed the study. The clinical response was significantly better among the combination recipients (marked improvement in 71% and 95% of patients after 2 and 5 days, respectively; no new lesions during the treatment course) than among the amoxicillin recipients (marked improvement in 44% and 68% of patients after 2 and 5 days, respectively; new lesions appeared in 20% of patients). Recurrence within 3 weeks occurred in 12 (26%) of 49 patients, and no difference was observed between the two groups.

In a double blind comparative Japanese study, 750 mg of amoxicillin given once daily for 7 days was compared to 1.5 g ampicillin in 112 patients with furuncle/carbuncle (33), phlegmon (48), infected sebaceous cyst (20), and wound infection (11). Seventy six percent of the patients in the amoxicillin group were successfully treated compared to 84% of patients treated with ampicillin. The infecting

pathogens were considered eradicated in 91% of patients treated with amoxicillin and 97% of patients treated with ampicillin.

A small randomized study evaluated the efficacy of 250 mg amoxicillin TID compared to 400 mg bacampicillin BID in 20 patients with cellulitis, impetigo, dermatitis and injured hand (Rosenberg, 1981). The majority of pathogens isolated were β-haemolytic *streptococci* and *S. aureus*. All 20 subjects achieved complete clinical and microbiological cure after 10 days.

In addition a recent randomised, open study evaluated the efficacy of amoxicillin compared to erythromycin for the treatment of severe pyoderma (Faye, 2007). One hundred and thirty-two patients with severe pyoderma were randomised to an oral treatment by either amoxicillin (50 mg/kg/day) or erythromycin (30 mg/kg/day) for seven days. In addition to antibiotic treatment, topical application of povidone iodine was used. Treatment was successful in 89% patients treated with amoxicillin versus 58 of 89% patients treated with erythromycin. The authors concluded that amoxicillin was as efficacious as erythromycin in the treatment of severe pyoderma.

Nine open studies conducted in the seventies in a total of 473 adults and children with a wide range of skin infections using various doses of amoxicillin were presented to further support this indication. Cure rates ranged from 89% to 72%.

Wise, 1974, has reviewed the clinical trials conducted in the United States with amoxicillin in the early 1970s which included patients treated with SSTI. Three hundred and forty two patients (including 135 children) were treated with different doses of oral amoxicillin which included a variety of different skin infections. The clinical diagnoses were 89 abscesses, 129 impetigo, 41 superficial cutaneous infections, 17 cellulitis, 46 post-operative traumatic wound infections and 20 miscellaneous skin infections. Overall the clinical response rate was 97%, no significant difference was.

The recently updated Infectious Diseases Society of America (IDSA) Practice Guideline for the Diagnosis and Management of Skin and Soft Tissue Infections only recommends amoxicillin for erysipeloid type infections (Stevens, 2014). The guidelines also consider amoxicillin as a suitable therapy for typical cases of cellulitis as amoxicillin is active against *streptococci*.

Several reviews also consider that amoxicillin is a useful agent for the treatment of SSTI (Scher, 2005; Hedrick, 2006).

Dental infections

Winkel, 2001, conducted a double-blind randomised placebo controlled, parallel study which evaluate the adjunctive effects of systemically administered 375 mg amoxicillin plus 250 mg metronidazole TID for 7 days in a group of 49 adult periodontitis patients who also received supra- and subgingival debridement. Clinical measurements and microbiological assessments were taken at baseline and 3 months after completion of initial periodontal therapy with additional placebo or antibiotic treatment. Except for plaque, there was a significantly larger change in the bleeding, probing pocket depth (PPD) and clinical attachment level in the amoxicillin plus metronidazole group as compared to the placebo-group after therapy. The number of patients positive for *Porphyromonas gingivalis*, *Bacteroides forsythus* and *Prevotella intermedia* in the antibiotic treatment group showed a significant decrease compared to placebo. The authors concluded that systemic usage of metronidazole and amoxicillin, when used in conjunction with initial periodontal treatment in adult periodontitis patients, achieves significantly better clinical and microbiological efficacy results than initial periodontal treatment alone.

A comparative double blind trial was undertaken to compare the efficacy of 5 days of cephradine 500 mg BID, amoxicillin 250 mg TID and phenoxymethylpenicillin 250 mg QID in the treatment of acute dentoalveolar abscesses with systemic involvement in 100 male and female patients (Fazakerley,

1993). Clinical efficacy was evaluated from accumulative score of the signs and symptoms of pain, swelling, temperature and lymphadenopathy. All patients improved after 2 days of therapy with surgical drainage, although the cephadrine group had slightly better scores of pain, swelling and temperature. At day 5 all patients had improved and the clinical scores where similar in all groups apart from some elevated temperatures. The authors concluded that all three antibiotics were effective in the treatment of dentoalveolar abscesses.

An Italian randomized clinical and microbiological study was conducted that evaluated the efficacy of (intramuscular) IM and oral amoxicillin and lincomycin in 49 subjects with dentoalveolar abscesses that necessitated parenteral therapy (Eftimadi, 1990). Patients either received 1g IM of amoxicillin TID for 2 days followed by oral 500 mg amoxicillin TID for 3 days or IM lincomycin 600 mg BID for 2 days followed by oral 100mg lincomycin for 3 days. Clinical efficacy was evaluated by assessing signs and symptoms of temperature, blood pressure, respiratory rate, morbidity and lymphadenopathy. The patients were assessed at day 3 and day 6. In general it appeared that lincomycin achieved a more rapid resolution of signs and symptoms of infection, however at day 6 the majority of patients were clinical successes.

Thirty patients with dental infection were enrolled in a randomised study and were treated with amoxicillin (1g IV TID for 24h followed by oral 500 mg TID) and metronidazole (500mg IV TID followed by oral 250mg TID) or Augmentin (1.2g IV TID for 24h followed by oral 500 mg TID) (Chomarat, 1991).The majority of signs and symptoms had resolved by day 3 or 4 of treatment. The clinical success rate in the two treatment groups was ≥92%. After 10 days treatment there were two failures, one in either treatment group.

An outcome audit by Kuriyama, 2005, was to measure the outcome of treatment of acute dentoalveolar infection and to determine if this was influenced by choice of antibiotic therapy or the presence of penicillin-resistance. A total of 112 patients with dentoalveolar infection were included in the audit. All patients underwent drainage, either incisional (n=105) or opening of the pulp chamber (n=7) supplemented with antibiotic therapy. Clinical signs and symptoms were recorded at the time of first presentation and re-evaluated after 48 or 72 hours. Penicillin V (500 mg, every six hours) or amoxicillin (500 mg, every eight hours) was prescribed to 65 patients. All antibiotic regimens produced a satisfactory outcome and there was no significant difference in the improvement score between the regimens.

Robertson, 2009, did a comprehensive review of the microbiology of dental infections and recommends that antibiotics should only be prescribed in patients exhibiting signs of local spread or systemic involvement and considers that amoxicillin is the first choice for dental infections. Similarly a review by Ellison, 2009, reviewed the literature and together with evidence based research has recommended amoxicillin as the first choice antibiotic for treating dentoalveolar infections.

The primary care guideline from the UK (2013) recommends amoxicillin 500 mg TID for 3 to 5 days for the treatment of dentoalveolar abscess and pericoronitis. In addition, numerous European Dental Societies and national guideline (ANSM, 2011) recommend amoxicillin as the first choice treatment for dental infections in adults and children.

