

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as amended**

**Amoxicillin/Amimox
(amoxicillin)**

SE/W/009/pdWS/001

This module reflects the scientific discussion during the article 45 procedure concerning paediatric data. The procedure was finalised at 2010-05-13. Date of this report 2010-06-30.

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Annex 1

I. EXECUTIVE SUMMARY

A harmonised text for paediatric data in relevant sections of the SmPC was mutually agreed on at the finalisation of the procedure 13 May 2010. The MAH is requested to submit a type IB variation within 60 days in order to implement the agreed text in the product information.

Final proposed SmPC text for relevant paediatric sections:

Section 4.2

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Children weighing < 40 kg

The daily dosage for children is 40 - 90 mg/kg/day in two to three divided doses (not exceeding 3 g/day) depending on the indication, severity of the disease and the susceptibility of the pathogen (see special dosage recommendations below and sections 4.4, 5.1 and 5.2).*

**PK/PD data indicate that dosing three times daily is associated with enhanced efficacy, thus twice daily dosing is only recommended when the dose is in the upper range.*

Children weighing more than 40 kg should be given the usual adult dosage.

Special dosage recommendation

Tonsillitis: 50 mg/kg/day in two divided doses.

Acute otitis media: In areas with high prevalence of pneumococci with reduced susceptibility to penicillins, dosage regimens should be guided by national/local recommendations.

Early Lyme disease (isolated erythema migrans): 50 mg/kg/day in three divided doses, over 14-21 days.

Prophylaxis for endocarditis: 50 mg amoxicillin/kg body weight given as a single dose one hour preceding the surgical procedure.

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Dosage in impaired renal function:

The dose should be reduced in patients with severe renal function impairment. In patients with a creatinine clearance of less than 30 ml/min an increase in the dosage interval and a reduction in the total daily dose is recommended (see section 4.4 and 5.2).

Renal impairment in children under 40 kg:

Creatinine clearance ml/min	Dose	Interval between administration
> 30	Usual dose	No adjustment necessary
10 – 30	Usual dose	12 h (corresponding to 2/3 of the dose)
< 10	Usual dose-	24 h (corresponding to 1/3 of the dose)

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Section 4.4

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Precaution should be taken in premature children and during the neonatal period: renal, hepatic and haematological functions should be monitored.

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Section 5.2

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In preterm infants with gestational age 26-33 weeks, the total body clearance after intravenous dosing of amoxicillin, day 3 of life, ranged between 0.75 – 2 ml/min, very similar to the inulin clearance (GFR) in this population. Following oral administration, the absorption pattern and the bioavailability of amoxicillin in small children may be different to that of adults. Consequently, due to the decreased CL, the exposure is expected to be elevated in this group of patients, although this increase in exposure may in part be diminished by decreased bioavailability when given orally.

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The PL should be updated after the finalization of the SmPC. A type IB variation will be requested from the MAHs within 60 days after finalising this procedure.

II. INTRODUCTION

Amoxicillin is a beta-lactam antibacterial agent which has been in clinical use in Europe and globally in almost two decades. It has been extensively used in hospitalised and ambulant patients, including paediatric patients of all ages, and the safety and efficacy profile is well acknowledged. The indications vary to some extent between MS, but these are not an issue for the present procedure.

The wording of the posology section varies somewhat in different countries and also between different amoxicillin products. It is therefore suggested that the paediatric posology and other information relevant for paediatric use of amoxicillin should be harmonised.

On April 6, 2009, the CMD requested relevant MAH to submit the paediatric studies for Amoxicillin within one month to the attention of the Rapporteur for the Work-sharing for paediatric studies submitted according to Article 45 of the Regulation No 1901/2006. Documentation was received from Aurobindo, InfectoPharm, Recip and Sandoz including 1A Pharma Hexal. All companies submitted published studies and/or unpublished study reports.

In accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use, the MAH submitted published studies and/or unpublished study reports on paediatric data for amoxicillin. Documentation was received from InfectoPharm, Recip and Sandoz including 1A Pharma Hexal. An assessment on current available data on paediatric use of amoxicillin was performed in a MR procedure with SE acting as Rapporteur.

III. SCIENTIFIC DISCUSSION

III.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Amoxicillin is available as tablets and powder for oral suspension.

III.2 Clinical aspects

Since indications are generally not specific for paediatric patients, this AR will mainly focus on dosage regimens as well as on safety and pharmacokinetic issues specifically related to children. Thus, justification of the specific indications will not be assessed in this AR.

Rapporteur's general comments:

The proposed wording is justified by published scientific data from clinical studies, treatment guidelines, recent finalised generic procedures and PK/PD considerations.

The recommended normal daily dosage in children is 40-90 mg/kg/day, divided in two to three doses, according to clinical practice and international treatment guidelines. This treatment regimen is supported by a number of published clinical studies of which some are stated below. Twice daily dosing may be sufficient in some indications such as tonsillitis and cystitis, as well as in less severe infections. However, a statement of PK/PD data supporting the t.i.d. dosing regimen is considered justified, since a concentration of antibiotic greater than the MIC for at least 40% to 50% of the therapeutic interval is necessary for an effective treatment in most indications. Furthermore, a higher dose is needed for the treatment of pneumococci with decreased susceptibility to penicillins, which is considered important information for the prescriber. A dose of amoxicillin at 75 mg/kg/day in 3 divided doses or 90 mg/kg/day in 2 divided doses is necessary for strains of *Streptococcus pneumoniae* that are intermediate in susceptibility to penicillin (Amoxicillin Dosage. PAEDIATRICS. 2002; 110;195). Amoxicillin has been given as an intravenous dose of 50 mg/kg/day (given as 2 daily doses) in 17 preterm infants (mean age 29±1.9 weeks gestational age, mean weight 1175±278 g), (Huisman-de Boer, et al. Antimicrob Agents Chemother, 1995; 39(2) 431-434. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC162555/pdf/390431.pdf>).

Justification for the dosage regimens in the different indications:

Short review on selected publications:

Infections in the upper respiratory tract

Acute otitis media.

Damoiseaux R et al. Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children under 2 years. BMJ. 2000; 320:350-354.

(240 children with AOM, aged 6 months to 2 years were randomised to placebo or amoxicillin, 40mg/kg/day in three divided doses. Conclusion: Efficacy was superior in the amoxicillin group but the NNT to improve symptomatic outcome at day 4 (6-7 patients) does not justify prescription of antibiotics at first visit provided close surveillance can be guaranteed.)

