

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

**Clarithromycin**

**Clarithromycin\_SK/W/0001/pdWS/001**

**Marketing Authorisation Holders:**

Abbott Laboratories Limited  
Grunenthal GmbH  
Pharmex

Rapporteur:	SK
Start of the procedure (day 0):	03.07.2009
Date of this report:	26.10.2010

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Clarithromycin
INN (or common name) of the active substance(s):	Clarithromycin
MAH:	Abbott Laboratories Limited
Currently approved Indication(s) as provided by the MAHs	<p><b>Clarithromycin</b> is indicated for treatment of infections caused by susceptible organisms. Indications include:</p> <ul style="list-style-type: none"> <li>• Lower respiratory tract infections, for example acute and chronic bronchitis and pneumonia.</li> <li>• Upper respiratory tract infections, for example sinusitis and pharyngitis.</li> <li>• Skin and soft tissue infections of mild to moderate severity, for example folliculitis, cellulitis and erysipelas</li> <li>• Helicobacter pylori infection (used in an appropriate combination with another antimicrobial agent and a proton pump inhibitor)</li> </ul> <p>Consideration should be given to official guidance on the appropriate use of antibacterial agents.</p>
Pharmaco-therapeutic group (ATC Code):	Antibacterials for systemic use - macrolides (J01FA09)
Pharmaceutical form(s) and strength(s):	<p><b>Oral formulations</b></p> <ul style="list-style-type: none"> <li>• Clarithromycin tablets 250 mg, 500 mg</li> <li>• Clarithromycin Granules for Oral Suspension 125 mg/5ml or 250 mg/5 ml</li> <li>• ClaroSip® - clarithromycin in a drinking straw 125 mg or 187,5 mg</li> </ul> <p><b>Parenteral formulation</b></p> <ul style="list-style-type: none"> <li>• Clarithromycin Powder for Solution for Injection 500 mg/vial</li> </ul>

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## **I. INTRODUCTION**

In response to Article 45 of the Pediatric Regulation, the request from EMEA to MAHs for clarithromycin-containing products, three companies (Abbott Laboratories Limited, Grunenthal GMBh and Pharmex) - have provided answers for pharmaceutical presentations used in children.

**The Abbott Laboratories Limited** identified fifty-one studies with clarithromycin involving children or having a potential interest for pediatric indications, after a detailed review of the clinical study reports it appears that one of them was a duplicate reference. Finally, fifty studies have been reviewed in accordance with Article 45 of the Regulation (EC) No 1901/2006 on medicinal products for pediatric use. Short critical expert overviews have also been provided. Only literature that provided clinically significant adequately supported information was included in this review. A total of 33,079 patients have been enrolled in these clinical studies, the number of patients for each study category is shown in Table 1, the titles of the individual studies are listed in Table 2.

**Grunenthal GmbH** submitted four studies on an innovative pediatric formulation of Clarithromycin in a drinking straw, while **Pharmex** provided three papers on the combined treatment of Helicobacter pylori infection in children involving Clarithromycin.

**Table 1. Number of studies and patients enrolled by study category  
(Abbott Laboratories Limited)**

Study Category	Number of Studies	Number of Patients
Stability	1	N/A
Toxicity	3	N/A
Bioavailability	1	22
Pharmacokinetic, Phase I/II	1	24
Pharmacokinetic, Phase II	5	130
Pharmacokinetic, Phase IV	2	105
Clinical Phase II	1	11
Clinical Phase III	26	1531
Clinical Phase IV	4	2098
Post-Marketing (PMOS)	6	29,158

The MAH has not requested any consequential regulatory action which should be taken into account following assessment of the above mentioned documentation. In the clinical overview the MAH sustains that the submitted pediatric studies do not influence the benefit risk for clarithromycin and strongly suggest efficacy of clarithromycin in this population.