The treatment of acute skin infections was effective in about 60-90% of patients depending on the study. Amoxicillin could be an option in these indications, however as most cases would be due to *staphylococci* or *streptococci*, agents with broader spectrum of activity would be required. Recent guidelines (Public Health England guideline 2015, IDSA guideline 2014, Surgical Society Infections guideline 2011) recommend antibiotics other than amoxicillin for the treatment of most skin and soft tissue infections. Therefore the CHMP considered this indication no longer appropriate for amoxicillin.

However amoxicillin alone or in combination with metronidazole was found effective in the treatment of severe dental infections in several studies conducted between 1990 and 2005. In addition several guidelines recommend the use of amoxicillin as first choice in these infections. The indication "*dental abscess with spreading cellulitis"* for the oral formulation and "severe *dental abscess with spreading cellulitis"* for the parenteral formulation was therefore considered acceptable by CHMP.

Other infections

Prosthetic joints infections (PJIs) – all formulations

The treatment of chronic bone and joint infections remains difficult. It requires a multidisciplinary approach that combines the identification of the responsible pathogen(s), surgical intervention, and prolonged antibiotic therapy. Because of the usual need for prolonged administration, the choice of the antibiotic to be used relies on several characteristics: in vitro activity against the isolated microorganism(s), good or excellent bone penetration, and good tolerance. "*Osteomyelitis*" is authorised in 8 out of the 12 MS where Amoxil has a marketing authorisation and "*acute arthritis*" is authorised in 2 out of those 12 MS. The MAH proposed delete the acute arthritis indication and reword the other indication as follows "*bone and joint infections, in particular osteomyelitis*", however the CHMP was of the view that the data submitted only supported use a subset of this broad indication, namely in infections of prosthetic joints.

There are few well-designed randomised controlled trials in patients comparing efficacy of different antibiotics. Several reviews and meta-analysis including two Cochrane reviews, concluded that the available literature on the treatment of osteomyelitis, bone and joint infections, in adults and children is inadequate to determine the best antimicrobial agent, route or duration of antibiotic therapy (Lazzarini, 2005; Stengel, 2001; Conterno, 2009; Faust, 2012). The MAH presented two small clinical trials and five retrospective case studies as well as reviews and guidelines summarised below.

Peltola, 2009, evaluated the efficacy of different antimicrobial regimens in a prospective, randomized trial of 10 days versus 30 days of antimicrobial treatment, including a short-term course of parenteral therapy. Amoxicillin 200 mg/kg/day was given to 20 children with septic arthritis due to *H. influenzae* and was effective in curing the disease.

Amoxillin was evaluated in 22 Japanese patients with bone and joint infections (Kondo, 1973). Four patients had chronic osteomyelitis, two patients had suppurative arthritis and the remainder had post-operative infections. The post-operative infections occurred as a result of primary closure of compound fractures. The predominant pathogen was *S. aureus*. Amoxicillin dosing regimen ranged from 250 mg BID to 250 mg four times daily for a duration of 3 days to more than 28 days. Of the 22 patients treated, 17 were cured and therapy failed in 5 patients.

Charlier, 2012, retrospectively reviewed bone and joint infections caused by *L. monocytogenes*. Forty-three adults and adolescent (median age 72 years) were studied, thirty-six patients (84%) had orthopedic implant device since 0.1 to 22 years (median time after insertion was 9 years). Subacute infection was more frequent than acute infection. Antibiotics, primarily amoxicillin (80%) with aminoglycosides (48%), were prescribed for a median duration of 15 weeks (range, 2–88). Eighteen patients (50%) underwent prosthesis replacement; all were successful after median follow-up of 10 months (range, 1–75). Five of 13 patients for whom material was not removed had protracted infection despite prolonged antibiotic therapy; 3 of these patients later underwent prosthesis replacement with sustained recovery. The authors concluded that amoxicillin in combination with an aminoglycoside was effective therapy in patients with bone and joint infections due to *L. monocytogenes*.

A retrospective review of 139 patients with prosthetic hip infections was conducted by Zeller, 2009. Seventeen patients with Group B streptococcus (GBS) PJIs were treated with amoxicillin and gentamicin followed by amoxicillin and rifampicin and five with vancomycin and gentamicin followed by vancomycin and rifampin and two with another regimen. With a median follow-up of 22 months, seven subjects experienced treatment failure (three relapses, one infection- and one treatment-related death). Patients that relapsed were placed on prolonged oral suppressive therapy with amoxicillin. The authors concluded that PJI in hip joints appear to have a higher failure rate than other PJIs and concluded that GBS PJI was more frequent than that of other PJIs and considered that prescription of prolonged suppressive antibiotic therapy in some patients to prevent relapses, might improve the outcome of these patients.

A retrospective review of 103 patients with anaerobic bone and joint infections (with a majority of orthopaedic devices) was conducted by Walter, 2014. *P. acnes* and *Finegoidia magna* were the predominant pathogens isolated. In 30% of the patients amoxicillin was prescribed and the mean duration of therapy was 150 days with the majority of patients receiving 84 days. Fifty-seven (57) patients with bone and joint infections also received surgical treatment in addition to antibiotic treatment. Fourteen patients (14) of the 20 patients with *P. acnes* infection were treated with amoxicillin no relapse of infection was observed.

Prendkia, 2014, conducted a retrospective observational study in 38 patients with a median age of 84 years (80–95 years) which included 24 hip infections, 13 knee infections, and one shoulder infection. The main causative organisms were *Staphylococcus aureus* (39%) and *Streptococcus agalactiae* (16%). All patients were treated with prolonged chronic suppressive therapy for a PJI due to an infected prosthesis that could not be removed. Thirty-two patients initially received IV antibiotic therapy for a median of 30 days (range 10-45 days) prior to receiving high dose oral therapy for 4 to 6 weeks to reduce the bacterial burden and then with a lower dose for prolonged antimicrobial suppression. Beta-lactams were used in 24 patients, 10 of whom received IV amoxicillin for initial treatment and then 8 received high dose amoxicillin 2 g TID for 4 to 6 weeks. Following initial therapy, 14 of the 38 patients were prescribed amoxicillin 1000 mg TID as prolonged chronic suppressive therapy, 60% were event free at 24 months. Of note was that six of seven patients with Streptococcal PJI were treated successfully with amoxicillin.

Ispahani, 1987, evaluated cases of septic arthritis between 1985 and 1998. Thirty-two (32, 8.2%) of 389 cases of septic arthritis in adults and children (including 6 children < 2 years old) were due to *S. pneumoniae*. Patients received intravenous therapy with benzylpenicillin plus flucloxacillin, pending blood and/or synovial fluid culture results. Thereafter, benzylpenicillin alone was the mainstay of antimicrobial therapy for 26 (81%) of the patients. The mean duration of intravenous therapy was 8 days for children and 17 days for the 17 adults who survived. Of those who survived, 7 children and 14 adults received a course of oral antimicrobial therapy, most commonly with amoxicillin (dose not specified), for varying periods of time. Seven children and 11 adults had completely recovered.