Le Saux N et al. A randomised, double blind, placebo-controlled non-inferiority trial of amoxicillin for clinically diagnosed acute otitis media in children 6 months to 5 years of age. CMAJ. 2005; 172:335-341.

(512 children were randomised to placebo or amoxicillin, 60mg/kg/day in three divided doses for 10 days. Conclusion: The results did not support the hypothesis that placebo was non-inferior to amoxicillin at 14 day assessment.)

Garbutt J et al. Developing Community-specific recommendations for first-line treatment of acute otitis media: Is high dose Amoxicillin necessary? Paediatrics. 2004; 114:342-347.

*(A cross-sectional prevalence study including 224 patients younger than 7 years. Conclusion: Although the prevalence of nonsusceptible *S. pneumoniae* (NSSP) was high (48%), the probability of NSSP not susceptible to standard dose amoxicillin(40-50 mg/kg/day) infection among symptomatic children is low (<5%). The data support that most children with uncomplicated AOM should be treated with standard dose amoxicillin.)*

Acute bacterial sinusitis

Falagas M. et al. Comparison of antibiotics with placebo for treatment of acute sinusitis: a meta-analysis of randomised controlled trials. The Lancet Infection. 2008; 8:543-552.

(Compared with placebo, antibiotics were associated with a higher rate of cure or improvement (2648 patients, odds ratio [OR] 1.64 [95% CI 1.35–2.00], data from 16 RCTs), or cure alone (1813 patients, OR 1.82 [1.34–2.46], 12 RCTs), but also with more adverse events (1963 patients, OR 1.87 [1.21–2.90], 12 RCTs). In the trials that specifically compared amoxicillin (40-50 mg/kg/d in 3 daily doses to children) to placebo, cure or improvement was more likely in patients who received amoxicillin

alone (1702 patients, OR 1· 48 [1· 17–1· 89]). The rate of symptom resolution was faster with antibiotics in most RCTs. In conclusion, use of antibiotics for acute sinusitis confers a small therapeutic benefit over placebo with a corresponding rise in the risk for adverse events. The authors suggest that antibiotics should be reserved for carefully selected patients with a higher probability for bacterial disease.)

Documented Group A beta-hemolytic streptococcal tonsillitis

Aguilar A et al. Clinical and bacteriological efficacy of amoxicillin b.d. (45mg/kg/day) versus amoxicillin t.d.s. /40mg/kg/day) in children with group A beta-hemolytic streptococcal tonsillopharyngitis. JAC. 2000; 12:396-405.

*(517 children aged 2-12 years, were randomised to bid or tid dosing of amoxicillin for 7 days. conclusion: **Twice daily regimen of amoxicillin, 45mg/kg/day, was as effective and as well tolerated as the standard three-times daily regimen, 40mg/kg/day, in the treatment of acute bacterial tonsillopharyngitis in children.**)*

American heart Association. prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. Circulation. March 24, 2009.

(Recommendation: Oral antibiotics of choice are penicillin V and amoxicillin)

Infections in the lower respiratory tract

Community acquired pneumonia (mild to moderate)

Hazir T et al. Comparison of standard versus double dose of amoxicillin in the treatment of non-severe pneumonia in children aged 2 to 59 months: a multicentre, double blind, randomised controlled trial in Pakistan. Arch. Dis. Child. 2007; 92: 291-297.

*(876 children were randomised to either standard dose (45mg/kg/day) or double dose (90mg/kg/day) amoxicillin, **divided into three equal doses**, for 3 days. Conclusion: Clinical outcome in children aged 2-59 months with non-severe pneumonia is the same with standard and double dose oral amoxicillin. Non-severe pneumonia can be treated effectively and safely with a **3 days course of a standard dose.**)*

ISCAP study group. Three days versus five days treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomised controlled trial. BMJ, March, 2004.

*(2188 children aged 2-59 months were randomised to 3 or 5 days treatment with oral amoxicillin **31-54mg/kg/day, divided into three daily doses**. Conclusion: Treatment with oral amoxicillin for **three days was as effective as for five days** in children with non-severe pneumonia.)*

MASCOT pneumonia study group. Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: A multicentre double-blind trial. The Lancet. 2002; 360: 835-841.

*(2000 children with non-severe pneumonia were randomised to either 4 or 5 days treatment with oral amoxicillin (**15 mg/kg x 3**). Conclusion: Treatment with oral amoxicillin for **3 days was equally as effective as treatment for 5 days** in children with non-severe pneumonia.)*

Tsarouhas N et al. Effectiveness of intramuscular penicillin versus oral amoxicillin in the early treatment of outpatient paediatric pneumonia. Paediatric emergency care. 1998; 14:338-341.

*(77 patients aged 6 months to 18 years received **50 mg/kg/day in three divided doses** for 10 days. Conclusion: There does not appear to be a significant difference between PO amoxicillin and IM penicillin in the early outpatient treatment of paediatric patients with presumed bacterial pneumonia.)*

Community acquired pneumonia (severe)

Addo-Yobo A et al. Oral amoxicillin versus injectable penicillin for severe pneumonia in children age 3 to 59 months: a randomised multicentre equivalence study. *The Lancet*. 2004; 364:1141-1147.

(857 children with severe pneumonia received oral amoxicillin 45mg/kg/day, divided in three doses, for 5 days. Conclusion: Injectable penicillin and oral amoxicillin are equivalent for severe pneumonia treatment in controlled settings.)

Hazir T et al. Ambulatory short-course high-dose oral amoxicillin for treatment of severe pneumonia in children: a randomised equivalence trial. *The Lancet*. 2008; 371: 49-56.

(1035 children aged 3-59 months received oral amoxicillin, 80-90 mg/kg/day divided in two doses, for 5 days. Conclusion: Home treatment with high-dose oral amoxicillin is equivalent to currently WHO recommended hospitalisation and parenteral ampicillin for treatment of severe pneumonia without underlying complications.)

Infections in the lower urinary tract

Grabe M et al. Guidelines on urological infections. European Association of Urology. 2009.

(The recommended dosage of amoxicillin in children, 3 months to 12 years, with lower UTI is 50 -100 mg/kg/day divided in two to three doses, for 5 to 7 days.)

Prophylaxis of endocarditis

ESC Guidelines: Guidelines on Prevention, Diagnosis and Treatment of Infective Endocarditis Executive Summary. The Task Force on Infective Endocarditis of the European Society of Cardiology. *European Heart Journal* (2004) 25, 267–276.

*(The following Prophylactic antibiotic regimen is recommended in the ESC Guidelines: Dental, oral, respiratory, and esophageal procedures:
– not allergic to penicillin: amoxicillin 2.0 g (children 50 mg/kg) p.o. 1 h before procedures.)*

Guidelines from by American Heart Association: Prevention of infective endocarditis. 2007.

