ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF AUGMENTIN AND ASSOCIATED NAMES (SEE ANNEX I)

Augmentin is a well-established and widely-used antibacterial combination product consisting of the semi-synthetic antibiotic amoxicillin (as amoxicillin trihydrate) and the β-lactamase inhibitor clavulanic acid (as the potassium salt). Amoxicillin/clavulanic acid was originally developed in response to the need for an oral broad-spectrum antibiotic that covered β-lactamase-producing pathogens. Oral formulations of Augmentin have been available worldwide since 1981 and intravenous formulation since 1984. Over the years, the ratio of amoxicillin to clavulanic acid has been varied to reflect prescribing needs, to improve dosing convenience, and as a response to recommendations for the treatment of more severe infections or those caused by resistant organisms. Amoxicillin works by inhibiting the transpeptidase enzyme responsible for cross-linking peptidoglycan in the bacterial cell wall, weakening, the cell wall and making the cell swell and rupture. Because amoxicillin is readily hydrolysed by β-lactamase, Augmentin also contains the β-lactamase inhibitor, clavulanic acid, which protects amoxicillin from degradation and extends its antibacterial spectrum to many bacteria normally resistant to penicillins and cephalosporins.

A wide range of different presentations of Augmentin with an increasing ratio of amoxicillin to clavulanic acid are approved for oral (2:1, 4:1, 7:1, 8:1, 14:1 and 16:1) and parenteral (5:1 and 10:1) use in adults and children. All EU approvals have been obtained via National registration; leading to a number of differences in the PI, particularly in the Indication and Posology sections and a referral was therefore triggered in order to resolve the divergences amongst the nationally authorised SPCs and thus to harmonise the SPCs across the EU. The MAH discussed and assessed a number of indications in light of the MAH Global Data Sheets (GDS), published data, literature, relevant studies and current clinical practice. The benefit/risk assessment for the series of formulations approved in different Member States was conducted with reference to the existing resistance patterns in those Member States where the product is marketed. The benefit/risk assessment conducted by the CHMP has not addressed the use of these products in other markets, where different resistance patterns may apply.

The MAH provided rationales for the various formulations grouped according to amoxicillin/clavulanic acid ratios, irrespective of strengths and pharmaceutical forms within each of those ratios grouping. For sections 4.1 and 4.2 of the SPC, the proposed text for formulations with the same amoxicillin/clavulanic acid ratio is discussed in sequence, starting with the lowest ratio 2:1, via the highest oral ratio 16:1 to the intravenous (IV) ratio 10:1. For other sections of the SPC and the PL, the proposed text is applicable to all formulations, irrespective of the ratio, except when clearly stated. During the evaluation, outstanding issues were identified, to be addressed by the MAH.

2.1 Critical Evaluation

Section 4.1 –Therapeutic indications

Prior to harmonisation, at start of procedure, the indications for the various ratios were grouped as follows:

- Lower-ratio oral presentations (2:1, 4:1, and 7:1), authorised broadly for the same set of indications.
- Two intravenous ratios (5:1 and 10:1), authorised for the same set of indications.
- Augmentin ES (Extra Strength) and Sustained Release (SR), developed to meet specific clinical needs related to the occurrence of resistant pathogens. This set of indications differs from that for the lower ratio formulations.
- The 8:1 ratio formulations, for general use in the renally-normal population, approved in France only, and associated with their own set of indications.

THERAPEUTIC INDICATIONS COMMON TO SEVERAL AUGMENTIN RATIOS:

Tonsilitis

The MAH acknowledged that Augmentin is not the first drug of choice for the treatment of acute streptococcal tonsillitis, however it is recommended as a possible alternative for the treatment of patients who have multiple recurrent episodes of streptococcal tonsillitis because Augmentin has been shown to yield high rates of eradication of streptococci from the nasopharynx. The MAH therefore considered that Augmentin is an effective treatment for recurrent tonsillitis, as it is effective and widely used for upper respiratory tract infections in general, plus it is active against Gram-positive and Gram-negative cocci and anaearobes. In addition, clavulanic acid protects amoxicillin from inactivation in cases where infections may be polymicrobial or when β-lactamase-producing non-pathogens may be present. The CHMP noted that tonsillitis/pharyngitis and uncomplicated sinusitis are often viral in origin, and when due to bacteria, the most common pathogen is *S. pyogenes*, which is always susceptible to penicillin, to be treated with amoxicillin alone or with penicillin. Treatment of recurrent tonsillitis with Augmentin is based on the assumption that betalactamases of other bacteria of the oral cavity excrete their betalactamse in the environment and so inactivate unprotected penicillins. The CHMP agreed that the available evidence for this indication is not sufficient unless supported by clinical data and deleted this indication for all formulations.

Septicaemia

The CHMP requested the withdrawal of the septicaemia indication in general, since the focus of septicaemia has to be treated sufficiently and therefore this indication is not acceptable. The MAH agreed to the withdrawal of the septicaemia indication from of all the oral and parental formulations SPCs.

THERAPEUTIC INDICATIONS COMMON TO AUGMENTIN 2:1, 4:1, 7:1 AND 8:1 RATIO (ORAL)

The MAH proposed the same indications for the 2:1, 4:1, 7:1 and 8:1 ratios and these are discussed in common. Equivalence of the different dosing regimens has been confirmed by randomised clinical trials in adults in several community acquired infections and paediatrics.

Genito-Urinary tract infections

The CHMP concluded that this general indication is not acceptable as neither amoxicillin/clavulanic acid nor amoxicillin are currently indicated for the treatment of diseases caused by N. gonorrhoeae. After assessment of the MAH responses, the CHMP agreed that Augmentin is a suitable drug for the claimed indications cystitis and pyelonephritis. Although many pathogens important for urinary tract infections exhibit resistance rates of > 10% towards Augmentin, it is considered a suitable alternative, as all antimicrobial agents with this indication share the problem and the choice of the agent depends on the patient and epidemiological situation. The CHMP adopted the indications *"Cystitis"* and *"Pyelopnephritis"*.