Not many treatment guidelines for PJIs and prolonged therapy are established. Consensus and evidence based guideline for the treatment of PJIs produced by six French societies (SPLIF, 2009) consider amoxicillin the first choice antibiotic for PJIs in adults and children for the coverage of beta haemolyitic *Streptococci*, *Enterococci* and *P. acnes/Peptostreptococcus* spp. The guideline also recommends that in some cases initial therapy can be combined with gentamicin for 5-7 days. The Infectious Diseases Society of America guideline for the treatment of PJIs, recommends oral amoxicillin 500 mg TID as the preferred option for chronic prolonged treatment for PJIs due *Streptococci* spp., *Propionibacterium* spp. and *Enterococci* spp. (penicillin susceptible) (Osmon, 2013).

Several review articles also support the use of amoxicillin in the treatment of PJIs. A review by Trampuz, 2008, on the diagnosis and treatment of implant associated septic arthritis and osteomyelitis recommends amoxicillin for infections due to *Streptococci* spp. and *Enterococcus* spp. (penicillin susceptible). Zimmerli, 2004, considers that amoxicillin is a usefull follow-on therapy for PJIs caused *Streptococci* spp. A review of the treatment of infected knee prosthetic joints, recommends amoxicillin for long term oral use for infections due to Group B Streptococci, *S. viridans*, *Enterococcus* spp. and *P. acnes* (Chen, 2012). Oral amoxicillin (750 mg to 1000 mg TID) is recommended as first choice switch therapy following IV therapy with a cephalosporin for PJIs (surgical removal of prosthesis) due *Streptococcus* spp. by Barberán, 2006. The same review recommends oral amoxicillin (750 mg to 1 g TID) for chronic prolonged suppressive therapy for PJIs due *Streptococcus* spp.

The MAH provided data suggesting that the penetration of amoxicillin into bone is adequate, even when the tissue is infected and PK/PD data supporting the use of amoxicillin in these conditions however the clinical evidence is very limited. The few studies presented include different conditions, which further decreases the evidence in support for each condition. In addition, in some studies amoxicillin was only used as follow-on therapy after intravenous use of other antibiotics. However several retrospective studies point to indicate a good efficacy in the treatment of prosthetic joints infections. While not many guidelines are in place for this type of infection several learned societies recommend amoxicillin as a first choice treatment. Therefore the CHMP considered this specific indication acceptable.

Treatment and prophylaxis of endocarditis – all formulations

"*Endocarditis*" is authorised in all MS where Amoxil has a marketing authorisation. The MAH proposed to further specify it by adding "*treatment and prophylaxis of endocarditis*", which was accepted by the CHMP.

There are very few randomised trials that have evaluated the efficacy of antibiotic prophylaxis in infectious endocarditis. Owing to the very low incidence, clinical studies would have to be sufficiently powered to demonstrate a benefit. Additionally because of the end points, very large numbers of subjects would need to be enrolled to demonstrate a true effect.

The MAH presented numerous non-clinical studies conducted between 1983 and 2007 assessing the efficacy of amoxicillin in preventing and treating endocarditis in animal models. Amoxicilling was compared to to cephadrine, daptomycin, vancomycin azithromycin, clarithromycin, erythromycin and linezolid in rabbits and rats models of endocarditis. Amoxicillin was consistently found effective in preventing and treating endocarditis and was found superior to cephadrine and erythromycin.

In addition, the MAH presented three studies on the efficacy of amoxicillin in the prevention of bacteraemia following dental extractions, an open study and two case studies of amoxicillin in treatment of endocarditis which are summarised below.

Prophylaxis

Diz-Dios, 2006, compared the efficacy of oral prophylactic treatment with 2 g amoxicillin, 600 mg clindamycin or 400 mg moxifloxacin in the prevention of bacteraemia following dental extractions (BDE) in 221 adults randomly allocated to one of the treatment groups or to a group that did not receive antibiotic treatment. The prevalence of BDE in the control group, amoxicillin group, clarithromycin group, and moxifloxacin group were 96%, 46%, 85%, and 57%, respectively, at 30 seconds; 64%, 11%, 70%, and 24%, respectively, at 15 minutes; and 20%, 4%, 22%, and 7%, respectively, at 1-hour. *Streptococcus* spp. was the most frequently identified bacteria in all groups (44% to 68%), with the lowest percentage being detected in the amoxicillin group (44%).

Shanson, 1992, compared the efficacy of amoxicillin 1g IM to Teicoplanin 400 mg, given as an intravenous bolus dose after induction of general anaesthesia, in reducing the prevalence of streptococcal bacteraemia following dental extraction. *Viridans streptococci* were isolated from one of 40 patients receiving teicoplanin (2.5%) and from 10 of 40 (25%) receiving amoxicillin compared with 13 of 40 (32.5%) who received no treatment patients. The mean serum teicoplanin and amoxicillin concentrations at the time of extraction were 37 and 10 mg/L, respectively. Although amoxicillin was administered with lignocaine, patients occasionally complained of pain following intramuscular injection. The results of this study suggest that the 400 mg intravenous bolus dose of teicoplanin is more suitable than 1.0 g intramuscular amoxicillin for the parenteral prophylaxis of streptococcal endocarditis in patients with cardiac lesions who require a dental procedure.

A controlled clinical trial investigated the effects of oral amoxicillin for the prophylaxis of infective endocarditis in children having treatment under local anaesthesia (Cannon, 1987). A total of 26 healthy children were given an oral dose of amoxicillin: 750 mg if aged between 1 to 5 years, and 1.5 g if aged between 6 to 10 years. The mean serum concentration 4 hours after amoxicillin administration was for all patients was 14.34 mg/L. These levels are well in excess of the minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC) of the *viridans streptococci* associated with endocarditis. The authors concluded that adequate protection for children at risk from bacterial endocarditis can be provided by the oral regimen given 4 hours prior to operation under general anaesthesia and suggested that a second dose be administered when patients recover from the anaesthetic in order to maintain an adequate blood concentration during the post-operative period.

Treatment

In an open randomised prospective study, 30 patients with infectious endocarditis (IE) caused by penicillin-susceptible streptococci were enrolled in one of two groups (Stamboulian, 1991). Fifteen patients received ceftriaxone (2 g once daily) for 4 weeks; the other 15 received the same dosage of ceftriaxone for 2 weeks and then received oral amoxicillin (1 g four times a day) for 2 weeks. For the 27 patients treated predominantly as outpatients, 380 days of hospitalization were avoided. Clinical cure was achieved for all patients in both groups. All 15 patients treated with ceftriaxone followed by oral amoxicillin were cured and although initially all patients that received ceftriaxone were cured, one patient had a relapse of infection.

A retrospective observational study of 52 adult elderly patients with definite diagnosis of IE due to enterococci evaluated the once daily administration of aminoglycoside which included IV amoxicillin (Patrat-Delon, 2013). *Enterococcus faecalis* was involved in 48 cases. Most patients received IV amoxicillin and gentamicin as therapy for a mean duration of 29.5 days. Majority of patients were effectively treated with only 3 patients relapsing. The authors concluded that a combination of amoxicillin and once daily gentamicin was safe and effective for the treatment of enterococcal endocarditis in a population of elderly patients with major co-morbidities.

A case study of IE due to *Streptococsus bovus* presented by Garcia Rodriguez, 1992, demonstrated that a patient was successfully treated with a two week course of ceftriaxone followed by oral amoxicillin 2 g four times daily for a further two weeks.