**Table 1. List of submitted studies**

**ABBOTT Laboratories Limited**

1. AUSTR-1004 I. Haider-Salaberger\* Klacid Uno PMOS Study 2004
2. F87-114 C. J. Eason et al. Single-dose bioavailability of two experimental formulations of clarithromycin' granules for suspension versus a tablet formulation under fasting and nonfasting conditions
3. F88-127 C. J. Eason et al. Single-dose bioavailability of three experimental formulations of clarithromycin granules for suspension versus a tablet formulation
4. F89-153 C. J. Easonetal. Comparison of the *bioavaiability* from two formulations of clarithromycin granules for suspension versus a tablet formulation
5. FRAN2000-01 G. Roger Diffusion of clarithromycin and roxithromycin into tonsils
6. FRAN 03-004 P. Reinert Traitement des angines aigue's de l'enfant par la clarithromycine dans les conditions de pratique medicale courante
7. FRA 03-005 P. Reinert Traitement des infections respiratoires basses de l'enfant par la clarithromycine dans les conditions de pratique medicale courante
8. KOR-03-003 D. Ghee\* A multi-center, post-marketing surveillance study to obtain further findings in the safety of Klaricid® XL therapy in patients with upper or lower respiratory tract infections
9. KOR-03-004 D. Ghee\* A multi-center, post-marketing surveillance study to obtain further findings in the safety of Klaricid® XL therapy in patients with upper or lower respiratory tract infections
10. KOR-03-005 D. Ghee\* A multi-center, post-marketing surveillance study to obtain further findings in the safety of Klaricid® DR therapy in patients with upper or lower respiratory tract infections
11. KORE-05-002 D. Ghee\* Observational study on impact of smoking to *H.pylori* eradication rate in Korean patients who has duodenal ulcer disease
12. M88-118 L. Sundberg Penetration of clarithromycin through respiratory mucosa: a study using secretory otitis media as a model
13. M88-121 R. S. Rodriguez Comparative safety and efficacy of clarithromycin and penicillin V suspensions in the treatment of streptococcal pharyngitis
14. M88-244 R. S. Rodriguez A safety and efficacy comparative study of clarithromycin and amoxicillin suspensions in the treatment of patients with acute otitis media
15. M88-245 R. S. Rodriguez Comparative safety and efficacy of clarithromycin and erythromycin ethylsuccinate suspensions in the treatment of patients with mild to moderate skin or skin structure infection
16. M89-307 J. H. Levenstein Comparative safety and efficacy of clarithromycin and penicillin V suspensions in the treatment of streptococcal pharyngitis
17. M89-308 J. C. Craft\* Comparative safety and efficacy of clarithromycin and penicillin V suspensions in the treatment of streptococcal pharyngitis
18. M89-309 J. H. Levenstein Comparative safety and efficacy of clarithromycin and cefadroxil suspensions in the treatment of children with mild to moderate skin or skin structure infection
19. M89-310 J. C. Craft\* Comparative safety and efficacy of clarithromycin and cefadroxil suspensions in the treatment of children with mild to moderate skin or skin structure infection
20. M89-313 J. C. Craft\* Comparative safety and efficacy of clarithromycin and amoxicillin / clavulanate suspensions in the treatment of patients with acute otitis media
21. M89-314 J. C. Craft\* Comparative safety and efficacy of clarithromycin and amoxicillin / clavulanate suspensions in the treatment of patients with acute otitis media