Intra-abdominal sepsis

Amoxicillin/clavulanic acid is not recommended for intra-abdominal sepsis. Empirical antibacterial therapy must provide broad-spectrum coverage of both aerobic and anaerobic pathogens. Augmentin has the appropriate PK/PD that would predict clinical efficacy against Gram-positive and many Gram-negative pathogens including anaerobic pathogens, and penetrates well into the peritoneum. These features make it an appropriate antibiotic for intra-abdominal infections. The CHMP endorsed the MAH data and rationale, especially the polymicrobial nature of intra-abdominal infections and the recent use of Augmentin in controlled trials support the use of Augmentin for both initial empirical IV treatment and continued oral treatment after switch from IV treatment. This is further supported by several Guidance documents and the CHMP adopted the indication: *"Intra-abdominal infections"* for the IV Augmentin formulations.

Upper Respiratory Tract Infections

The CHMP noted the clinical trials comparing the efficacy of the different dosing regimens of amoxicillin/clavulanic acid in recurrent tonsillitis and that a number of national guidelines recommend

Augmentin or penicillin + betalactams inhibitor as first line therapy for acute otitis media (AOM), usually a bacterial super-infection, with purulent or micropurulent middle ear fluid. In adults, AOM is rare but the bacteria involved are the same as in children and the therapeutic choices do not differ. A recommended therapy is amoxicillin/clavulanic acid, especially if no bacteriological markers are available. For infections other than acute media otitis, initial antibiotic therapy is not usually recommended. Overall, the indication is well-established and the CHMP concluded that the indication should be limited to *"acute otitis media"*.

Lower Respiratory Tract Infections and Acute Bronchitis

According to guidelines, antibiotic treatment should be considered in patients with LRTI in the following situations: suspected or definite pneumonia, selected exacerbations of chronic obstructive pulmonary disease, patients aged > 75 years and fever, cardiac failure, diabetes mellitus and serious neurological disorder. These indications are approved in all EU countries and Augmentin is accepted as an effective treatment in several national guidelines. For acute bronchitis in children, guidelines state that in the average patient with an uncomplicated LRTI in primary care, not suspected of pneumonia, antibiotic treatment has shown no benefit over placebo. A Cochrane review concluded that antibiotic treatment in patients with acute bronchitis had a modest beneficial effect not outweighing the side-effects of treatment. The CHMP considered that most acute bronchitis are of viral aetiology and the systematic need for antibiotic treatment is questionable. The MAH agreed to withdraw the indication acute bronchitis, as the wording *"Acute exacerbations of chronic bronchitis (adequately diagnosed)"* reflects the indication more adequately.

Skin and Soft Tissue Infections

The CHMP noted that amoxicillin/clavulanic acid has been evaluated in uncomplicated skin and soft tissue infections, including conditions such as wound infection, abscess, cellulitis, furunculosis and impetigo. Various comparative and non-comparative studies have been conducted in SSTIs including adults and children. Regarding cellulitis, the CHMP considered that therapy for the typical case of erysipelas or cellulitis should include an antibiotic active against streptococci and therefore considered that amoxicillin/clavulanic acid can be an alternative for the treatment of uncomplicated SSTI. For animal bites, the administration of oral or parenteral antibiotics depends on the depth and severity of the wound and on the time since the bite occurred. The CHMP agrees that amoxicillin/clavulanic acid is widely used as first-line therapy for the treatment of animal bites and therefore adopted the following wording: *"Skin and soft tissue infections in particular cellulitis, animal bites and severe dental abscess with spreading cellulitis"*

Bone and joint infections

Bone infections represent a diagnostic or therapeutic challenge as numerous exogenous and endogenous factors contribute to the onset of bone/joint infection. The MAH did not submit any data supporting this indication but proposed to re-classify this indication as osteomyelitis, providing an extensive justification, along with a discussion on PK/PD. Data on a few hundreds of patients and a summary of the clinical data in support of the treatment of osteomyelitis were provided. Safety data indicates that prolonged administration does not increase the incidence and severity of side effects compared to shorter therapeutic courses. There is no consensus on the appropriate treatment duration, as other factors such as the extent of infection, type of pathogen, clinical response, and presence of underlying risk factors are important considerations but the current SPCs only stipulate that patients on extended therapy beyond 14 days should be closely monitored. The MAH concluded that Augmentin therapy for osteomyelitis should be initially parenteral, followed by a switch to oral. Augmentin is considered suitable for the treatment of osteomyelitis as it has appropriate PK/PD properties, provides efficacy against MSSA, Gram-negative (susceptible isolates) and also anaerobic cover for polymicrobial infections. The IV and oral formulations facilitate switch or sequential therapy from initial intravenous therapy to subsequent oral treatment. The CHMP acknowledged the arguments and agreed that Augmentin is suitable for this indication. The CHMP adopted the following indication:

"Bone and joint infections, in particular osteomyelitis."

The discussion also focused on treatment duration and the CHMP agreed to amend Section 4.2 of the SPC. The CHMP adopted the following wording:

"The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review. See also section 4.4 regarding prolonged therapy."

THERAPEUTIC INDICATIONS FOR AUGMENTIN 2:1 RATIO (ORAL)

The 2:1 ratio has become a well-established dosing regimen in many countries, and has been the subject of numerous clinical studies, many of them by independent research groups and individuals. The data is largely from the extensive published literature and includes comparative data with other antibacterial agents in a range of infections for which Augmentin is indicated. The MAH provided a review of the currently authorised indications, and discussed each group of indications, referring to clinical development, studies and guidelines. The major indications discussed for the 2:1 Augmentin ratio included genito-urinary tract infections, RTIs, and SSTIs. The MAH also discussed the PK/PD of the 2:1 ratio, stating that time above minimum inhibitory concentration (T>MIC) is a determinant of efficacy for β-lactam antibacterials.

The CHMP considered the indications for the 2:1 ratio in light of the increasing resistance spectrum of the causative agents and the risk of underdosing in the treatment of bacteria with higher MIC values and resistance development. The pattern of evolution of penicillin non-susceptible strains and the current rates of resistance differ widely across Europe and resistance rates have also changed through time. In addition, the number of intermediate penicillin susceptibility strains should also be considered, creating a need for high concentrations of amoxicillin. In contrast, in some countries, the level of PRSPs has not changed through time, where the non-susceptibility trends of *S. pneumoniae* from community-acquired respiratory tract infections and from bacteraemias demonstrated no evidence of an increase in non-susceptibility over time. This suggests that the lower doses of amoxicillin as used in some currently-approved regimens are appropriate. The MAH concluded that the PK/PD data supports the continued use of 2:1 oral formulation and that it continues to be active for many pathogens.