Guidelines

The recently updated American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines (which have been endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and by the International Society of Chemotherapy (ISC) for Infection and Cancer) recommend amoxicillin as one of the drugs of choice for prophylaxis of IE in adults and children

considered at highest risk (underlying cardiac conditions associated with the highest risk of IE) (Wilson, 2007; Habib, 2009).

National guidelines in Europe also continue to recommend amoxicillin for the treatment and prophylaxis for IE and include the Italian Federation of Cardiologists and the Italian Society of Infectious and Tropical Diseases (Cecchia, 2010), British Society of Antimicrobial Chemotherapy (BSAC, Gould, 2012), the Dutch Working Party on Antibiotic Policy guidelines (SWAB, 2003).

Several review articles of prophylaxis and treatment of IE support the use of amoxicillin and actually mention it as first choice treatment for infective endocarditis due to streptococci or enterococci including *E. faecalis* (Hoen, 2013; Sandoe, 2013; Hoen, 2006; Chirouze, 2012; Borbolla, 2010; Watkin, 2009; Tomas, 2007; Que, 2011).

The clinical data provided, while limited, supports the efficacy of amoxicillin in prevention of bacteraemia as well as in treatment of infectious endocarditis. In addition the MAH provided data from recognised animal models to support the prophylaxis and treatment indication. Recently updated international guidelines support the use of amoxicillin in prophylaxis of infectious endocarditis for patients at higher risk. Several national guidelines support the use of amoxicillin, including as a first choice, for treatment and prophylaxis of endocarditis. Finally amoxicillin is mentioned as first choice for treatment of endocarditis in several reviews also supporting the use in prophylaxis. Therefore the CHMP was of the view that the prophylaxis indication continues to be appropriate for all formulations. However the CHMP considered that due to the seriousness of the condition and in line with the ESC, AHA, British Society of Antimicrobial Chemotherapy (BSAC) and British Cardiac Society (BCS) guidelines only the parenteral formulation was useful in treatment of endocarditis and requested that the indication be removed from the oral formulation.

Helicobacter pylori eradication – oral formulations

This indication is authorised in 8 out of the 12 MS where Amoxil has a marketing authorisation. The MAH did not propose any change to the wording and the indication as such was supported by the CHMP.

The MAH has provided a number of controlled clinical trials in adults and children with amoxicillin generally in triple therapy as first (9 trials including one specifically in children and a meta-analysis of 22 studies), second (4 trials) and to a lesser extent third (1 trial) line further supported by uncontrolled studies, relevant examples are summarised below.

Mazzoleni, 2011 evaluated the eradication of *H. pylori* in 400 patients with functional dyspepsia by studying the effects on symptoms and quality of life. *H. pylori* positive adult patients with functional dyspepsia meeting the Rome III International Consensus criteria were randomly assigned to receive omeprazole, amoxicillin trihydrate (1000 mg BID), and clarithromycin, or omeprazole plus placebo for 10 days. Endoscopy and *H. pylori* tests were performed at screening and at 12 months. Outcome measures were at least 50% symptomatic improvement at 12 months using a validated disease-specific questionnaire (primary end point), patient global assessment of symptoms, and quality of life. A total of 389 patients (96.3%) completed the study. The proportion of patients who achieved the primary outcome was 49.0% (94 of 192) in the antibiotics group and 36.5% (72 of 197) in the control group (P =0.01; number needed to treat, 8). In the patient global assessment of symptoms, 78.1% in the antibiotics group (157 of 201) answered that they were better symptomatically, and 67.5% in the control group (137 of 203) said that they were better (P =0.02). The antibiotics group had a significantly larger increase in their mean (SD) Medical Outcomes Study 36-Item Short Form Health Survey physical component summary scores than the control group did (4.15 [8.5] vs 2.2 [8.1]; P=0.02).

A study by Nguyen, 2008, compared two 2-week triple therapies in a randomised double-blind trial in 238 *H. pylori*-infected children, aged 3 to 15 years (mean 8.6). Children were divided in two weight categories receiving at weights 13-22 kg: lansoprazole 15 mg once-daily and amoxicillin 500 mg twice-daily with metronidazole 250 mg twice-daily or clarithromycin 250 mg once-daily; at weights 23-45 kg: lansoprazole 15 mg and amoxicillin 750 mg with metronidazole 500 mg or clarithromycin 250 mg, all administered twice daily. *H. pylori* status was assessed by culture and a monoclonal based antigen-in-stool test and side effects by structured questionnaires. The overall per-protocol eradication (n = 233) was similar in the two treatment regimens, 62.1% for the metronidazole and 54.7% for the clarithomycin-containing therapy. Eradication rate was higher in children (greater-than or equal to) 23 kg (70.9%) than in children < 23 kg (45.7%). In children (greater-than or equal to) 23 kg (n = 117) that received twice-daily administration of all drugs, efficacy of the methronidazole and clarithromycin-containing treatments were 69.5% and 72.4%, respectively. It was concluded that the two treatment regimens gave similar eradication rates; however significant differences for both treatments were found by weight, which could be the result of the once-daily proton pump inhibitor and clarithromycin and/or more antibiotic resistant strains in younger children.

Miehlke, 2011, evaluated triple therapy with esomeprazole, moxifloxacin, and amoxicillin in second-line or rescue treatment of 80 patients and the impact of treatment duration on eradication success. *H. pylori*-infected patients with at least one previous treatment failure were randomized to oral esomeprazole 20 mg BID, moxifloxacin 400 mg OD and amoxicillin 1000 mg BID for either 7 (EMA-7) or 14 days (EMA-14). Eradication was confirmed by 13C urea breath test. Antimicrobial susceptibility testing was performed in all patients at baseline and in patients who failed treatment. Eighty patients were randomized, and 60% had ≥2 previous treatment failures. Pre-treatment resistance against clarithromycin and metronidazole was found in 70.5% and 61.5% of cases, respectively. The intention-to-treat eradication rate was significantly higher after EMA-14 compared with EMA-7 (95.0 vs 78.9%, p =0.036). There were no serious adverse events. Five of the EMA-14 patients (12.5%) compared with none of the EMA-7 patients discontinued prematurely because of adverse events (p =0.031). Post-treatment resistance against moxifloxacin was found in one of seven patients with isolated organisms (14.3%).

Zullo, 2003 investigated the efficacy of a levofloxacin-amoxicillin combination was in patients who had previously failed two or more therapeutic attempts for *H pylori* eradication. Overall, 36 patients, aged between 20-75 years, were enrolled into the study and bacterial infection was assessed by rapid urease test and histology on gastric biopsies at endoscopy. All patients received a 10 day triple therapy comprising of rabeprazole 20mg b.i.d., levofloxacin 250 mg b.i.d., and amoxicillin 1 g b.i.d. At 4-6 weeks after treatment, the eradication of *H. pylori* was assessed by a further endoscopy or 13C urea breath test. *Helicobacter pylori* infection was successfully cured in 30 patients giving an 83.3% and 88.2% eradication rate for the ITT and PP populations, respectively.

Amoxicillin in triple therapy achieved eradication rates around 80-85% in the various studies presented. Furthermore amoxicillin is recommended in several guidelines (e.g. American College of Gastroenterology, NICE) in combination with a proton pump inhibitor and clarithromycin. The CHMP considered the efficacy of amoxicillin in tripled therapy for *Helicobacter pylori* eradication adequately demonstrated in adults and in children, as a first line or as rescue therapy.

