Annex II

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

Scientific conclusions

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

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 European Union (EU) Member States (MS). 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 strength of powder for oral suspension (125 mg/1.25 ml, 125 mg/5 ml, 250 mg/5 ml, 500 mg/5 ml), four strength of powder for oral suspension in sachets (250, 500, 1g and 3g) and four strength 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 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 (MAH).

Quality aspects

The harmonised dossier was provided for the active substance (amoxicillin sodium and amoxicillin trihydrate) and for the different formulations of the finished product containing this substance. 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. The quality of the product is considered satisfactory.

Clinical aspects

The MAH has submitted small clinical trials conducted as part of the initial clinical development of oral and parenteral amoxicillin, numerous clinical studies conducted since then, mostly by independent research groups and individuals and studies published in the literature in peer-reviewed journals in support of the proposed harmonised PI. The MAH has taken 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 guidelines 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.

Section 4.1 - Therapeutic indications

The MAH proposed a harmonised set of indications on the different indication 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 some 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 influenza. 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 CHMP accepted the MAH proposal for replacement by specific terms as detailed below.

Acute bacterial sinusitis (ABS) - oral formulations

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. Treatment with amoxicillin generally produced high clinical and bacteriological response rates (around 90%), with efficacy similar to the antibiotic comparators. The CHMP was of the view that amoxicillin remains an effective treatment for acute bacterial sinusitis.

Acute otitis media (AOM) - oral formulations

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 "*acute otitis media*". 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. Although there is a paucity of clinical studies in adult AOM patients, taking into account the similarity in bacteriological aetiology and pathogenesis of adult sinusitis 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. 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

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). The use of varying dose regimens showed efficacy rates of around 90% in majority of the trials, with efficacy comparable to the comparators. 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

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 CHMP accepted the MAH proposal to replace it by specific terms, as detailed below.

Acute exacerbations of chronic bronchitis (AECB) – all formulations

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. In clinical trials amoxicillin given either at a dose of 1000mg twice a day (BID) or at a dose of 500mg BID or three times a day (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). Therefore, the CHMP considered this indication adequate.

Community acquired pneumonia (CAP) – all formulations

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. Treatment with oral amoxicillin at a dose 1000mg TID or 500mg TID for 7 to 10 days produced similar results to other antibiotics with clinical response rates ranging from 86% to 90% and bacteriological response rates ranging from 82% to 92%. In the paediatric studies submitted, amoxicillin showed comparable efficacy to that of the comparators and comparable responses rates to that seen in adults, better greater efficacy was seen with the higher doses. 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. The CHMP accepted the MAH proposal when it was adequately specified by infection site as detailed below for oral and parenteral formulations.

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

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. 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 urinary tract infections 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. The MAH presented six clinical trials conducted between 1975 and 1986 as well as a more recent review of antibiotics in postpartum infection. 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

The MAH presented 4 clinical trials, comparing the efficacy of oral amoxicillin to chloramphenicol or ampicillin in adults and children. In addition the MAH presented an open study in 30 adults comparing amoxicillin (1 g amoxicillin four-times daily) to chloramphenicol (1g TID until defervesence followed by 500 mg four times a day (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. 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

The MAH presented five randomised double blind trials conducted between 1981 and 1989 comparing the efficacy of amoxicillin to other antibiotics, one open study, 9 non-comparative studies and a review in patients with various acute skin infections. In addition the MAH presented 4 clinical studies conducted between 1990 and 2005 in patients with dentoalveolar abscesses of different severity and an outcome audit to determine the influence of different antibiotic therapy on outcome treatment of acute dentoalveolar infection. 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, Infectious Diseases Society of America guidelines 2014 and 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

There are few well-designed randomised controlled trials in patients comparing efficacy of different antibiotics. The MAH presented two small clinical trials and five retrospective case studies as well as reviews and guidelines. The MAH provided data suggesting that the penetration of amoxicillin into bone is adequate, even when the tissue is infected and pharmacokinetic/pharmacodynamic 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

There are very few randomised trials that have evaluated the efficacy of antibiotic prophylaxis in infectious endocarditis. 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. 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. This clinical data, 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. 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 European Society of Cardiology (ESC), American Heart Association (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

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. 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, National Institute for Health and Care Excellence) 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

The MAH submitted results of six randomised controlled trials comparing amoxicillin alone or in combination with probenecid 500 mg TID to other antibiotics 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). 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. 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 national and 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

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

The MAH provided data demonstrating 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. Considering that amoxicillin has been in use for many years and is indicated for use in a broad range of infections, in line with the Addendum to the Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013), the CHMP was of the view that, based on the available data, the proposed indication was adequately justified..

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).

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.

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, in patients with infectious mononucleosis, in combination with methotrexate and in patients with acute lymphocytic leukaemia were in place in a few member states. The CHMP concluded that the risks associated with them were considered sufficiently addressed by wording in other sections of the PI and were removed from this section.

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 statement 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. The risk of Jarisch-Herxheimer reaction when amoxicillin is used in treatment of Lyme disease was also 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.

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 (probenecid, allopurinol, tetracyclines, oral anticoagulants, methotrexate) and the MAH's proposed harmonised wording was accepted by the CHMP. The possible interaction with oral contraceptives through an effect on the gut flora 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). 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. The interaction with test results was moved to section 4.4 in line with the SmPC Guideline.

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.

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. In line with the SmPC guideline the adverse events that may however occur and could influence the ability to drive or use machines are listed in the section; this was accepted by the CHMP.

Section 4.8 - Undesirable effects

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.

Section 4.9 - Overdose

The CHMP accepted the MAH proposal for a harmonised wording including information on possible gastrointestinal symptoms, crystalluria, with the addition of the potential the risk of seizures. The risk of precipitation in bladder catheter for the parenteral formulation was also included.

Section 5.1 - Pharmacodynamic properties

The wording on the pharmacotherapeutic group, mechanism of action and ATC code was harmonised. The list of organisms susceptible to amoxicillin was updated. The breakpoint table was updated based on EUCAST (version 4) dated 01 January 2014. The mechanism of resistance was also harmonised.

Section 5.2 - Pharmacokinetic properties

The MAH updated the section in line with the SmPC Guideline which was accepted by CHMP.

Section 5.3 - Preclinical safety data

As this section was not included in national SmPCs, the MAH proposal for a general wording considering the SmPC of the fixed combination amoxicillin/clavulanic SmPC (EMEA/H/A-30/979) was accepted by the CHMP with minor modifications.

Other sections of the SmPC

Other sections of the SmPC have been updated in line with their respective Quality harmonised documentation provided in Module 3 and in line with the current QRD template. Section 1, 6.3 and 6.4 have only been partially harmonised as it is considered that these should be adapted nationally.

Labelling

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

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 and bridging reports or justification for not providing either were provided for the package leaflet of the different formulations and were considered acceptable by CMHP.

Grounds for the variation to the terms of the marketing authorisations

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. Furthermore 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 the Quality documentation in 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.