In proposing a series of harmonised indications treatable using the 2:1 and 4:1 ratios, the MAH has taken into consideration clinical data, T>MIC values, local and national guidelines, and publications in peer-reviewed journals. The various ratios provide the prescriber with a degree of choice for treating infections, depending on the nature of the infection, relevant patient factors and also the local or regional susceptibility of the probable pathogens. The time above minimum inhibitory concentration (T>MIC) is one of the major determinants of efficacy for β-lactam antibacterials. This has been shown in *in-vitro* studies, *in-vivo* in numerous animal models, and has been confirmed by clinical trial data. Resistance to amoxicillin in *S. pneumoniae* is currently low in a number of Member States, with the majority of MICs ≤ 1 μg/mL. PK/PD analyses predict that the 2:1 Augmentin oral formulation (250/125mg) TID would achieve maximum eradication against *S. pneumoniae* strains with amoxicillin or amoxicillin/clavulanic acid MICs of ≤1 μg/mL whereas the 4:1 ratio (500/125mg) TID would be effective against strains with MICs of ≤ 2μg/mL. The published amoxicillin PK/PD data therefore support the continuing effectiveness against many pathogens of the 250/125mg (2:1) TID and 500/125mg (4:1) TID Augmentin oral formulations.

In addition, only a very small concentration of clavulanic acid (0.12mg/l) is needed to restore susceptibility of these isolates to amoxicillin. The unit dose of clavulanic acid (125mg) for the 2:1 and 4:1 formulations is the same as the other oral Augmentin formulations, this concentration being sufficient to inhibit the target β-lactamases. Hence, the daily dose of clavulanic acid will depend upon the frequency of administration and not the formulation. The MAH concluded that all available scientific evidence, clinical data, T>MIC values, guidelines and publications demonstrate that the Augmentin 2:1 and 4:1 ratios are efficacious in a wide range of indications, and provide the

appropriate clinical cover against the key pathogens implicated in these infections. The availability of the 2:1 ratio continues to provide clinicians with a valuable broad-spectrum antibiotic suitable for treatment of a variety of bacterial infections in adults and paediatrics, particularly in areas with low resistance levels where the target organisms remain susceptible to this ratio. Similarly the 4:1 ratio is a well-established regimen, providing a valuable option for treatment of mild-to-moderate as well as more severe infections, in areas where bacterial resistance is not a significant concern.

The CHMP considered that due to the known adverse effects of clavulanic acid and the PK/PD profile of this ß-lactamase inhibitor, a dose of 125 mg three times daily should not be exceeded. Thus, the maximum daily dose of amoxicillin delivered with the 2:1 ratio is 750 mg. According to the data, this daily dose is only suitable for pathogens with a MIC_{90} of $\leq$ 1 µg/mL, i.e. pathogens where time over MIC is $\geq$ 40%. Therefore, the 2:1 ratio is appropriate for areas that do not currently have major problems with penicillin-insusceptible pneumococci. The CHMP expressed concern regarding the potential for future DCP/MRP procedures in which Member States that do not have the 2:1 ratio and which have problems with penicillin-insusceptible pneumococci might be asked to approve them. In order to pre-empt this situation the CHMP stated that:

"Not all the possible presentations of Augmentin suitable for use in all EU countries. The choice of presentations used in any one EU MS needs to be tailored to the prevalence of certain types of bacterial resistance, which is very variable between EU countries and will inevitably change over time. Therefore any future applications for marketing authorisation for Augmentin presentations should be supported by a discussion of the appropriateness of those specific presentations for the selected Concerned Member States. In particular, to discuss the prevalence of penicillin-insusceptible pneumococci across the CMS and the adequacy of the amoxicillin dose delivered by candidate presentations to treat these organisms. For example, the 250/125 mg tablets are not suitable for use in any EU Member State in which penicillin-insusceptible or penicillin-resistant Streptococcus pneumoniae occur commonly. This is because the daily dose of amoxicillin delivered by this presentation (750 mg) is insufficient to treat these bacteria. Also, achieving higher daily doses of amoxicillin by doubling the number of 250/125 mg tablets given daily is not recommended since this would result in administration of unnecessarily high doses of clavulanic acid. Therefore an alternative presentation of Augmentin should be selected."

The CHMP also considered the discussion on the indications commonly to the 2:1, 4:1, 7:1 and 8:1 ratios and the following harmonised wording for the harmonised SPCs was agreed and adopted by the CHMP:

- *Acute bacterial sinusitis (adequately diagnosed)*
- *Cystitis*
- *Pyelonephritis*
- *Cellulitis*
- *Animal bites*
- *Severe dental abscess with spreading cellulitis.*

THERAPEUTIC INDICATIONS FOR AUGMENTIN 4:1 RATIO (ORAL)

To date the 4:1 ratio has been approved widely in Europe and the approval in 1984 of the TID dosage was supported by clinical studies in paediatric and adult patients. The MAH stated the currently approved indications and discussed in particular the indications in genito-urinary tract, abdominal infections, respiratory tract infections and skin and soft tissue Infections (SSTIs), citing numerous clinical studies and guidelines recommending the use of the 4:1 ratio. The MAH concluded that treatment with Augmentin 4:1 is supported for the requested indications, providing patients and prescribers with a valuable option for treatment of mild-to-moderate as well as more severe infections, in areas where bacterial resistance is not considered to be a significant concern. The MAH discussed the arguments presented for the 2:1 ratio, considering the 4:1 ratio oral formulations to be active for many pathogens, and that its use is justified.

The CHMP agreed with the main conclusion drawn by the MAH, however new studies comparing the efficacy of the 4:1 and 8:1 ratio showed a clear inferiority of the 4:1 ratio, when bacteria with higher MIC values were the causative agents. For the indications already discussed for the 2:1 ratio, the only difference is an increased amoxicillin dose of 0.5 g TID (adults). This increase in amoxicillin dose clearly makes this ratio more suitable than the 2:1 ratio and this ratio might be appropriate for some indications in at least some areas. The biggest problem is huge regional even local differences across Europe and within countries. The MAH provided a common discussion on the rationale for use of Augmentin 2:1 and 4:1. The 4:1 ratio was further discussed by CHMP, noting that the maximum daily dose of amoxicillin delivered is 1500 mg. According to the data presented by the MAH, this daily dose is only suitable for pathogens with a MIC_{90} of $\leq$ 2 µg/mL, i.e. only in these pathogens the required time over MIC is $\geq$ 40%. Thus the 4:1 ratio is considered ineffective against penicillin-resistant *S. pneumoniae*.