Lyme disease – all formulations

"*Lyme disease*" is authorised in 6 out of the 12 MSs where Amoxil has a marketing authorisation. The MAH propose to clarify that the amoxicillin in only indicated for treatment of Lyme disease, which was supported by the CMHP. The MAH submitted results of six randomised controlled trials comparing amoxicillin alone or in combination with probenecid 500 mg TID to azithromycin, cefuroxime,

doxycycline, penicillin V and placebo, as well as an observational cohort study conducted in children and adults between 1989 and 2008 with amoxicillin, all in treatment of type I Lyme disease (erythema migrans). Relevant examples are summarised below.

A multicentre, double-blind, randomized prospective trial compared amoxicillin given 500 mg TID for 20 days (n=106) with azithromycin given 500mg OD for 7 days (n=111) for the treatment of erythema migrans skin lesions, the characteristic skin lesions of Lyme disease in adults (Luft, 1996). The patients, all aged ≥12 years of age and weighing ≥45 kg) were evaluated by a physician at baseline and 8, 20, 30, 90 and 180 days after initiation of therapy. At day 20 a complete response (defined as the complete clearance of erythema migrans and all objective signs with a greater than 75% relief of presenting symptoms) was seen in 88% of patients with amoxicillin and 76% of patients with azithromycin.

A randomised double-blind, placebo-controlled clinical trial was conducted evaluating the efficacy of amoxicillin versus placebo in treatment of Lyme disease (Cameron, 2008). A total of 84 adults with Lyme disease and persistent symptoms (LDPS) were studied; 52 received amoxicillin (3g/day) and 34 received placebo for 3 months. The SF-36 was used as the outcome measure of the patient's perceived Quality of Life (QOL). For subjects enrolling in this study, the average SF-36 physical component summary (PCS) of QOL (40, range 29-44) and mental component summary (MCS) of QOL (39, range 23-46) were worse than the general USA population and worse than individuals with diabetes, heart disease, depression, osteoarthritis or rheumatoid arthritis. The improvements in the SF-36 measure of QOL for subjects randomised to amoxicillin vs. placebo was significant (46% vs 18%, P=0.007).

While there is a paucity of clinical studies that evaluated antibiotic therapy in late stages of Lyme disease, the MAH provided three studies investigating the efficacy of amoxicillin in treatment of stages II/III Lyme disease.

Oksi, 2007, conducted a double-blind randomised placebo controlled study in patients with disseminated Lyme borreliosis to assess whether initial treatment with intravenous ceftriaxone should be extended to 3 weeks with a period of adjunct therapy. A total of 152 patients were enrolled with Lyme borreliosis and received either 1 g amoxicillin or placebo for 100 days. Of the patients with definite diagnosis 62 had neuroborreliosis, 45 arthritis or other musculoskeletal manifestations and 4 other manifestations of Lyme borreliosis. The outcome was evaluated using the visual analogue scale at the follow-up visits. The outcome after 1-year follow-up in patients with definitive Lyme borreliosis was excellent or good in 92.5% of patients treated with amoxicillin and 87% in patients treated with placebo.

Tory, 2009, conducted a retrospective review of case records of 99children diagnosed with Lyme arthritis (LA). Seventy-five percent of the 48patients treated with amoxicillin treated with oral amoxicillin (50 mg/kg/day) for 28 days had a positive outcome. Additionally of the cases resolved with antibiotic therapy, and none of the patients for whom follow-up data were available developed chronic arthritis, joint deformities, or recurrent infections.

Steere, 1994, evaluated the efficacy of amoxicillin compared to doxycycline in 38 adults with persistent LA treated with amoxicillin 500 mg given QID with probenecid or doxycycline 100 mg BID for 30 days. Eighteen of the 20 patients treated with doxycycline and 16 of the 18 patients who completed the amoxicillin regimen had resolution of the arthritis within 1-3 months after study entry.

The efficacy rates for amoxicillin were around 80%, which is comparable to the different active controls used in the studies presented. Amoxicillin treatment is furthermore mentioned in several European national and Pan European consensus and evidence based guidelines for Lyme disease including

disseminated Lyme disease and Lyme arthritis. The CHMP considered that this indication was supported by appropriate data.

Bacterial meningitis - Parenteral formulation

"*Meningitis*" is authorised in 3 out of the 12 MSs where Amoxil has a marketing authorisation, the MAH proposed to specify in the indication that it only applied to bacterial meningitis, to which the CHMP agreed. The MAH provided pharmacodynamic and pharmacokinetic data in animal models (a study in rats and another one in rabbits), children (five studies) and adults (two studies) which demonstrated a good penetration of amoxicillin in the cerebrospinal fluid (CSF).

Table 10. Mean amoxicillin levels of CSF in infants and Children with Meningitis

Study	No of patients	Route	Dose (mg/kg)	Time after dosing (h)	Mean CSF concentration (μg/mL)
Coquerel, 1985□	17 (day2)	IV	200 mg/kg/day (4 hourly on the first day and then 6 hourly)	1	7.74
Craft., 1979	18 (day 1) (day 5) (day 10)	IV	200 mg/kg/day	1	4.80 3.50 0.60
Denis, 1983	115 (day 2) (day 2) (day 2) (day 7) (day 7) (day 7)	IM	200 mg/kg/day (divided into 4 injections)	1 3 6 1 3 6	6.9 1.7 1.4 4.4 1.7 1.9
Nolan, 1979	11 (day 2-3) (day 6) (day 6) (day 14)	IV	200 mg/kg/day – 4 infusions of 15 min/day	2 0.5 4 0.5 4	3.25 0.94 0.58 0.63 0.36
Pesnel, 1983□	9 (day 3) 6 (day 4) 2 (day 7)	IV	240 mg/kg/day	3	3.60 1.60 4.45

Table 11. Amoxicillin concentrations in the blood and CSF of adult patients with purulent meningitis

Study	No of patients	Route	Dose (mg/kg unless specified)	Time after dosing (h)	Mean amoxicillin concentrations (μg/mL) blood	CSF
Lacut, 1981□	12 (day 1-2) 7 (day 3-5) 7 (day 8-12)	IV	152.6 ± 18.4	1 1 1	19.8 15.3 20.0	5.75 1.8 2.0
	6 (day 1) 8 (day 3) 7 (day 10)	IV	125.5 ± 5.2	3 3 3	4.3 2.5 3.0	3.4 1.9 1.3
	3 (day 1) 2 (day 4-5) 2 (day 10)	IV	125.5 ± 5.2	4 4 4	3.2 3.6 3.4	3.3 3.9 1.7
	1 (day 1) (day 2) (day 3) anuria (day 10)	IV	1,300 mg every 4 h	3 3 3.25 3.25	32.5 115 200 25.5	16.25 52 74 6.35
Strausbaugh, 1978	10	IV	2 g	1.5 4	no data	18.0 19.7

In addition the MAH provided results of several small clinical trials in children and in adults as well as case studies (Bibes, 2000; Mofredj, 2000) that support the efficacy of amoxicillin for the treatment of bacterial meningitis.