(The dosages recommended by AHA are: Adults: 2 g and children 50 mg/kg as a single dose 30-60 minutes before procedure. It is stated that administration after the procedure should normally not be given, only if the patient did not receive the pre-procedural dose.

Early localized Lyme Disease associated with erythema migrans

Eppes S et al. Comparative study of cefuroxime axetil versus amoxicillin in children with early Lyme disease. *Paediatrics*. 2002; 109:1173-1177.

(43 children aged 6 months to 2 years were randomized to cefuroxime axetil (20 or 30mg/kg/day) or amoxicillin (50mg/kg/day) each for 20 days. Conclusion: Both amoxicillin and cefuroxime axetil seem to be safe, efficacious treatments for children with early LD.)

Rapporteur's comments on dosage in impaired renal function:

No data supporting the dosage in renal impairment has been provided in this procedure, the proposed dosing in children with decreased renal function was adopted in the recent procedure AT/H/0187/04-06/DC. For children with a creatinine clearance between 10-30 ml/min, the suggested dose is 15 mg/kg twice daily resulting in a daily dose of 30 mg/kg/day (compared to the normal dosing of 45-50 mg/kg/day). For children with a creatinine clearance below 10 ml/min, the suggested dose is 15 mg/kg once daily. As renal elimination is the major eliminating pathway of amoxicillin and as the amoxicillin clearance closely resembles the renal clearance, the half-life of amoxicillin is expected to be prolonged with renal dysfunction. Therefore a longer dosing interval as well as a lower total daily dose in this group may be warranted.

Rapporteur's comments on wording in section 4.4 related to paediatric patients:

The following wording is suggested related to precautions in neonates and in premature children, as slightly amended from the recently finalised procedure DCP:

Precaution should be taken in premature children and during the neonatal period: renal, hepatic and haematological functions should be monitored.

Assessor's comments on wording in section 5.2 related to paediatric patients:

The following wording is suggested:

In preterm infants with gestational age 26-33 weeks, the total body clearance after intravenous dosing of amoxicillin, day 3 of life, ranged between 0.75 – 2 ml/min, very similar to the inulin clearance (GFR) in this population. Following oral administration, the absorption pattern and the bioavailability of amoxicillin in small children may be different to that of adults. Consequently, due to the decreased CL, the exposure is expected to be elevated in this group of patients, although this increase in exposure may in part be diminished by decreased bioavailability when given orally.

Assessor's comments:

Presently there is no wording in section 5.2 concerning paediatric patients. Amoxicillin is primarily cleared by the renal route and the renal function in preterm infants is limited. Therefore it is considered helpful for the physician to have information of the expected CL in this population. In a published article by *J Huisman-de Boer et al, Amoxicillin pharmacokinetics in preterm infants with gestational age of less than 32 weeks, Antimicrob Agents Chemother, 1995; 39(2) 431-434.*, total body clearance was related to gestational age and CL of amoxicillin was also compared to inulin clearance. Clearance estimates presented in this article was suggested to be included in section 5.2 of the SPC.

As these amoxicillin formulations are for oral use, the information that the absorption pattern of amoxicillin may be different in very young children compared to adults is important. Amoxicillin is absorbed by passive diffusion and also by saturable mechanisms. These saturable mechanisms are most probably transporters which may be immature in prematures and neonates.

Rapporteur's comments on wording in other sections of the SmPC related to paediatric patients.

The safety profile of amoxicillin is well known and similar between adults and children. Therefore, no update of section 4.8 is deemed necessary at present. No specific statements related to paediatric use are considered necessary in sections other than 4.2, 4.4 and 5.2.

IV. REQUEST FOR SUPPLEMENTARY INFORMATION

In order to suggest a scientifically based dosing regimen in children with decreased renal function, all Applicants are asked to answer the following:

1. The scientific rationale for the table concerning decreased renal function in children should be provided
2. It should be discussed if the CL_{crea} limits used for adults (>30 ml/min, 10-30 ml/min and < 10 ml/min) also apply for children, as they per se has lower CL_{crea} without being renally impaired, or if these values should be corrected for for example body weight or body surface area
3. In the light of the second point, it should be discussed if there is an age limit when the CL_{crea} limits in the table on decreased renal function in children are applicable, and if so, this age limit should be included in the table.
4. The safety of the proposed maximum dose of 90 mg/kg/day (*not exceeding 3g/day*) should be justified.

V. ASSESSMENT OF THE MAH'S RESPONSES TO RSI

Responses on the RSI were received from MEDA, InfectoPharm and Sandoz. Aurobindo Pharma Italia S.r.l requested to officially exit from the procedure as at the present the company is not MAH of any pharmaceutical form of Amoxicillin for pediatric use.

Question 1:

The scientific rationale for the table concerning decreased renal function in children should be provided.

Response from Meda:

We propose that the rapporteur contacts the assessment team of the implemented referral Augmentin/Spektramox - EMEA/H/A-30/979 in order to obtain full scientific background and rationale for the recommendations for use in decreased renal function. Note that those recommendations are specific for the combination amoxicillin and clavulanic acid.

The database Drugdex states, based on an article by Bennett 1994, that amoxicillin dosage interval may be increased in patients with mild renal failure (GFR more than 50 milliliters/min). Patients should in general receive amoxicillin every 8 hours; patients with moderate renal failure (10 to 50 milliliters/minute) should receive amoxicillin every 8 to 12 hours; and patients with severe renal failure should receive amoxicillin every 24 hours. This is partly in line with the rapporteurs proposal.

References given by Drugdex:

1. Bennett WM, Aronoff GR, Golper TA, et al: Drug Prescribing in Renal Failure, 3rd. American College of Physicians, Philadelphia, PA, 1994a.
2. Bennett WM, Aronoff GR, Golper TA, et al Bennett WM, Aronoff GR, Golper TA, et al: Drug Prescribing in Renal Failure, 3rd. American College of Physicians, Philadelphia, PA, 1994.

Also, a rationale is described in the implemented referral for Augmentin/Spektramox - EMEA/H/A-30/979. Note that those recommendations are specific for the combination amoxicillin and clavulanic acid.

The following table gives the recommended dosage in the referral for Augmentin/Spektramox - EMEA/H/A-30/979.

Children < 40 kg

CrCl: 10–30 ml/min	15 mg twice daily (maximum 500 mg twice daily).
CrCl < 10 ml/min	15 mg as single daily dose (maximum 500 mg).
Hemodialysis	15 mg once daily Before hemodialysis 15 mg. 15 mg/kg should be administered after hemodialysis to restore appropriate circulating concentration.