The CHMP also considered the discussion on the indications commonly to the 2:1, 4:1, 7:1 and 8:1 ratios and the following harmonised wording for the harmonised SPCs was agreed and adopted by the CHMP:

- *Acute bacterial sinusitis (adequately diagnosed)*
- *Acute otitis media*
- *Acute exacerbations of chronic bronchitis (adequately diagnosed)*
- *Community acquired pneumonia*
- *Cystitis*
- *Pyelonephritis*
- *Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.*
- *Bone and joint infections, in particular osteomyelitis.*

THERAPEUTIC INDICATIONS FOR AUGMENTIN 7:1 RATIO (ORAL)

The 7:1 ratio was developed for BID dosing to improve convenience and therefore compliance with the original lower-ratio TID regimens, because of the inconvenience associated with the mid-day dose and also because BID had become more of a standard regimen than TID. The ratio was approved in the 1990s. For both the adult and paediatric suspension, the unit dose of clavulanic acid remains unchanged, but is now given BID instead of TID; this remains sufficient to protect amoxicillin from the action of beta-lactamases. The MAH listed the currently approved indications, discussing in particular its use in SSTIs and recurrent tonsillitis, otitis media, sinusitis, LRTIs and UTIs, as well as URTIs and genito-urinary tract infections, and discussed the PK/PD, demonstrating the bacteriological equivalence of the BID and TID formulations. The MAH considered the 7:1 ratio as well established in clinical practice, and listed guidelines recommending Augmentin, concluding that the availability of the 7:1 ratio provides clinicians with a valuable broad-spectrum antibiotic suitable for the treatment of a variety of bacterial infections in adults and paediatrics. The indications are supported by clinical data, T>MIC values, and publications in peer-reviewed journals.

The CHMP also considered the discussion on the indications commonly to the 2:1, 4:1, 7:1 and 8:1 ratios and the following harmonised wording for the harmonised SPCs was agreed and adopted by the CHMP:

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis

- Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

THERAPEUTIC INDICATION FOR AUGMENTIN 8:1 RATIO (ORAL)

The 8:1 Augmentin ratio was licensed in 1990, developed in response to concerns over the increasing prevalence of resistant *S. pneumoniae* strains in France, particularly amongst young children with acute otitis media. At the time, the Augmentin 4:1 ratio was widely used for treating infections in children. The lower dose of amoxicillin contained in the 4:1 ratio was considered insufficient to achieve the required MIC levels of amoxicillin to eradicate *S. pneumoniae* strains with reduced susceptibility to penicillin. The MAH listed the currently approved indications and discussed data from clinical trials in paediatric patients and adults in the treatment of otitis media and UTIs, demonstrating the bioequivalence of the 8:1 adult regimen to the 8:1 paediatric regimen and the efficacy of the 8:1 ratio BID in adults; consequently this regimen has now become well established in France for the treatment of respiratory tract infections in adults, including CAP, AECB, acute bronchitis, AOM and sinusitis. The MAH also listed a number of published studies and discussed other indications, such as skin and soft tissue infections (SSTI), bone and joint infections, abdominal infection, pelvic inflammatory disease, UTI and dental infections. Finally, the MAH discussed the PK/PD of the 8:1 ratio, stating that the steady-state mean T>MIC values predict that this formulation given TID achieves maximum eradication against *S. pneumoniae* strains with amoxicillin or amoxicillin/clavulanic acid MICs of ≤2μg/mL and is to have some efficacy against strains with MICs of 4μg/mL. For severe infections, and for pathogens with higher MICs, the 8:1 ratio is active for many of the intended pathogens. The MAH concluded that the 8:1 ratio would be more appropriate than the 4:1 ratio for the treatment of certain infections and in vivo results support the PK/PD prediction that Augmentin 8:1 will be efficacious against infections caused by *S. pneumoniae* with high amoxicillin MICs (2-4μg/mL).

The CHMP concluded that the 8:1 ratio is comparable to the 7:1 ratio in terms of efficacy and safety data. The CHMP also considered the discussion on the indications commonly to the 2:1, 4:1, 7:1 and 8:1 ratios and the following harmonised wording for the harmonised SPCs was agreed and adopted by the CHMP:

- *Acute bacterial sinusitis (adequately diagnosed)*
- *Acute otitis media*
- *Acute exacerbations of chronic bronchitis (adequately diagnosed)*
- *Community acquired pneumonia*
- *Cystitis*
- *Pyelonephritis*
- *Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.*
- *Bone and joint infections, in particular osteomyelitis.*

THERAPEUTIC INDICATIONS FOR AUGMENTIN 14:1 RATIO (ORAL - ES)

Augmentin ES (extra strength), paediatric suspension, was developed using clinical studies in AOM (Acute Otitis Media) and PK/PD data from animal models, to provide improved eradication of Penicillin resistant *S. pneumoniae (*PRSPs) with penicillin MICs up to and including 4μg/mL. This ratio met a medical need established in treatment guidelines, which recommended increased dosages of amoxicillin for the treatment of respiratory tract infections, particularly in areas with high prevalence of resistant *S. pneumoniae*, particularly PRSPs. The MAH listed the currently approved indications and discussed respiratory tract infections (RTIs), AOM, community acquired pneumonia (CAP), tonsillo-pharyngitis and sinusitis, skin and soft tissue infections (SSTI) and urinary tract infections (UTI). The MAH agreed to withdraw the indication SSTI and tonsillopharyngitis, as well as the initially proposed indication UTI.