Table 12. Summary of clinical data for amoxicillin in the treatment of bacterial meningitis

Study	No of Patients	Dosage	Clinical Efficacy	Bacteriological efficacy	Pathogens isolated
Paediatric – controlled studies					
Nolan, 1979☐	11	200mg/kg/day	82%	100%	*H. influenzae*-9 *S. pneumoniae*-2
Coquerel, 1985	17	200 mg/kg/day	100%	Not evaluated	
Paediatric – uncontrolled studies					
Khurana, 1979	9	400mg/kg/day	100%	Not evaluated	*H. influenzae*-5 *S. pneumonia*-2
Maguire, 1979	21	318-377 mg/kg/day	67%	Not evaluated	Meningococcus-*6* *H. influenzae*-2 *S. pneumoniae*-3
US data Brogden, 1979	26	142-155 mg/kg/day	100%	100%	*H. influenzae*-26 *S. viridans*-1
EU data Brogden, 1979	23	249 (mean) mg/kg/day	78%	100%	Meningococcus-*4* *H. influenzae*-3 *S. pneumonia*e-1 Other – 1
Craft, 1979☐	43	200 mg/kg/day		95%	Meningococcus-*2* *H. influenzae*-38 *S. pneumoniae*-3
Adults					
European Data (unpublished)	26	12 (mean) mg/kg/day	100%	100%	Meningococcus-9 *S. pneumonia*e-2 *L.monocytogens* – 3 Other -5

Eleven children (aged ≥ 3 months) with bacterial meningitis were treated intravenously with amoxicillin 50 mg/kg in 15-minute infusions every 6 hour for 14 days (Nolan, 1979). During the course of this study, records of all patients treated with ampicillin for bacterial meningitis were reviewed and used as control cases. Patients with proven or suspected *H. influenzae* meningitis also received intravenous (IV) chloramphenicol, 100 mg/kg/day, until the infecting organism was shown not to produce β-lactamase. Every patient had the infecting organism eradicated from CSF and blood by the time the first specimens were obtained after initiation of therapy (48-72 hours). Nine of the 11 patients were reported as cured (82%) and the remaining two were classified as improved. The proportion of patients that were completely cured was similar to conventional treatment with ampicillin (7/10, 70%).

A second study investigated the safety, efficacy and pharmacokinetics of intravenous (IV) amoxicillin (n=17) and ampicillin (n=14) in children with purulent meningitis (Coquerel, 1985). All children were aged between 2 months and 11 years. Both antibiotics were used at a dosage of 200 mg/kg/day and the dose was divided with 4 hourly administrations on day 1, followed by 6 hourly administrations on subsequent days. All children were clinically cured and their CSF had returned to normal after 15 days of treatment.

Guidelines

De Gaudio, 2010, preformed a review of the global consensus and evidence based guidelines for the treatment of bacterial meningitis. In all guidelines, when therapy was targeted at a specific pathogen there was general agreement on the monotherapy of pneumococcal meningitis with penicillin G or ampicillin/amoxicillin or ceftriaxone/cefotaxime recommended for penicillin susceptible *S. pneumoniae*. Although rare, the guidelines were also in agreement that the use of cefepime and chloramiphenicol together with ampicillin or amoxicillin as alternative therapies for *H. Influenzae* type b meningitis. There were some differences for treatment of *L. monocyogenes*, with European guidelines advocating the use of amoxicillin in combination with an aminoglycoside.

The European Federation of Neurological Societies (EFNS) treatment guidelines recommend amoxicillin or ampicillin as empirical therapy if Listeria is suspected (EFNS, 2008). Additionally the EFNS guidelines also recommend amoxicillin for pathogen specific therapy for meningitis known to be due to *S. pneumoniae*, *H. influenzae* and *L.monocytogenes*. The guidelines also recommend amoxicillin in addition to a third-generation cephalosporin for community acquired bacterial meningitis, in patients with risk factors for Listerial meningitis (old age, immunosuppressed and/or signs of rhombencephalitis).

The French guideline from the Society of Pathologie Infectieuse de Langue Francaise (SPLIF, 2008), recommend amoxicillin (200 mg /kg/day) plus gentamicin for empirical treatment of community acquired bacterial meningitis suspected to be due to Listeria . The same guideline recommends a cephalosporin (cefotaxime or ceftriaxone) plus amoxicillin plus gentamicin in children less than 3 months with suspected listerial meningitis. The SPLIF guideline also recommends amoxicillin for bacterial meningitis in cases where the aetiology and susceptibility of the pathogens are known. The pathogens include *S. pneumoniae*, *N. meningitidis* and *L. monocytogenes*.

The Dutch Working Party on Antibiotic Policy (SWAB), guideline recommends amoxicillin, along with a third generation cephalosporin, for the initial treatment of bacterial meningitis in adult patients >60 years of age, and for patients >16 years of age with risk factors present such as alcohol abuse, altered immune status, recent head injury or a CSF leak (SWAB, 2012). This guideline also recommends amoxicillin as empirical therapy with or without a cephalosporin in neonates, children and adults as empirical therapy for community acquired bacterial infections suspected to be pneumococcal in origin or due to Listeria. Amoxicillin is also recommended by this guideline for pathogen specific therapy for *L. monocytogenes* and *S. agalactiae* infections.

The British guideline for the treatment of meningitis in children recommends amoxicillin as first line treatment for bacterial meningitis and also for treatment of meningitis due to *L. monocytogenes* (NICE, 2010).

There are several reviews in the published literature that recommend amoxicillin for the treatment of bacterial meningitis. A review on neonatal meningitis by Heath, 2010, considers a combination of amoxicillin (100 mg/kg) and cefotaxime an excellent combination for community acquired neonatal meningitis in cases where the pathogenesis is known. Heath, 2010, also recommended a combination of cefotaxime plus amoxicillin together with an aminoglycoside would be useful in cases where cephalosporin resistance is high in neonatal units. A review by Klein, 2009, on the therapy of community acquired bacterial meningitis recommended that when the definite diagnosis is established and the causative pathogen and its susceptibility to antibiotics is known that antibiotics such amoxicillin is one of the treatment choices for the following pathogens *S. pneumoniae*, *H. influenzae* and *L. monocytogens* meningitis. Stahl, 2009, did a review of the literature of the microbiology of bacterial meningitis to guide treatment regimens for this indication. It was concluded that for pneumococcal or meningococcal infection a third generation cephalosporin with amoxicillin remained a useful treatment option.

The data submitted shows that amoxicillin can penetrate the meninges well when inflamed, in both children and adults. The paucity of good quality clinical trials is acknowledged, however the few controlled and uncontrolled studies show the efficacy of amoxicillin for the treatment of bacterial meningitis, particularly when the pathogen is known to be susceptible to amoxicillin. Considering that meningitis is a relatively rare infection, and that several guidelines recommend the use of amoxicillin in meningitis, the CHMP considered that taken altogether the data provided supports the use of amoxicillin in this indication.

Bacteraemia that occurs in association with or is suspected to be associated with, any of the infections listed above - Parenteral formulation

"*Septicaemia*" is authorised in 7 out of the 12 MS where Amoxil has a marketing authorisation, the MAH proposed to reword it for clarity as bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections for which amoxicillin is indicated. The MAH provided data that demonstrates that amoxicillin achieves good tissue penetration and has been used for the treatment of bacteraemia, associated with a number of its approved indications. Furthermore many reviews and recommendations in the literature together with consensus and evidence based treatment guidelines, consider amoxicillin to be an important therapeutic option in the treatment of adult and paediatric bacterial meningitis. In line with the Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013), considering that amoxicillin has been in use for many years and is indicated for use in a broad range of infections, the CMHP was of the view that, based on the available data, the proposed indication was adequately justified.