22. M89-317 J. C. Craft\* A safety and efficacy comparative study of clarithromycin and cefaclor suspensions in the treatment of children with acute otitis media study
23. M89-337 J. R. Torres, Jr. A safety and efficacy comparative study of clarithromycin and amoxicillin suspensions in the treatment of patients with acute otitis media
24. M89-355 P. Begue Penetration of clarithromycin into tonsils in children undergoing tonsillectomy
25. M90-489 V. Gan A study of the pharmacokinetics in children of clarithromycin granules for suspension
26. M90-490 J. C. Craft\* Safety and efficacy of clarithromycin and penicillin V suspensions in the treatment of children with streptococcal pharyngitis and/or tonsillitis
27. M90-490A C. S. Hains Safety and efficacy of clarithromycin suspension in the treatment of children with *M. pneumoniae* pharyngitis
28. M90-491 J. C. Craft\* Comparative safety and efficacy of clarithromycin and cefadroxil suspensions in the treatment of children with mild to moderate skin or skin structure infection
29. M90-497 J. C. Craft\* A safety and efficacy comparative study of clarithromycin and Augmentin® (amoxicillin / clavulanate potassium) suspensions in the treatment of children with acute otitis media
30. M90-498 J. C. Craft\* A comparative study of the safety and efficacy of clarithromycin and EryPed® (erythromycin ethylsuccinate) suspensions in the treatment of children with community-acquired pneumonia
31. M90-521 J. C. Craft A phase I/II dose ranging, pharmacokinetic, drug interaction, safety and preliminary efficacy study of oral clarithromycin granules for suspension, in combination with Zidovudine or Dideoxyinosine, in the treatment of disseminated *Mycobacterium Avium Complex* infections in pediatric patients with AIDS
32. M91-649 J. C. Craft\* A safety and efficacy comparative study of clarithromycin and Augmentin® (Amoxicillin / Clavulanate Potassium) suspensions in the treatment of children with acute otitis media with tympanocentesis
33. M92-747 M. Hammerschlag An open-label study of the safety and efficacy of clarithromycin suspension in the treatment of children with Chlamydia pneumoniae and asthma
34. M92-835 D.A. Stamler A comparative study of the safety and efficacy of clarithromycin and Augmentin® (Amoxicillin / Clavulanate) suspensions in the treatment of paediatric patients with acute bronchitis
35. M93-017 J. M. McCarty, V. Gan Penetration of clarithromycin through respiratory mucosa: a study using acute otitis media as a model
36. M95-326 P. J. Sanchez A double-blind, Placebo Controlled Study of The Safety and Efficacy of Clarithromycin for the Prevention of Chronic Lung Disease in Very-Low- Birth-Weight Infants Colonized with *Ureaplasma urealyticum*
37. M96-505 J. C. Craft\* Double-blind, comparative efficacy study of clarithromycin 5-day versus 10-day therapy in the treatment of acute otitis media in children
38. M96-551 J. C. Craft\* A multi-center, observational study to observe the patients satisfaction and symptom improvement for Klaricid® XL in Korean patients with acute rhinosinutitis
39. M99-102 J. C. Craft\* A randomized, controlled, single-blind study assessing the safety and efficacy of clarithromycin versus erythromycin estolate in the treatment of children with pertussis
40. P05-101\_CSR D. Chee\* A multi-center, observational study to observe the patients satisfaction and symptom improvement for Klaricid®XL in Korean patients with acute rhinosinutitis
41. P92-078 G. Andretta Safety and efficacy of clarithromycin in children
42. PROT-EngAWB012004Jan04 I. Haider- Salaberger\* Klacid® Uno - PMOS Efficacy and safety

- of Klacid® Uno in adults and adolescents with pharyngitis / tonsillitis
43. RD92562 T. Hale\* Granulation of pediatric clarithromycin: effect of temperature control on carbopol and PVP granulation steps.
  44. Rr92009 D. Reid Patterson\* Overview of clarithromycin toxicity in young animals in support of pediatric NDA
  45. TA87-095 D. Reid Patterson\* Six- week toxicity study of Abbott-56268 granule for suspension administered orally to immature (juvenile) rats
  46. TA88-088 D. Reid Patterson\* Acute oral toxicity evaluation of three Abbott-56268 (te-031) pediatric formulations in rats
  47. W91-092 R. Fior An open, randomized, controlled multi-centric study on the efficacy and tolerability, in children, of clarithromycin oral suspension (Klaped®) in the treatment of acute otitis media, versus amoxicillin / clavulanate and cefaclor therapy
  48. W91-093 G. Cascio, N. Principi An open, controlled multi-centric study on the efficacy and tolerability of clarithromycin (Klaped®) versus amoxicillin/clavulanate and cefaclor treatment on children with a diagnosis of acute bronchopneumonia
  49. W91-094 E. Reali, M. Blatto An open, controlled multi-centric study on the efficacy and tolerability, in children, of clarithromycin suspension (Klaped®) versus benzathine penicillin, versus cefaclor, and versus amoxicillin treatment on children with streptococcal pharyngotonsillitis
  50. W91-107 J. C. Craft\* A single-blind, randomized, comparative, phase III, multi-center study of clarithromycin and cefaclor suspensions in the treatment of children with lower respiratory tract infections
  51. W91-108 C. M D Carnegie\* A Safety and Efficacy Comparative Study of 5-days treatment with clarithromycin and amoxycillin suspensions in the treatment of patients with acute otitis media