The development of Augmentin ES (14:1) was based on PK/PD data as well as clinical efficacy and safety studies, providing an increased dose of amoxicillin twice daily, while retaining the same dose of clavulanic acid as in existing Augmentin 7:1 ratio. The MAH considered the indications supported by clinical, PK/PD data and publications, and thus adequate for this ratio. The CHMP noted that Augmentin ES was studied for paediatric use in persistent or recurrent acute otitis media where there are risk factors for the involvement of beta-lactamase-producing strains or *S. pneumoniae* with reduced penicillin susceptibility. Due to such drug-resistant pathogens, this high-dose formulation could be acceptable for treatment of CAP. However, because no supporting documentation was provided in support of indications other than AOM and CAP, the remaining indications should be deleted. The MAH acknowledged that the Phase III programme studied only AOM and that the other indications including CAP, ABS and SSTI were extrapolated based on PK/PD principles, as results from AOM studies have shown that the PK/PD concept is predictive for clinical outcome. The MAH provided extensive justifications to retain the indication acute bacterial sinusitis (ABS).

The CHMP concluded that due to the lack of efficacy data, bridging from efficacy in AOM to ABS it not supported. Regarding CAP, the 14:1 ratio is considered to appropriately cover PRSP. While there are no clinical data on the efficacy in CAP in children, it is considered possible to extrapolate from experience in adults. It was also considered that use of Augmentin should be restricted to indications where both components are needed. As Augmentin ES was studied in the treatment of penicillin-resistant *S. pneumoniae*, a statement was retained to advise prescribers that this ratio is appropriate for use in treating infections that are caused, or suspected to be caused, by penicillin-resistant *S. pneumoniae*. In summary, the following harmonised wording for inclusion in the harmonised SPCs was agreed and adopted by the CHMP:

"Augmentin is indicated for the treatment of the following infections in children aged at least 3 months and less than 40 kg body weight, caused or thought likely to be caused by penicillin-resistant Streptococcus pneumoniae (see sections 4.2, 4.4 and 5.1):

- *Acute otitis media*
- *Community acquired pneumonia.*

THERAPEUTIC INDICATIONS FOR AUGMENTIN 16:1 RATIO (ORAL - SR)

Following the launch of Augmentin TID and BID regimens, resistance to penicillins in respiratory tract pathogens has generally increased significantly. Many guidelines for indications such as CAP and ABRS therefore recommended higher doses of amoxicillin to ensure that the eradication of infections caused by resistant pathogens continues and the potential for spread is reduced. Augmentin SR (Sustained-Release) was therefore developed to meet this new medical need. Augmentin SR is a pharmacokinetically-enhanced formulation, developed to maximise PK/PD and to provide more effective therapy against pathogens with reduced susceptibility to amoxicillin and penicillin, particularly *S. pneumoniae*. The tablet has one immediate-release amoxicillin trihydrate (562.5mg) and clavulanic acid (62.5mg) layer, and one sustained-release sodium amoxicillin (437.5mg) layer. The PK of the clavulanic acid components are the same as the conventional Augmentin formulations. The MAH listed the currently approved indications for Augmentin SR and discussed a number of indications in detail, as well as the PK/PD, stating that *in vivo* data supports the efficacy of Augmentin SR against infections caused by *S. pneumoniae* with high amoxicillin MICs (4-8μg/mL). The MAH considered that the Phase III results confirm the predicted efficacy of Augmentin SR in the clinical setting and cited a number of guidelines establishing Augmentin SR in clinical practice.

The CHMP noted that PK/PD principles were applied to the development of this ratio but that no true PK/PD analysis has been performed in the clinical database. The MAH responded that Augmentin SR was developed to address an unmet medical need (eradication of penicillin resistant *S. pneumoniae* with penicillin MICs ≥2 μg/ml in RTI) and that the clinical development programme included PK studies to assess the enhanced PD properties. The data reviewed demonstrates the clinical benefits of

the SR formulation, forming the scientific basis for authorisation of the current national licences for Augmentin SR. The MAH provided a comprehensive summary of the key studies evaluated and further justifications and data to support the indication in CAP, ABS and acute exacerbations of chronic bronchitis (AECB). The MAH concluded that Augmentin SR demonstrates bacteriological and clinical efficacy against susceptible and resistant key respiratory pathogens when used empirically. The drug has been shown to be extremely useful in areas with high incidence of amoxicillin- or multi-drug resistant *S. pneumoniae* and in selected patients (i.e. with *S. pneumoniae* isolates having amoxicillin+/- clavulanic acid MICs up to and including 4μg/mL).

The CHMP acknowledged the scientific rationale and the theoretical PK/PD consideration behind the development of this formulation and that it is exclusively intended to treat infections caused by PRSP. The indication in community acquired pneumonia (CAP) is supported but the indications for ABS and AECB required further discussion. It was noted that the recommended posology for the 16:1 ratio is a daily dose of 4g amoxicillin and 250 mg clavulanic acid, resulting in serum concentrations effective even against PRSP. Thus the 16:1 ratio should be effective in all indications where efficacy of the other formulations has been shown. However, as the clinical trial data is mainly restricted to data in patients with CAP in the presence of co-morbidities, the CHMP restricted the indication to CAP. In addition, the use of Augmentin should be restricted to indications where both components are needed. As Augmentin SR was developed, clinically tested and approved for treatment of PRSP, a statement was retained to advise prescribers that these formulations are appropriate for use in treating infections that are caused, or suspected to be caused, by penicillin-resistant *S. pneumoniae*. In summary, the following harmonised wording for inclusion in the harmonised SPCs was agreed and adopted by the CHMP:

"Augmentin is indicated for the treatment of community-acquired pneumonia in adults and adolescents aged at least 16 years, caused or thought likely to be caused by penicillin-resistant Streptococcus pneumoniae (see section 5.1).

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

THERAPEUTIC INDICATIONS FOR INTRAVENOUS AUGMENTIN 5:1 AND 10:1 RATIOS

Intravenous Augmentin is indicated for treatment of infections that are considered to require parenteral therapy because of the seriousness of the infection, or where the patient is unable to tolerate oral therapy. Two intravenous ratios have been developed: a 5:1 and a 10:1 formulation. These two ratios allow flexibility of the amoxicillin dosage, whilst delivering an appropriate clavulanic acid unit dose. The MAH provided comparative and non-comparative clinical studies establishing safety and efficacy and listed the studied indications. The studies suggested that a dose of 1.2g (1000/200 mg; 5:1 ratio) TID was generally adequate for treatment and that in many cases, IV treatment was followed by oral therapy. The MAH provided a large body of data supporting the use of IV Augmentin, including studies and review articles confirming the efficacy of both IV and sequential IV/oral Augmentin therapy in the treatment of LRTIs.