2.2.2.2. Section 4.2 - Posology and method of administration

The MAH proposed harmonised dosing recommendations based on the doses studied in clinical trials and supported by pharmacodynamic and pharmacokinetic data and in line with international, European and national guidelines. The variability across member states linked to the prevailing background level of resistance is reflected in those recommendations. The doses recommended in various national SmPCs in adults and children above 40kg range from 250mg - 1mg TID, expressed differently and are comprised in the proposed harmonised posology. The MAH proposed to harmonise the paediatric dosing recommendations using the most commonly approved mg/kg dose (40 – 90 mg/kg/day in divided doses).

Amoxicillin has been shown to be efficacious and well tolerated in a number of dose regimens and many clinical trials have demonstrated that amoxicillin is as efficacious and well tolerated when the total daily dose is divided in two doses as when divided in three doses. On the basis of its pharmacokinetics, the total daily recommended amount is usually given in three divided doses. However, in some patient groups (especially in infants and children) drug administration every 8 hours may give rise to some problems of compliance.. Therefore, these two possible regimens have been reflected in order for the prescriber to tailor the dosing regimen to the needs of the patient and to improve patient compliance.

In line with the Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2) the MAH was requested to provide the dose regimen and the duration of treatment courses tabulated by indication. These tables are preceded by general recommendations on factors to consider when selecting the dose and duration of treatment, with a cross reference to 4.4, and followed by a reference to treatment guidelines to be considered when selecting the posology.

Separated dosing recommendations are provided for the oral, parenteral and intramuscular formulations for adults and children above 40kg, for children below 40kg, for patients with renal impairment including those under haemodialysis. In addition, for the parenteral and intramuscular formulations further dosing recommendation are given for neonates above 4kg up to 3 months and premature neonates weighing less than 4kg.

Amoxicillin is only eliminated by the kidneys therefore renal impairment slows down the serum kinetics of amoxicillin which results in high serum levels spread out over time hence the need for adapted

dosing recommendation, as consistently reflected in the SmPC of almost all MSs (Brogden, 1975b; Chelvan, 1979; Francke, 1979). Similarly studies conducted in renally impaired patients undergoing long-term, intermittent dialysis found that amoxicillin is eliminated faster during the dialysis, therefore doses should be given before and after the dialysis in order to maintain the serum levels of antibiotic (Francke, 1979; Chelvan, 1979).

2.2.2.3. Section 4.3 - Contraindications

Only the contraindications around hypersensitivity to the active substance (or any of the penicillins and beta-lactam agents) and the excipients are harmonised. Other contraindications were in place in a few member states, however the CHMP concluded that the risks associated to them were sufficiently addressed by wording in other sections of the PI for the reasons that follow.

A contraindication in patients with infectious mononucleosis was present in three member states as those patients are susceptible to develop a morbilliform rash, however it is considered more appropriate to recommend against the use of amoxicillin in those patients rather than strictly contraindicating its use.

In one member state amoxicillin was contraindicated in patients with acute lymphocytic leukaemia, however the review mentioning a risk of developing cutaneous drug eruption and appeared to have misquoted the information from the original article which reported that another beta lactam was associated with a risk of rash in 60-100% of children with infectious mononucleosis. Therefore the MAH's proposal to remove this contraindication was accepted.

In one member state it was stated under 4.3 that "*This medicinal product must generally not be used in combination with methotrexate*" with a cross reference to section 4.5. Methotrexate is mentioned under 4.5 in two member state with the statement that administered concomitantly with amoxicillin it can reduce renal clearance. This statement is considered contradictory with the principle of a contraindication and considering the lack of data supporting it, the MAH's proposal to manage the risk of reduction in renal clearance when administered with methotrexate in section 4.5 is agreed.

2.2.2.4. Section 4.4 - Special warnings and precautions for use

Several warnings were in place in all (or all but one) member states with slightly different wordings (Hypersensitivity reactions, renal impairment, crystalluria, skin reactions (including in patients with infectious mononucleosis, anticoagulant), overgrowth of non-susceptible microorganisms, prolonged therapy) and the harmonised proposal of the MAH was considered acceptable. A harmonised wording of the warning around the potential interference with diagnostic tests already present in 5 member states was also proposed to be implemented across all MS, which was accepted. Several statements regarding important information about excipients present in some member states (sodium, aspartame, sodium benzoate, lactose and sorbitol) were harmonised as well. The CHMP requested that the warning of the potential occurrence of seizures in patients treated with high doses or with renal insufficiency or seizures history, treated epilepsy and meningeal damage, present in one MS, be maintained as related adverse experiences such as myoclonic activity and seizures have been reported with beta-lactam antibiotics, especially when recommended dosages based on renal function and body weight were exceeded. The risk of Jarisch-Herxheimer reaction when amoxicillin is used in treatment of Lyme disease included in one member state was requested to be included in the harmonised PI.

In addition considering the resistance rate of specific microorganisms, a general warning against the use of amoxicillin for the treatment of some types of infection unless the pathogen is already

documented and known to be susceptible or very likely to be susceptible was requested to be included, together with a cross reference to section 5.1 for more details on the specific pathogens.

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

Most of the existing statements on interactions across the MSs were considered supported the (probenecid, allopurinol, tetracyclines, oral anticoagulants, methotrexate) and the MAH's proposed harmonised wording was accepted by the CHMP. The possible interaction with oral contraceptive through an effect on the gut flora which was in all but one member state was removed, in line with the recent Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) recommendation to remove this interaction from the PI of numerous antibiotics including amoxicillin (CMDh/326/2015, Rev.0) as "*the clinical evidence for the interaction between non-enzyme inducing antibiotics is questionable, evidence shows that antibiotics do not affect the pharmacokinetics of combined oral contraceptive pills*". In three member states it was mentioned that sulfasalazine plasma concentration may be reduced with aminopenicillins, however studies do not support this effect for amoxicillin and no relevant reports were identified in the safety database of the MAH; therefore it was considered acceptable to remove this statement. Interaction with test results was moved to section 4.4 in line with the SmPC guideline.

2.2.2.6. Section 4.6 - Fertility, pregnancy and lactation

The content of this section was the same across MSs, however the wording used varied slightly. Available data in animal and human do not suggest a reproductive toxicity. The proposed wording from the MAH was accepted with minor clarifications and available information on effect on fertility was requested to be included.

Furthermore a recently published article (Lin et al., 2012) suggested a possible risk of oral cleft associated with maternal exposure to amoxicillin. As this risk is not currently reflected in the PI for amoxicillin in any MS and conflicting results were observed in the four observational studies presented, the CHMP considered that a thorough assessment in a separate regulatory procedure was warranted.

2.2.2.7. Section 4.7 - Effects on ability to drive and use machines

Information in this section consistently reflects across MSs that amoxicillin does not affect the ability to drive or use machines however in line with the SmPC guideline MAH proposed to list the adverse events that may however occur and could influence the ability to drive or use machines; this was accepted by CHMP.

2.2.2.8. Section 4.8 - Undesirable effects

There were no divergences across member states in this section. The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and skin rash. In line with the SmPC guideline and QRD template, the MAH has listed the ADRs derived from clinical studies and post-marketing surveillance with amoxicillin, sorted by MedDRA System Organ Class.