Adults and children ≥ 40 kg

CrCl: 10–30 ml/min	500 mg twice daily
CrCl < 10 ml/min	500 mg once daily
Hemodialysis	500 mg/125 mg once daily. 500 mg during dialysis, which shall be repeated at the end of the dialysis (because the serum concentrations of amoxicillin are reduced)

Response from InfectoPharm:

The table for dosage in patients with impaired renal function proposed in the assessment report has been adopted from a recent procedure (AT/H/0187/04- 06/DC). InfectoPharm has not been involved in this DCP. In Germany, the wording of the SPCs of all marketing authorisation holders (MAHs) is in principle based on the proposed text in the so-called “BfArMMustertext” (SPC template) issued by the Federal Institute for Drugs and Medical Devices (BfArM). This SPC template proposes the following information on dosage in patients with renal impairment: *In patients with severe renal impairment (glomerular filtration rate < 30 ml/min) a dose reduction is recommended, as an accumulation of amoxicillin has to be expected. In patients with a creatinine clearance of 20 to 30 ml/min the dose should be reduced to 2/3 of the standard dose. In patients with a creatinine clearance below 20 ml/min the dose should be reduced to 1/3 of the standard dose. An extension of the dosage interval under control of amoxicillin plasma levels is also possible.* This text also forms part of the SPC of InfectoPharm. The proposed dose adjustments in the German SPC template are similar, although not equivalent, to those in the SPC of the recently approved amoxicillin product: Approved text during DCP (AT/H/0187/04-06/DC):

Creatinine clearance [ml/min]	Dose	Interval between administration	Daily dose
> 30	No adjustment necessary.	Daily dose should be divided into 2 or 3 equal doses	
10-30	15 mg/kg	12 h	30 mg/kg
< 10	15 mg/kg	24 h	15 mg/kg

Text of German SPC-Template:

Creatinine clearance [ml/min]	Dose	Interval between administration	Daily dose
> 30	No adjustment necessary.	Daily dose should be divided into 2 or 3 equal doses	
20-30	2/3 of the standard dose (i.e. 2/3 of 50 mg/kg)	Daily dose should be divided into 2 or 3 equal doses	33.3 mg/kg
< 20	1/3 of the standard dose (i.e. 1/3 of 50 mg/kg)	Daily dose should be divided into 2 or 3 equal doses	16.7 mg/kg

Also the proposed creatinine clearance categories for classification of renal insufficiency cover the same gross range (irrespective of patient age), with however a more narrow frame for creatinine clearance in the German SPC template in which only a slight dose reduction is necessary. The German SPC template does not contain any explicit comments on age ranges for which the provided dosing information is valid. InfectoPharm has not conducted any studies on this special issue. A literature search in diverse text books, SPCs of other MAHs and the Medline database did not result in any significant publications in this field. A deduction of dose recommendations from the general scientific evidence on renal function in infants and children in combination with the sparse pharmacokinetic data for amoxicillin in infants and children appears to be very arguable in the view of the applicant and was thus omitted. Moreover, since the proposed table on dosing in renal insufficiency is derived from a very recent DCP one has to suppose that this text has been extensively reviewed by the competent authorities involved in this procedure. The proposed dosage table is also clearly supported by the outcome of a recent Article 30 referral procedure for augmentin 4:1 ratio (amoxicillin plus clavulanic acid) (Doc. Ref. EMEA/CHMP/97898/2009). During the referral, the Committee harmonised the text of the posology section of the SPC to highlight to prescribers the need to check, amongst others, the age, weight and kidney function of the patients. The recommendations for dosing in patients with reduced renal function have also been simplified and harmonised. The amoxicillin posology for children with a body weight of less than 40 kg and with a creatinine clearance of 10-30 ml/min as well as a creatinine clearance < 10 ml/min is the same as in the SPC approved during the above mentioned DCP (AT/H/0187/04-06/DC). The referral outcome also confirms that the following posology for the amoxicillin/clavulanic acid 4:1 ratio in patients with renal impairment is widely recommended across the EU: Renal impairment Dose adjustments are based on the maximum recommended level of amoxicillin. No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

Response from Sandoz:

In the DCP **AT/H/0187/004-006/DC** (CMS: BE, BG, CZ, DE, EE, FI, LT, LV, NL, PL, RO,SI, SK, UK) and its subsequent CMD(h) referral EMEA/CMDh/569057/2009 the following dosage table in renal impairment was approved:

Renal impairment in children under 40 kg:

Creatinine clearance ml/min	Dose	Interval between administration
> 30	No adjustment necessary	
10 – 30	15 mg/kg	12 h
< 10	15 mg/kg	24 h

This table had already been approved as well in the earlier procedure **AT/H/116/001-005/II/022** (CMS: BE, EL, IE, LU, NL, NO, PT, SE, UK). We consider therefore the scientific rationale for this table as acknowledged by the 19 Member States participating in total to the above mentioned procedures: BE, BG, CZ, DE,EE, EL, IE, FI, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK. Furthermore, in the recent Article 30 Referral for Augmentin 4:1 ratio (Commission Decision C (2009) 8266, EC Annex I-III, EMEA/CHMP/97898/2009), the same clearance categories (> 30, 10-30 and < 10 ml/min) were defined and approved for adults and children:

Adults and children ≥ 40 kg

CrCl: 10-30 ml/min	500 mg/125 mg twice daily
CrCl < 10 ml /min	500 mg/125 mg once daily
Haemodialysis	500 mg/125 mg every 24 hours, plus 500 mg/125 mg during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40 kg

CrCl: 10-30 ml/min	15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily).
CrCl < 10 ml /min	15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg).
Haemodialysis	15 mg/3.75 mg/kg per day once daily. Prior to haemodialysis 15 mg/3.75 mg/kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis.

In particular the same dosage expressed in amoxicillin component was approved by CHMP as in DCP AT/H/0187/004-006/DC for clearance categories 10-30 and < 10 ml/min, without mentioning any age category. No dose adjustment is considered required in patients with CrCl > 30 ml/min. We acknowledge that differences in definitions of clearance categories might still exist across Europe for amoxicillin products for historical reasons of disharmony in product information across EU, however based on the above findings, we consider that the clearance categories and their corresponding amoxicillin doses are sufficiently recognized in many Member States and that no further justification is needed. We confirm that Sandoz has not conducted any pediatric PK studies in renal impairment and that no further data are available.