The CHMP generally agreed with the MAH conclusion, but further discussed the indications in LRTIs, URTIs, UTIs, gynaecological infections, SSTIs, bone and joint infections and the prophylaxis of surgical infections and agreed and adopted the following harmonised wording for inclusion in the harmonised SPCs:

- *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 (adequately diagnosed)*
- *Community acquired pneumonia*
- *Cystitis*
- *Pyelonephritis*

- *Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis*
- *Bone and joint infections, in particular osteomyelitis*
- *Intra-abdominal infections*
- *Female genital infections.*

Prophylaxis against infections associated with major surgical procedures in adults, such as those involving the:

- *Gastrointestinal tract*
- *Pelvic cavity*
- *Head and neck*
- *Biliary tract surgery.*

Section 4.2 - Posology and method of administration

The several Augmentin formulations differing in terms of ratio of amoxicillin to clavulanic acid allow the prescriber to vary the dose of each component independently and the convenience of a combined tablet or injection. The rationale has been to maintain a fixed dose of clavulanic acid for each Augmentin dose, whilst varying the quantity of amoxicillin according to the severity of infection, the site of infection (and hence likely range of pathogens) and the local pattern of amoxicillin/clavulanic acid susceptibility of the likely pathogens. In order to provide harmonised dosing recommendations for all countries, a standard dosage and higher dosage are proposed for each formulation, for both adults and children. A higher regimen may be appropriate in some indications, and in regions with higher prevalence of resistant organisms, even if the infection is not categorised as 'severe'. Hence, when considering the appropriate total daily dose of amoxicillin for the varying severity of infection, there is some overlap in the recommendations, allowing the prescriber to choose the most suited dosing regimen to the individual patient's needs (including age, weight and renal function). The paediatric recommendations have been harmonised according to weight ranges rather than age, with the sole exception of a lower age limit for very young patients. The recommendations for dosing patients with reduced renal and hepatic function have also been simplified and harmonised.

Statements were also added for formulations containing 125 mg clavulanic acid per dose, stating that if a higher daily dose of amoxicillin is required, it is recommended to use another ratio of Augmentin to avoid administration of unnecessarily high daily doses of clavulanic acid. All discussions specific to a particular Augmentin ratio are reflected below.

POSOLOGY AND METHOD OF ADMINISTRATION FOR AUGMENTIN 2:1 RATIO (ORAL)

This ratio is not recommended for use in children less than six years of age. In adults, the higher dosage is recommended for severe infections, including chronic and recurrent UTIs and LRTIs. In children, the higher dosage is recommended for infections such as otitis media, sinusitis, LRTIs and UTIs. The CHMP agreed on dosing recommendations based on weight ranges in the paediatric population, as well as the proposal for the different dosing regimens taking into account the argument that "the choice of dosage regimen is determined by the prevailing background level of resistance, and also by factors such as the severity of infection". However, in view of the results of the most recent studies, the CHMP included a statement that the lower dosage regimens (2:1 and 4:1) are not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. The section on daily dose was revised and the readability was improved. The posology text was revised, providing dosing guidance for the use of Augmentin suspension in children over 6 years and less than 40 kg. The CHMP also differentiated between the 2:1 tablets (and dispersible tablets) and the powder for oral suspension. The lower limit for the tablets is 40 kg bodyweight based on the minimum dose (250/125 mg TID) whereas the lower limit for the age is restricted to 6 years, based on currently approved 2:1 formulations.

POSOLOGY AND METHOD OF ADMINISTRATION FOR AUGMENTIN 4:1 RATIO (ORAL)

No clinical data are available on doses higher than 40/10 mg/kg/day in children under 2 years. In adults, the higher dosage is recommended for severe infections, including chronic and recurrent urinary tract infections and lower respiratory tract infections. In children, the higher dosage is recommended for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections. Overall, the CHMP agreed to dosing recommendations according to weight ranges in the paediatric population, as well as the proposal for the different dosing regimens taking into account the argument that "the choice of dosage regimen is determined by the prevailing background level of resistance, and also (in some Member States) by factors such as the severity of infection". However, in view of the results of the most recent studies, the CHMP included a statement that the lower dosage regimens (2:1 and 4:1) are not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. The section on daily dose was revised and the readability was improved.

POSOLOGY AND METHOD OF ADMINISTRATION FOR AUGMENTIN 7:1 RATIO (ORAL)

No clinical data are available on doses higher than 45/6.4 mg/kg/day in children under 2 years and dosing recommendations in this population can therefore not be made. In adults, the higher dose is recommended for severe infections, including chronic and recurrent urinary tract infections and lower respiratory tract infections. In children, the higher dosage is recommended for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections. Overall, the CHMP agreed and added a statement reflecting the regimen proposed in terms of PK/PD reasoning and prevalence of resistance across Europe.

The text on daily dose was revised and the redability was improved. The available data supporting the BID and TID regimens was reflected and the BID regimen was stated as the standard dose while the TID regimen was mentioned as the higher dose *particularly for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections*, allowing the prescriber the flexibility to choose the most appropriate dosing regimen based on clinical and local/regional factors.

POSOLOGY AND METHOD OF ADMINISTRATION FOR AUGMENTIN 8:1 RATIO (ORAL)

There is no clinical data for children under 1 month of age. Dosing recommendations in this population can therefore not be made. In adults, the higher dosage is recommended for severe infections, including chronic and recurrent urinary tract infections and lower respiratory tract infections. In children aged one month and older, the higher dosage is recommended for more severe infections. The CHMP recommended the withdrawal of the recommendation to double the 2:1 and 4:1 ratio regimens in preference for using the higher ratio of amoxicillin to clavulanic acid formulations such as the 7:1 and 8:1 ratios.

Data are lacking to support a specific mention of an acceptable maximal daily dose of clavulanic acid. As a daily dose of 375 mg is considered to sufficiently inhibit the sensitive beta-lactamases, the proposed statement was considered to better reflect the situation than mentioning of a maximum daily dose. The CHMP agreed, as it should result in a standard daily dose of clavulanic acid for all formulations with 125 mg clavulanic acid per dose. This standard daily dose should not be exceeded, and is in fact a maximum daily dose contributing to the safe use of Augmentin. The standard dose is TID and the CHMP restricted the lower dose to SSTI and non-severe sinusitis.