### **Grunenthal GbmH**

1. DE-AWB-CLARI-01 of 29-Jan-2008 ClaroSip® - R. Schmid, Clarithromycin im Trinkhalm Multizentrische Anwendungsbeobachtung mit einer neuen Darreichungsform für Kinder
2. DE-AWB-CLARI-01 of 29 Jan 2008 ClaroSip® - Clarithromycin in a drinking straw Multicentre postmarketing surveillance study with a new paediatric formulation
3. C Treviño: Observational study on a novel paediatric dosage form of NeoClaroSip® - clarithromycin in a drinking straw
4. C Treviño: Observational study on the usage of NeoClaroSip® in paediatric patients with RTIs - Postmarketing surveillance study

### **Pharmex**

1. Edward L. Kaplan, 1 W. Manfred Gooch III, 2 Gerard F. Notario,3 and J. Carl Craft3 Macrolide Therapy of Group A Streptococcal Pharyngitis: 10 Days of Macrolide Therapy (Clarithromycin) Is More Effective in Streptococcal Eradication than 5 Days (Azithromycin). • CID 2001:32 (15 June) 1798-1801
2. Moshkowitz M, Reif S, Brill S, Ringel Y, Arber N, Halpern Z and Bujanover Y. Nitroimidazole for Helicobacter pylori Infection in Children and Adolescents One-Week Triple Therapy With Omeprazole, Clarithromycin, and Nitroimidazole for *Helicobacter pylori* Infection in Children and Adolescents *Pediatrics* 1998 <http://www.pediatrics.org/cgi/content/full/102/1/e14>
3. Kawakami E, Ogota SK, Portorreal ACM, Magni AM, Pardo MLE, Patricio FRS. Triple therapy with clarithromycin amoxicillin and omeprazole for Helicobacter pylori eradication in children and adolescents. *Arq Gastroenterol* 2001, 38, 203-206

## II. SCIENTIFIC DISCUSSION

Clarithromycin is a well-established, semi-synthetic, second-generation macrolide antibiotic. It was invented by scientists at the Japanese drug company Taisho Pharmaceutical in the 1970s. The product emerged through efforts to develop a version of the antibiotic erythromycin that did not experience acid instability in the digestive tract and thereby cause side effects, such as nausea and stomach ache. In 1985 Taisho had partnered with the American company Abbott Laboratories for the international rights (Abbott-56268), and Abbott also gained FDA approval for Biaxin in October 1991. The drug went generic in Europe in 2004 and in the U.S. in mid-2005.

Clarithromycin (6-O-methyl-erythromycin A) is obtained by substitution of a methoxy group for the hydroxyl group in position 6 of the erythromycin lactonic ring. This structural change results in improved bioavailability and tolerability and an expanded spectrum of activity over erythromycin. The presence of a methyl group at this position significantly decreases acid catalyzed degradation of clarithromycin to inactive products. Clarithromycin exerts its antibacterial action by inhibiting the intracellular protein synthesis of susceptible bacteria. It selectively binds to the 50S subunit of bacterial ribosomes and thus prevents the translocation of activated amino acids.