Rapporteur's comment:

No documentation supporting the dose recommendations has been provided by any of the MAHs. The dose adjustments were approved in AT/H/116 in 2003 with the following concerned member states BE, EL, LU, NL, PT, UK, DK, NO and SE. It has been included in more than one procedure after that. Documentation from the above mentioned procedure has not been submitted, hence no re-assessment of earlier approved recommendations has been performed.

Conclusion: This issue will not be further pursued. See Annex 1 for RMS' proposed SPC text.

Question 2:

It should be discussed if the CL_{crea} limits used for adults (>30 ml/min, 10-30 ml/min and < 10 ml/min) also apply for children, as they per se has lower CL_{crea} without being renally impaired, or if these values should be corrected for example body weight or body surface area.

Response from Meda, InfectoPharm and Sandoz:

See question 1

Rapporteur's comment:

It appears as the earlier approved dose recommendations apply to creatinine clearance as such, i.e. not corrected for body surface area or body weight. Sandoz confirmed that they have not obtained any paediatric PK data in renal impairment and that no further data is available. The appropriateness of the dosing has not been re-assessed.

Conclusion: This issue will not be further pursued. See Annex 1 for RMS' proposed SPC text.

Question 3:

In the light of the second point, it should be discussed if there is an age limit when the CL_{crea} limits in the table on decreased renal function in children are applicable, and if so, this age limit should be included in the table.

Response from Meda:

We propose that the weight limits described in the referral for Augmentin/Spektramox - EMEA/H/A-30/979 and given above could be used.

Response from InfectoPharm:

See question 1

Response from Sandoz:

See question 1

Rapporteur's overall comment on dosing in renal impairment:

The MAHs has not provided any data. Although it is known that maturation as well as body size is of importance for the glomerular filtration and thereby of importance for the elimination of this drug, this procedure concerns orally administered drug and the bioavailability is unknown. Therefore exposure cannot easily be predicted. The appropriateness of the dosing has not been re-assessed during this procedure but rather rely on previously approved dosing recommendations within Europe.

Conclusion: This issue will not be further pursued. . See Annex 1 for RMS' proposed SPC text.

Question 4:

The safety of the proposed maximum dose of 90 mg/kg/day (*not exceeding 3g/day*) should be justified.

Response from Meda:

The dose range which is justified according to clinical use and safety experience for Meda's amoxicillin products in Sweden ranges from 25 mg/kg/day for uncomplicated lower urinary tract infections up to 50 mg/kg/day as standard dose and up to 75 mg/kg/day for less sensitive bacteria, in upper and lower respiratory tract infections. Meda has no data for available their products justifying the proposed maximum dose of 90 mg/kg/day for <40 kg and pretermes and neonates.

Toxicity is rarely reported. Even large doses are usually well tolerated. One case in our SPC describes severe intoxication after intake of 7 g for a 3 year old child. This is well above the dose that could be achieved with the dosage 90 mg/kg/day.

Response from InfectoPharm:

The proposed maximum dose of 90 mg/kg body weight per day is an established dose in severe infections. The maximum dose in the German SPC template issued by the BfArM and also in the SPC of the applicant is 100 mg/kg body weight per day. The discrepancy in the dosing recommendations and especially in the approved maximum daily doses has to be ascribed to the heterogeneous resistance situation in Europe. Particularly with regard to otitis media caused by penicillin-resistant pneumococci the maximum daily doses recommended in middle Europe (e.g. France, Germany) exceed those recommended in the Scandinavian region.

The applicant performed a literature search in diverse text books, SPCs of other MAHs and the Medline database to identify recommended and approved maximum daily doses for amoxicillin.

The average maximum daily doses range between 90 and 100 mg/kg body weight. In single cases, maximum daily doses up to 150 mg/kg body weight were administered (see also comment from the CMS France in the current work-sharing procedure). There is no clear evidence for a significant increase of adverse drug reactions by the application of higher doses in the range of 90- 100 mg/kg body weight. Therefore, a recommended maximum dose of 90- 100 mg/kg body weight appears to be adequate to account for different epidemiologic resistance situation Europe.

Response from Sandoz:

A posology up to 100 mg/kg/day for more severe infections is actually approved in several European SmPCs for amoxicillin (reference product and/or generics), such as Germany, Austria. In France higher dosages up to 150 mg/kg/day are approved.

The American recommendations published in 2004 by the AAP (Clinical Practice Guideline. Diagnosis and Management of Acute Otitis Media. Paediatrics 2004;113:1451-65) recommend the administration of high dose amoxicillin (80-90 mg/kg/day). Actually, 80 mg/kg/day in three daily doses (Piglansky et al. 2003) and 90 mg/kg/day in two daily doses (Arguedas et al. 2005) have been shown to be effective. Most studies performed with high dose amoxicillin/clavulanic acid in Acute Otitis Media have used a 70 or 90 mg/kg/day dosage regimen

It was therefore agreed during DCP AT/H/0187/004-006/DC to specify the paediatric dosage range as: **40-90 mg/kg/day** in two to three divided doses (see discussion below on SPC wording).

Furthermore, during the Article 30 Referral for Augmentin CHMP has approved for the 8:1 oral suspension and the Extra Strength formulation (14:1 ratio), **80 mg/kg/day** respectively **90 mg/kg/day** dosage regimen for the amoxicillin component, confirming that there are no safety concerns related to this high dose regimen (EC Annex I-III, EMEA/CHMP/97898/2009).

Rapporteur's comment:

The MAH's position that there are substantial clinical data supporting a positive benefit – risk ratio for a maximum dose of 90 mg/kg/day in the treatment of severe infections is supported by the Rapporteur. This maximum dose is also in line with the recently finalised Article 30 Referral for Augmentin, where a 90 mg/kg/day dosage regimen for the amoxicillin component in the oral suspension (14:1 ratio) were approved by the CHMP, supporting a positive benefit-risk for high dose regimen. Furthermore, in some MS with high prevalence of resistant S. pneumoniae, the maximum daily dose recommended for the treatment of otitis media caused by penicillin-resistant pneumococci is 150mg/kg/day in 3 divided doses.

Issue resolved.

Discussion of proposed SPC wording taking CMS comments into account

Response from Meda:

Meda agrees with the overall conclusion of the Rapporteur and have no additional SPC suggestions, besides supporting 2 g as a maximum dose for endocarditis prophylaxis.