POSOLOGY AND METHOD OF ADMINISTRATION FOR AUGMENTIN 14:1 RATIO (ORAL - ES)

The Augmentin 14:1 ratio was specifically developed for use in children (weighing less than 40kg) where higher concentrations of amoxicillin are required, but with the same unit dose of clavulanic

acid. Dosing recommendations for Augmentin ES are supported by clinical safety and efficacy data in AOM. Augmentin ES suspension is recommended for dosing at 90/6.4 mg/kg/day in two divided doses at 12-hourly intervals for 10 days. There are no clinical data on amoxicillin/clavulanic acid in children under 3 months of age.

POSOLOGY AND METHOD OF ADMINISTRATION FOR AUGMENTIN 16:1 RATIO (ORAL - SR)

The Augmentin 16:1 ratio was developed for, and studied in, specific indications in adults and adolescents aged 16 years and above, where higher concentrations of amoxicillin to clavulanic acid are required. Dosing recommendations for Augmentin SR are supported by extensive clinical safety and efficacy data. Augmentin SR plays an important role in the management of infections, particularly in countries and local areas of high levels of *S. pneumoniae* resistance. The MAH discussed the dosing regimen and stated that the mechanism of inhibition of bacterial β-lactamases by clavulanic acid is different from that of amoxicillin: whereas amoxicillin is a highly bactericidal agent that acts by binding to one or more of the penicillin-binding proteins (PBPs) involved in cell-wall synthesis, clavulanic acid is a competitive irreversible inhibitor of certain intracellular bacterial β-lactamases, and prevents these enzymes from inactivating amoxicillin. Thus, efficient eradication of β-lactamase-producing organisms by amoxicillin/clavulanic acid relies on effective initial inhibition of the β-lactamase by clavulanic acid. Furthermore, a post-β-lactamase inhibitor effect (PLIE) provides further support for the conclusion that the inhibitory effects of clavulanic acid against β-lactamases persists significantly once the clavulanic acid itself has effectively disappeared from the serum. The clinical studies in CAP and AECB further confirm the efficacy of Augmentin SR in treating infections due to beta-lactamase-producing *H. influenzae* and *M. catarrhalis.* The MAH considered that the available data confirms that the Augmentin SR regimen contains sufficient clavulanic acid to provide full protection from *H. influenzae* and *M. catarrhalis* beta-lactamase. The CHMP agreed that the dose of 125 mg clavulanic acid twice daily is considered appropriate to inhibit the beta-lactamases of *H. influenzae* and *M. catarrhalis*.

POSOLOGY AND METHOD OF ADMINISTRATION FOR AUGMENTIN 5:1 RATIO (INTRAVENOUS)

Surgical prophylaxis with Augmentin IV should aim to protect the patient for the period of risk of infection. Clear clinical signs of infection at operation will require a normal course of intravenous or oral therapy post-operatively. The CHMP agreed to remove the mention of addition of amoxicillin alone for the 5:1 ratio, as the 10:1 presentations provide a suitable alternative. The MAH proposed that a frequency of administration superior to three times a day (every 8 hours) is appropriate in some Member States depending on the type of infection or surgical procedure. The CHMP disagreed as the restriction to three times a day is based on the maximum dose for clavulanic acid which should not be exceeded without clear scientific evidence.

The 12-hour dosing for the 5:1 ratio was revised for the treatment of infections, the majority of clinical studies evaluated a TID regimen. Additionally, a BID regimen of the 5:1 ratio in adults (≥40kg) would not provide the appropriate PK/PD and the pharmacokinetic parameters for a 1.2 g intravenous dose have not been determined. However, for 1.1 g amoxicillin/clavulanic acid given intravenously three times daily, T>MIC was present for 40% of the dosing interval for pathogens with an MIC of up to 4 µg/mL. A BID regimen would therefore probably not attain the required PK/PD target required to eradicate pathogens with higher MICs. Pathogens with higher MIC tend to be more prevalent in patients with more serious infections, and a BID IV regimen could potentially lead to poorer outcomes. Finally, the paediatric posology for the 5:1 ratio was revised as IV doses of clavulanic acid greater than 5 mg/kg are not recommended and Section 4.2 already contains texts advocating the use of different strengths where higher amoxicillin doses are needed.

POSOLOGY AND METHOD OF ADMINISTRATION FOR AUGMENTIN 10:1 RATIO (INTRAVENOUS)

Surgical prophylaxis with Augmentin IV should aim to protect the patient for the period of risk of infection. Clear clinical signs of infection at operation will require a normal course of intravenous or

oral therapy post-operatively. Based on the argumentation to remove addition of amoxicillin alone for the 5:1 ratio, information was added on increasing the dose of clavulanic acid. The frequency of administration was revised, as it should not be greater than three times a day (every 8 hours), based on the maximum dose for clavulanic acid which should not be exceeded without clear scientific evidence. In line with the previous discussion on 12-hour dosing, the CHMP changed the posology for the 10:1 IV ratio accordingly.

ORAL SWITCH THERAPY

The CHMP agreed with the MAH proposal to include wording in the SPC of several Augmentin formulations regarding the possibility to switch from IV to oral treatment for a number of indications but was of the opinion that switch from IV to oral therapy is not restricted to particular indications and should be an option for all indications. In addition, IV-to-oral switch therapy for Augmentin 14:1 (ES) and 16:1 (SR) was considered a valuable option for switch from IV treatment in infections where PRSP are, or are thought to be the causative agent and where oral continuation of Augmentin treatment is necessary. Therefore the following wording was adopted for all Augmentin IV formulations by the CHMP:

"Treatment with Augmentin may be initiated by the use of an intravenous preparation and completed with an appropriate oral formulation as considered appropriate for the individual patient."

POSOLOGY IN SPECIAL PATIENT POPULATIONS

For renal impairment, the published literature on the PK of amoxicillin and clavulanic acid, when administered to patients with renal impairment, indicates a decrease in the renal clearance of both drugs and that declining renal function has a greater influence on the clearance of amoxicillin than on that of clavulanic acid. The MAH considers that for treatment regimens using 7:1 and 8:1 ratios and 10:1 intravenous ratios, there are insufficient data on which to base a dosage recommendation for patients with severe renal impairment (<30 mL/min). Instead, prescribers are directed to use 4:1 ratio, where therapeutic levels of clavulanic acid in such cases have been detailed in the literature. The MAH also confirmed that the posology for the 4:1 ratio in patients with renal impairment is widely recommended across the EU. For hepatic impairment, there is insufficient data for dosage recommendations; prescribers are advised to dose with caution, and monitor hepatic function at regular intervals. A text was included in Section 4.4 for all formulations to reiterate that Augmentin should be used with caution in patients with hepatic impairement.