Based on scientific publications for amoxicillin the MAH was requested to justify why the adverse event "aseptic meningitis" and "Kounis syndrome" were not added to Section 4.8 with the frequency "unknown". A search of the literature and the MAH's safety database retrieved a few cases, however

the review of the MAH concluded that there was insufficient evidence of a causal relationship between amoxicillin and any of those events; this was accepted.

2.2.2.9. Section 4.9 - Overdose

Generally there were no significant divergences across the national SmPCs, all MSs included statements regarding the symptoms of electrolyte imbalance and removal by haemodialysis. Only one MS did not include a statement regarding crystalluria, and four MSs did not include a statement regarding nausea, vomiting and diarrhoea. The MAH proposed a harmonised wording including all this information which was accepted with the inclusion of a minor clarification on the type of gastrointestinal symptoms that may occur and of the risk of seizures with a cross reference to sections 4.4 and 4.8. The risk of precipitation in bladder catheter for the parenteral formulation was also included.

2.2.2.10. Section 5.1 - Pharmacodynamic properties

The proposed harmonised wording on the pharmacotherapeutic group, mechanism of action, ATC code, already included in most MS with minor differences, was accepted.

The list of organisms susceptible to amoxicillin was updated. The breakpoint table that was already in the PI in 5 MSs was updated based on EUCAST version 4 dated 01 January 2014. The mechanism of resistance was included in two MS, the proposed harmonised text was considered acceptable. The MAH also considered the fixed combination amoxicillin/clavulanic SmPC (EMEA/H/A-30/979) taking into account the differences between the antibiotics, in proposing the harmonised text for amoxicillin.

The tables were then revised in line with the indications agreed. Therefore *Bacillus anthracis*, *bordetella pertussis*, *Shigella* spp, *Vibrio cholera*, *Neisseria gonorrhoeae, Leptospira icterohaemorrhagiae, Treponema pallidum* and *Corynebacterium* spp. were removed and *Pasteurella* spp. and *Salmonella* spp. were substituted by *Pasteurella multocida, Salmonella typhi* and *Salmonella parathyphi* respectively.

2.2.2.11. Section 5.2 - Pharmacokinetic properties

Due to different national requirements at the time of product approval there are differences in the approved wordings of this section. Most required information is presented in most countries, but the statements differ in the depth of elaborations. The MAH updated the section in line with the SmPC guideline which was accepted by CHMP.

2.2.2.12. Section 5.3 - Preclinical safety data

As this section was not included in national SmPCs, the MAH proposed a general wording considering the SmPC of the fixed combination amoxicillin/clavulanic SmPC (EMEA/H/A-30/979) taking into account the differences between the antibiotics, in proposing the harmonised text for amoxicillin which was accepted by the CHMP with minor modifications:

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Carcinogenicity studies have not been conducted with amoxicillin.

2.2.2.13. Other sections of the SmPC

Sections 2 (qualitative and quantitative composition), 3 (pharmaceutical form), 6.1 (list of excipients), 6.2 (incompatibilities), 6.3 (shelf life), 6.4 (special precautions for storage) 6.5 (nature and contents of container) and 6.6 (Special precautions for disposal and other handling) have been updated in line with their respective harmonised Quality documentation provided in module 3 and in line with the current QRD template. Section 6.3 and 6.4 have only been partially harmonised as it is considered that the storage conditions can be adapted nationally based on the available data and national requirements. The proposed harmonised text was accepted by CHMP with minor changes for consistency and completeness or clarity.

2.2.2.14. Labelling

Changes introduced in the SmPC were consistently reflected in the labelling, however most sections were left to be completed nationally.

2.2.2.15. Package Leaflet

The package leaflet (PL) was amended in accordance with the changes made to the SmPC. In addition minor editorial changes were introduced to improve readability. A user test was conducted for the oral suspension and showed that 90% of participants were able to find and understand the information within the PL. The test protocol and the study sample were considered appropriate. User testing bridging reports were presented for the capsules, the sachets and the solution for injection. The PL for the dispersible tablets being essentially identical to that of the capsule the justification for not providing a user test or bridging report was accepted.

2.3. Risk Management Plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Recommendation

The CHMP recommended the revision and harmonisation of the Product Information for Amoxil and associated names and adopted the following harmonised indications:

For oral formulations

Amoxil is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1):

- *Acute bacterial sinusitis*
- *Acute otitis media*
- *Acute streptococcal tonsillitis and pharyngitis*
- *Acute exacerbations of chronic bronchitis*
- *Community acquired pneumonia*
- *Acute cystitis*
- *Asymptomatic bacteriuria in pregnancy*
- *Acute pyelonephritis*
- *Typhoid and paratyphoid fever*
- *Dental abscess with spreading cellulitis*
- *Prosthetic joint infections*
- *Helicobacter pylori eradication*
- *Lyme disease*

Amoxil is also indicated for the prophylaxis of endocarditis

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

For parenteral formulations

Amoxil is indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1):

- *Severe infections of the ear, nose and throat (such as mastoiditis, peritonsillar infections, epiglottitis, and sinusitis when accompanied by severe systemic signs and symptoms)*
- *Acute exacerbations of chronic bronchitis*
- *Community acquired pneumonia*
- *Acute cystitis*
- *Acute pyelonephritis*
- *Severe dental abscess with spreading cellulitis*
- *Prosthetic joint infections*
- *Endocarditis*
- *Lyme disease*
- *Bacterial meningitis*
- *Bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above*

Amoxil is also indicated for the prophylaxis of endocarditis.

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

A harmonised Quality documentation (Module 3) was also adopted. Five minor unresolved quality issues which have no impact on the benefit/risk balance of the products were pending at the time of opinion. The MAH has committed to revise the limits for specified and any unknown impurities in the specification of the active substance and finished product in line with the updated EDQM monograph within 6 months of its publication. In addition, the MAH committed to submit a variation to amend the PI in line with the results of the recent reconstitution study to validate the in-use shelf life for the IV products, once the report is available. Finally, the MAH committed to submit a variation to introduce a common limit for the capsule filling mix regardless of the source of active substance, once the corresponding studies will have been undertaken.

2.5. Conclusions

The basis for this referral procedure was a harmonisation of the SmPC, labelling and package leaflet, as well as a harmonisation of the Module 3 at the request of the MAH.

Whereas

- The committee considered the referral under Article 30 of Directive 2001/83/EC
- The committee considered the identified divergences for Amoxil and associated names, for the indications, posology, contraindications, special warnings and precaution for use, as well as the remaining sections of the SmPC, labelling and package leaflet.
- The committee reviewed the data submitted by the MAH in support of the proposed harmonisation of the Product Information, including clinical trials, open studies, literature studies and reviews as well as evidence based and consensus guidelines. In addition, the committee considered the advice of the Infectious Diseases Working Party.

- In addition, the committee reviewed the documentation submitted by the MAH in support of the proposed harmonised Quality documentation (Module 3).
- The committee agreed the harmonisation of the summary of product characteristic, labelling, package leaflet and Quality documentation (Module 3) proposed by the marketing authorisation holders.

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

The CHMP as a consequence, concluded that the benefit-risk balance of Amoxil and associated names remains favourable, subject to the agreed changes to the product information.