Response from InfectoPharm:

Although the applicant agrees with the proposed posology in general, the recommendation concerning the dosing interval (behind the asterisk) should be revised, because no evidence has been found that using three times daily dosing in the initial stage of infections will increase clinical efficacy in nonsevere infections. Moreover, no clinical evidence has been identified to support the recommendation of three times daily dosing in severe infections such as pneumonia. The applicant proposes to change the text behind the asterisk according to the SPC approved since 2007 by the Federal Institute for Drugs and Medical Devices (BfArM) for the applicant's products InfectoMox 250 Saft, InfectoMox 500 Saft and InfectoMox 750 Saft (powder for oral suspension). This SPC contains the following information on dosing frequency:

To maintain effective antibacterial concentrations, two times daily dosing is only recommended when the daily dose is in the upper range.

Response from Sandoz:

General MAH comment:

The MAH would like to draw to the attention of the Sandoz study AMX 1/97 “*Double-blind, randomized, multicenter study comparing the efficacy and tolerance of amoxicillin 30 mg/kg b.i.d. versus amoxicillin 15 mg/kg t.i.d. in the treatment of acute otitis media in children*” (Study Report CSR-AMX 1/97- 9/00, amended 05/02). The study report was submitted in full in DCP AT/H/0187/004-006/DC (clinical overview, module 2.7.3 and module 5.3.5) and was also submitted in the present Paediatric Worksharing procedure. This study provided adequate support for a 60 mg/kg/day bid dosage regimen in acute otitis media in 516 children, showing the non-inferiority of the bid regimen in comparison to the standard tid regimen (accepted as oral presentation at the 40th ICAAC, Toronto, September 2000, Guggenbichler et al. 2000).

Daily frequency of dosing:

We disagree with the Rapporteur’s statement that “*twice daily dosing may be sufficient in some indications such as tonsillitis and cystitis, as well as in less severe infections*” and with the statement on PK/PD data added as *note.

In particular we disagree with Norway’s comment on three times daily dosing based on serum half-life consideration. Actually there is a wealth of published PK/PD data supporting the efficacy of twice daily regimen with sufficiently high amoxicillin dosages (including with the combination amoxicillin/clavulanic acid). An extensive discussion on the PK/PD rationale of bid dosing was provided in the clinical overview submitted in AT/H/0187/004-006/DC (see extract of clinical overview section 3.2.3 below; for full documentation refer to DCP AT/H/0187/004- 006/DC):

Pharmacodynamic studies have shown that for beta-lactam antibiotics, the time that the serum concentration exceeds the MIC value of the target pathogen (i.e. time above MIC, T>MIC) is a key pharmacodynamic parameter in predicting a successful clinical and bacteriological outcome. For penicillins, it has been considered that T>MIC needs only to be 40-50% of a dose interval to achieve maximum bacteriological cure. This has led recently to the definition of a pharmacodynamic breakpoint, defined as the serum concentration exceeded for at least 40% of the dosing interval for a particular dosing regimen. For amoxicillin, the pharmacodynamic breakpoint has been set at 2 µg/ml for standard amoxicillin dosing regimens such as 500 mg tid (T>MIC: 41% for a MIC of 2 µg/ml) and 875 mg b.i.d (T>MIC: 38% for a MIC of 2 µg/ml). This value is further supported by in vitro pharmacodynamic models that showed that a 875 mg dose of amoxicillin produced concentrations exceeding the MIC for amoxicillin of penicillin resistant *S. pneumoniae* (i.e. 2 µg/ml) for 42% of a 12 hours dosing interval.

Investigations in children have shown that the serum amoxicillin concentrations exceed a target MIC of 1 µg/ml for respectively 52% (6.2 ± 0.9 h) of dosing interval after a 22.5 mg/kg bid dosage regimen and for 59% (4.7 ± 0.7 h) of dosing interval after a 13.3 mg/kg tid regimen. The T>MIC of 2 µg/ml has been reported to be 46% of the 8-hourly dosing interval for a 13.3 mg/kg tid regimen. In a rat pneumoniae model the rat plasma levels simulating those achieved in paediatric patients showed a T>MIC of 34% for a MIC of 2 µg/ml after a 22.5 mg/kg bid dosage and a T>MIC of 45.8% for a 45 mg/kg bid regimen.

According to the CPMP Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products (CPMP/EWP/2655/99), appropriate dosing regimens should be designed to provide a pharmacokinetic profile in blood that is appropriate to the PK/PD properties of the drug.

The PK/PD data available in the literature support a standard 500 mg tid dosage regimen in adults and at least a 875 mg bid regimen. There are no published PK/PD data available that support a 750 mg bid dosage regimen in adults. In children published PK/PD data support a standard 40 mg/kg/day tid regimen (i.e. 13.3 mg/kg tid) that ensures T>MIC values comparable to those observed with 500 mg tid in adults. A twice daily administration in children should therefore use at least a 22.5 mg/kg dosage regimen in order to ensure similar T>MIC in comparison to the recommended standard tid regimen of 40 mg/kg/day.

The pharmacokinetic data obtained in studies documenting the bioequivalence of Ospamox® formulations to the respective reference formulations have been used to calculate the relevant PK/PD data for amoxicillin. The T>MICs have been compared for various dosage regimens (500 mg tid, 750 mg bid and 1 g bid) and for various MIC values (respectively 0.5, 1 and 2 µg/ml). The T>MIC values for a target MIC of 2 µg/ml were 37.7% (95% CI 34.7%; 40.7%) for the 500 mg tid regimen and 42.8% (38.6%; 46.9%) for the 1 g bid regimen. These T>MIC values showed that the 500 mg 8-hourly and the 1 g 12-hourly regimen could be considered as pharmacodynamically equivalent, supporting the pharmacodynamic rationale for a 1 g bid dosage regimen.

This PK/PD data observed in adult volunteers for the studies above, together with the PK/PD data of amoxicillin in serum in children and MEF, support a 30 mg/kg bid dosage regimen in children with otitis media. The adult dosage regimen of 1g bid reaches an equivalent T>MIC to the 500 mg tid regimen, therefore a paediatric dosage regimen of 30 mg/kg bid may be expected to reach similar T>MIC when compared to a 15 mg/kg tid (i.e. 45 mg/kg/day), regimen which corresponds to the standard dosage recommendation (40-50 mg/kg/day up to 60 mg/kg/day).

To our knowledge, there are no stratified randomized comparative PK/PD studies which support the statement that three times daily dosing is associated with enhanced efficacy “*in the initial stage in other infections*”. Although we acknowledge that in adults, amoxicillin is recommended as 8-hourly dosing in Community Acquired Pneumonia (CAP), we remind that CHMP approved for Augmentin 7:1 ratio a posology (expressed in amoxicillin component) of up to 70 mg/kg/day given as two divided doses for infections such as **acute otitis media**, sinusitis and **lower respiratory tract infections** (i.e. CAP approved in section 4.1) (EC Annex I-III, EMEA/CHMP/97898/2009).