Section 4.3 – Contraindications

The contraindications section of the SPC defines those situations where the drug must not be administered to the patient for safety reasons. The contraindications discussed apply to all Augmentin ratios. In particular, the contraindications referring to mononucleosis, severe hepatic impairment or hepatic insufficiency, to the presence of aspartame in the oral suspension and hypersensitivity to amoxicillin, clavulanic acid or to any excipients were discussed. The CHMP considered a contraindication for all beta-lactams to be inappropriate and unnecessarily restrictive, potentially excluding the use of several beta-lactams in patients who could receive them safely. The following statements were agreed for the harmonised SPC to address this issue:

"Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid (see section 4.8)."

Section 4.4 - Special warnings and precautions for use

This section contains detailed information of the conditions and special patient groups where Augmentin should be used with caution. For all formulations of Augmentin, the same warnings and precautions are applicable, apart from a number of formulation-specific statements, such as IV specific statements referring to the sodium and potassium content of Augmentin. In particular, data on renal impairment, crystalluria and overgrowth of fungal infections and acute generalised exanthematous pustulosis (AGEP) was reviewed and proposals for a harmonised wording were made. The MAH also reviewed the additional statements present within the SPCs of some Member States. Most statements were either already covered by the proposed harmonised text, or lacked supportive evidence. Statements regarding the treatment of elderly patients (>60 years), the possible effect of amoxicillin on glucose tests, Glucose-Galactose Malapsorption and false-positive test results with the Platelia *Aspergillus* antigen test during treatment were discussed. In summary, a harmonised wording for inclusion in the harmonised SPCs was agreed and adopted by the CHMP.

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

The interactions apply to all Augmentin ratios. Amoxicillin, like other beta-lactam antibiotics, is largely excreted renally and is not metabolised by CYP450 enzymes; clavulanic acid is partially metabolised by the liver and mostly excreted unchanged in the urine. Accordingly, metabolic drug interactions affecting the levels of either compound to a significant extent are unlikely to be of clinical significance. The CHMP noted the detailed literature search and analyses of available data carried out by the MAH, and agreed with the text on oral anticoagulants but requested the MAH to include a statement on the interaction with methotrexate. The CHMP agreed a text clearly stating that concomitant use of probenecid and Augmentin is not recommended. The scientific basis for inclusion of a statement on the interaction with oral contraceptives was assessed and there is a lack of evidence for an interaction between Augmentin and oral contraceptives.

Section 4.6 - Pregnancy and lactation

The information provided for this section applies to all Augmentin ratios. The CHMP noted the detailed analyses of the authorised texts and the wording proposed and in summary, the CHMP considered that the use of Augmentin should be avoided during pregnancy, unless considered essential by the physician and that amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge. A harmonised wording was agreed by the CHMP for inclusion in the harmonised SPCs.

Section 4.7 - Effects on ability to drive and use machines

For all Augmentin ratios, the CHMP considered that undesirable effects may occur and included recommendations in the harmonised SPC.

Section 4.8 - Undesirable effects

In recent years the MAH has developed a pro-active process for identifying safety signals, consisting of the ongoing review of important individual cases, the review of aggregate adverse event data through the use of disproportional analyses and the review of published medical literature. The CHMP requested that frequency data should be used in accordance with the SPC Guideline recommendations and recommended the use of an introduction describing the frequencies. The verbal statement of the frequencies should be in accordance to the updated QRD-Templates and the frequencies should be listed in a table. The CHMP adopted a harmonised text for this section.

Section 4.9 - Overdose

The CHMP recommended including the following in the harmonised SPC:

"Symptoms and signs of overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4).

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can be removed from the circulation by haemodialysis."

5. PHARMACOLOGICAL PROPERTIES

Section 5.1 - Pharmacodynamic properties

This is a particularly important section for antibacterials. The MAH updated the Augmentin SPCs in line with the CHMP's guidance on the development of antibacterial agents. Proposals were made for each sub-section ("Mode of Action" and "Mechanisms of resistance", "PK/PD relationship" and "Breakpoints"). The EUCAST Breakpoints should be used exactly as written by EUCAST and the lists of pathogens for all formulations were also restricted to the pathogens important for the harmonised indications. The CHMP adopted the following sentence to state that Augmentin ES (14:1) and SR (16:1) ratios can be used to treat *S. pneumoniae* with decreased susceptibility to penicillin in the approved indications:

"This presentation of amoxicillin/clavulanic acid is suitable for treatment of Streptococcus pneumoniae *that are resistant to penicillin in the approved indications only (see section 4.1)."*

Section 5.2 - Pharmacokinetic properties

The MAH discussed the pharmacokinetic data for all the existing Augmentin formulations, grouped according to their respective ratios. The data forms the basis of the corresponding sections in the proposed harmonised SPCs. The ADME properties of amoxicillin and clavulanic acid, alone and in combination, were also summarised. The CHMP agreed to the MAH proposal. In summary, a harmonised wording for inclusion in the harmonised SPCs was agreed and adopted by the CHMP.

Section 5.3 - Preclinical safety data

The CHMP noted the MAH presentation and summary of the different available data of this section and agreed and adopted a harmonised text.

6. PHARMACEUTICAL PARTICULARS

Sections 1, 2 and 3 are to be completed nationally. Similarly, Sections 6.1, 6.2, 6.3, 6.4 and 6.5 will also be completed nationally. For Section 6.6, there are "No special requirements" for disposal of surplus materials.

PACKAGE LEAFLET AND USER TESTING

The proposed changes mentioned for the SPCs were reflected adequately in the PLs, if relevant for the patients**.** A full PIQ review was also conducted and the PL was revised accordingly. The option of breaking Augmentin SR tablets for ease of swallowing was assessed and agreed upon. A full and comprehensive user testing of the PL was carried out, and the CHMP considered that the two legibility test reports provided, together with the bridging reports, are acceptable.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics, labelling and package leaflet.

- the Summaries of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Augmentin and associated names (see Annex I).