Furthermore, Augmentin 14:1 ratio has been approved by the CHMP for **acute otitis media** and **CAP** with a recommended dose of 90 mg/kg/day in two divided doses. In particular the 14:1 formulation of Augmentin has been approved for the treatment of infections likely to be caused by penicillin-resistant *S. pneumoniae*, pathogen for which only the amoxicillin component is relevant.

According to the CHMP discussion (Annex II), extrapolation to the efficacy in CAP in children was based on PK/PD considerations.

In our opinion the statement “*PK/PD data indicate that dosing three times daily is associated with enhanced efficacy and is thus recommended for severe infections such as pneumonia*” is therefore inadequate for amoxicillin and should be deleted.

Dosage range:

As extensively reviewed in the clinical overview submitted in DCP AT/H/0187/004-006/DC and discussed during the procedure, the lowest dosage in *older* studies was 40 mg/kg/day tid or 45 mg/kg/day bid in tonsillitis; in Otitis Media, 50 mg/kg/day were used. Recent studies have used much higher dosages (80-90 mg/kg/day). For these reasons, the dosage range was approved as 40-90 mg/kg/day in two to three divided doses. As cited by the Rapporteur, the standard dosage range has been repeatedly reported as **40-50 mg/kg/day**; we see therefore no rationale to deviate from the lower range limit of 40 mg/kg/day approved in AT/H/0187/004-006/DC and set the lower limit at 45 mg/kg/day. Furthermore, the proposed SPC wording does not introduce any relevant new information for the prescriber with regard to dosage range which would not be covered already by the standard sentences in section 4.2 such as:

The dosage of amoxicillin is dependent on age, bodyweight and renal function of the patient, on the seriousness and localization of the infection and on the expected or proved causative agent.

We agree with the Rapporteur that the standard statement in section 4.1 “*consideration should be given to official guidance on the appropriate use of antimicrobial agents*” allows sufficiently for a wider (lower) dose range.

Epidemiological situation across EU:

The amoxicillin dosage range as approved in the DCP AT/H/0187/004-006/DC covers the upper range of doses provided by and approved for the various Augmentin formulations. In analogy to the CHMP position on the choice of Augmentin formulations (see scientific discussion Annex II):

“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”

the MAH is of the opinion that the dosage range and the standard sentences included in the SPC in section 4.1 and 4.2 (see proposed wording below) take into account the various epidemiological situations that the prescriber may face across Europe and that the adequacy of amoxicillin doses delivered is adequately reflected in the SPC.

Special dosage recommendations:

The changes proposed by the Rapporteur are endorsed, since they are fully in line with the outcome of DCP AT/H/0187/004-006/DC, in particular the bid dosage recommendation in tonsillitis.

Sections 4.4 and 5.2:

The changes proposed by the Rapporteur are endorsed.

MAH proposal for SPC wording:

We propose therefore to maintain the dosage range and the wording approved in AT/H/0187/004 006/DC and its subsequent referral EMEA/CMDh/569057/2009, but agree to add the sentence proposed by the Rapporteur *and the susceptibility of the pathogen (see sections 4.4, 5.1 and 5.2).*

Treatment duration is maintained with the range of 6-10 days, as approved in AT/H/0187/004-006/DC.

All other changes proposed by the Rapporteur in section 4.2 are endorsed. The changes proposed by the Rapporteur in sections 4.4 and 5.2 are endorsed.

Rapporteur’s comment (taking CMS’ comments into account)

The companies have all addressed the proposed text for section 4.2. While Meda generally agrees with the proposed wording, InfectoPharm accepted the general text but disagreed with the recommendation concerning the dosing interval (behind the asterisk) suggested by the Rapporteur. However, this MAH concurs that the information regarding enhanced efficacy of tid. dosing compared to bid. dosing, but suggested an alternative text for clarification of this fact; To maintain effective antibacterial concentrations, two times daily dosing is only recommended when the daily dose is in the upper range.

Sandoz provided the most elaborative response, addressing clinical data, PK/PD considerations, epidemiological differences throughout Europe and the outcome of the recently DCP (AT/H/0187/004 006/DC) also previously addressed by the Rapporteur. Based on this the MAH ends up in a wording similar to that agreed in AT/H/0187/004 006/DC.

Taking the current situation into account with very diverse situations within Europe with regard to epidemiology of resistance, primarily penicillin-resistant pneumococci, and also wide differences in local clinical practices and national guidelines, also exemplified by the MS comments in the present procedure, the Rapporteur acknowledges that the recommended dosage range may have to be widened. Antibiotic treatment should only be initiated when clearly needed and then aim at providing reassuring active concentrations. PK/PD data support the use of 40 mg/kg/day divided in three doses for MIC of 2 mg/ml. Accordingly, a lower limit of 40 mg/kg/day is considered acceptable, in particular with a statement explaining the advantage of the t.i.d. dosing.

The upper limit of the dosage range is more delicate in light of differences in prevalence of resistance and national antibiotic policies. Recent studies on otitis media support the use of high-dose amoxicillin, mainly 80 - 90 mg/kg/day in 2-3 divided doses. The safety of this dose is considered well justified, see response to Q 4. However, some MS recommend even higher doses, e.g. 150 mg/kg/day in specific situations for the treatment of acute otitis media caused by pneumococci with reduced susceptibility to

penicillins. As this dosage regimen is not justified by firm clinical data, and depending on the various epidemiological situations with regard to prevalence and types of antibiotic resistance, the Rapporteur is not in favour of increasing the currently suggested maximum recommended dose of 90 mg/kg/day (not exceeding 3g/day). However, a statement under the subheading “Special dosage recommendations” regarding acute otitis media addressing the local differences across EU is suggested in order to allow for differences in national practices. Although this statement may be considered covered by the standard statement: Consideration should be given to official guidance on the appropriate use of antibacterial agents, we are of the opinion that the present very variable and dynamic epidemiological situations throughout Europe are particularly relevant for the indication acute otitis media.

Regarding the recommended treatment duration, we suggest that this statement is deleted in the context of the present art 45 procedure, since this information is not specific for paediatric patients. Furthermore, the specification for neonates and premature is suggested to be deleted to be in line with other dosing information in this SmPC.

VI. RAPPORTEUR’S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

Amoxicillin has been extensively used worldwide in paediatric patients, and the safety and efficacy profile of the drug is well acknowledged. The posology as proposed by the Rapporteur is considered justified by treatment guidelines, published scientific data from clinical studies, PK/PD considerations and recent mutually approved generics. The benefit-risk for paediatric use of amoxicillin is considered positive.

➤ Recommendation

Based on responses from the MAHs and comments from MS, the following specific wording related to paediatric use is proposed for sections 4.2, 4.4 and 5.2, see Annex 1. The PL should be updated after the finalization of the SmPC.

A type IB variation will be requested from the MAHs within 60 days after finalising this procedure.

Section 4.2

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Children weighing < 40 kg

The daily dosage for children is 40 - 90 mg/kg/day in two to three divided doses (not exceeding 3 g/day) depending on the indication, severity of the disease and the susceptibility of the pathogen (see special dosage recommendations below and sections 4.4, 5.1 and 5.2).*

**PK/PD data indicate that dosing three times daily is associated with enhanced efficacy, thus twice daily dosing is only recommended when the dose is in the upper range.*

Children weighing more than 40 kg should be given the usual adult dosage.

Special dosage recommendation

Tonsillitis: 50 mg/kg/day in two divided doses.

Acute otitis media: In areas with high prevalence of pneumococci with reduced susceptibility to penicillins, dosage regimens should be guided by national/local recommendations.

Early Lyme disease (isolated erythema migrans): 50 mg/kg/day in three divided doses, over 14-21 days.

Prophylaxis for endocarditis: 50 mg amoxicillin/kg body weight given as a single dose one hour preceding the surgical procedure.

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Dosage in impaired renal function

The dose should be reduced in patients with severe renal function impairment. In patients with a creatinine clearance of less than 30 ml/min an increase in the dosage interval and a reduction in the total daily dose is recommended (see section 4.4 and 5.2).

Renal impairment in children under 40 kg:

<i>Creatinine clearance ml/min</i>	<i>Dose</i>	<i>Interval between administration</i>
> 30	Usual dose	No adjustment necessary
10 – 30	Usual dose	12 h (corresponding to 2/3 of the dose)
< 10	Usual dose	24 h (corresponding to 1/3 of the dose)

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Section 4.4

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Precaution should be taken in premature children and during the neonatal period: renal, hepatic and haematological functions should be monitored.

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Section 5.2

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In preterm infants with gestational age 26-33 weeks, the total body clearance after intravenous dosing of amoxicillin, day 3 of life, ranged between 0.75 – 2 ml/min, very similar to the inulin clearance (GFR) in this population. Following oral administration, the absorption pattern and the bioavailability of amoxicillin in small children may be different to that of adults. Consequently, due to the decreased CL, the exposure is expected to be elevated in this group of patients, although this increase in exposure may in part be diminished by decreased bioavailability when given orally.

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VII. LIST OF MARKETING AUTHORISATION HOLDERS INVOLVED

Marketing Authorisation Holder	Name of the medicinal product
Sandoz GmbH	OSPAMOX 125 mg/ 5 ml OSPAMOX 250 mg/5 ml, OSPAMOX 500 mg/5 ml Amoxicillin Sandoz, 100 mg/ml pulver til mikstur, suspensjon Amoxi-Sandoz 250 mg/ 5 ml Pulver zur Herstellung einer Suspension zum Einnehmen Amoxi-Sandoz 500 mg/ 5 ml Pulver zur Herstellung einer Suspension zum Einnehmen
1A Pharma GmbH, Germany	Amoxi 250 TS - 1 A Pharma, Amoxi 500 TS - 1 A Pharma
HEXAL AG	Amoxihexal® forte Saft Amoxi-Tri 10 TS Triamoxi 10 TS Amodrink® 10 TS Amoxisalut® 10 TS Amoxitrihydrat 10 % TS Amoxihexal® Saft Amoxi-DELTA
Infectopharm Arzneimittel GmbH	Amoxicillin Infectopharm 750 tabs Infectomox 250 Saft Infectomox 500 Saft Infectomox 750 Saft Infectomox 500 Tabs Infectomox 1000 Tabs Infectomox 1000 mg
Recip AB, Sweden	Imacillin

ANNEX I

PROPOSED SPC WORDING RELATED TO PAEDIATRIC USE

The following wording in sections 4.2, 4.4 and 5.2 related to paediatric data is proposed as justified in the current AR.

Section 4.2

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Children weighing < 40 kg

The daily dosage for children is 40 - 90 mg/kg/day in two to three divided doses (not exceeding 3 g/day) depending on the indication, severity of the disease and the susceptibility of the pathogen (see special dosage recommendations below and sections 4.4, 5.1 and 5.2).*

**PK/PD data indicate that dosing three times daily is associated with enhanced efficacy, thus twice daily dosing is only recommended when the dose is in the upper range.*

Children weighing more than 40 kg should be given the usual adult dosage.

Special dosage recommendation

Tonsillitis: 50 mg/kg/day in two divided doses.

Acute otitis media: In areas with high prevalence of pneumococci with reduced susceptibility to penicillins, dosage regimens should be guided by national/local recommendations.

Early Lyme disease (isolated erythema migrans): 50 mg/kg/day in three divided doses, over 14-21 days.

Prophylaxis for endocarditis: 50 mg amoxicillin/kg body weight given as a single dose one hour preceding the surgical procedure.

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Dosage in impaired renal function

The dose should be reduced in patients with severe renal function impairment. In patients with a creatinine clearance of less than 30 ml/min an increase in the dosage interval and a reduction in the total daily dose is recommended (see section 4.4 and 5.2).

Renal impairment in children under 40 kg:

<i>Creatinine clearance ml/min</i>	<i>Dose</i>	<i>Interval between administration</i>
<i>> 30</i>	<i>Usual dose</i>	<i>No adjustment necessary</i>
<i>10 – 30</i>	<i>Usual dose</i>	<i>12 h (corresponding to 2/3 of the dose)</i>
<i>< 10</i>	<i>Usual dose</i>	<i>24 h (corresponding to 1/3 of the dose)</i>

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Section 4.4

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Precaution should be taken in premature children and during the neonatal period: renal, hepatic and haematological functions should be monitored.

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Section 5.2

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In preterm infants with gestational age 26-33 weeks, the total body clearance after intravenous dosing of amoxicillin, day 3 of life, ranged between 0.75 – 2 ml/min, very similar to the inulin clearance (GFR) in this population. Following oral administration, the absorption pattern and the bioavailability of amoxicillin in small children may be different to that of adults. Consequently, due to the decreased CL, the exposure is expected to be elevated in this group of patients, although this increase in exposure may in part be diminished by decreased bioavailability when given orally.

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