Clarithromycin has a broad spectrum of in vitro activity against many clinically important Gram-positive and Gram-negative aerobes and anaerobes. Clarithromycin is usually active against the following organisms in vitro:

- Gram-positive bacteria: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes* (Group A beta-hemolytic streptococci); alpha-hemolytic streptococci (viridans group); *Streptococcus* (*Diplococcus*) *pneumoniae*; *Streptococcus agalactiae*; *Listeria monocytogenes*.
- Gram-negative bacteria: *Haemophilus influenzae*; *Haemophilus parainfluenzae*; *Moraxella* (*Branhamella*) *catarrhalis*; *Neisseria gonorrhoeae*; *Legionella pneumophila*; *Bordetella pertussis*; *Campylobacter jejuni*.
- Mycoplasma: *Mycoplasma pneumoniae*; *Ureaplasma urealyticum*.
- Other organisms: *Chlamydia trachomatis*; *Mycobacterium avium*; *Mycobacterium leprae*; *Mycobacterium kansasii*; *Mycobacterium chelonae*; *Mycobacterium fortuitum*; *Mycobacterium intracellulare*; *Chlamydia pneumoniae*.
- Anaerobes: *Clostridium perfringens*; *Peptococcus species*; *Peptostreptococcus species*; *Propionibacterium acnes*.

Besides its bacteriostatic effect, clarithromycin also has bactericidal effect on certain strains such as *Haemophilus influenzae*; *Streptococcus pneumoniae*; *Streptococcus pyogenes*; *Streptococcus agalactiae*; *Moraxella* (*Branhamella*) *catarrhalis*; *Neisseria gonorrhoeae* and *Campylobacter* spp. Additionally, the 14(R)-OH-clarithromycin metabolite also has clinically significant antimicrobial activity. The 14(R)-OH-clarithromycin metabolite is twice as active against *Haemophilus influenzae* microorganisms as the parent compound. The in vitro activity of clarithromycin is generally one log, dilution more potent than erythromycin. In addition, clarithromycin is more acid stable than erythromycin.

Clarithromycin has a more favorable pharmacokinetic profile than erythromycin. However, the pharmacokinetics of clarithromycin are nonlinear in adults. Mean peak plasma levels in adults after a single oral dose of a clarithromycin tablet/capsule occurred approximately two hours after administration and ranged from 0.35 pg/mL to 3.97 pg/mL after 100 mg and 1200 mg doses, respectively. The mean half-life appeared to be dose-dependent and ranged from 2.27 hours after a 100 mg dose to 5.98 hours after the 1200 mg dose. When a microbiological assay was also used, peak

plasma levels were generally higher, indicating the presence of an active metabolite (14(R)-hydroxyclearithromycin).

Clarithromycin is principally excreted by the liver and kidney. Caution should be exercised in administering this antibiotic to patients with impaired hepatic and renal function.

Pharmacokinetic data from an adult oral multi-dose study on the tablet/capsule formulation again indicated that the half-life appeared to be dose dependent. The half-life ranged from 2.7 hours after doses of 100 mg BID to 5.9 hours following doses of 800 mg BID. Mean peak plasma concentrations obtained by high performance liquid chromatography (HPLC) ranged from 0.37 pg/mL at doses of 100 mg BID to 3.73 pg/mL at doses of 800 mg BID.

## **II.1 Pharmaceutical formulations used in the clinical studies**

Clarithromycin is an established chemical entity with a proven efficacy and safety profile and has been marketed worldwide for more than 15 years in various formulations. Clarithromycin is formulated in various tablet presentations, granules for oral suspension and powder for solution for intravenous infusion.

In the clinical studies reviewed, Clarithromycin was used either in tablet forms (in children older than 12 years and in adults) or in specific paediatric formulations (in infants and children aged from 6 months to 12 years). According to the MAH, liquid formulations are most appropriate for paediatric patients up to 12 years of age.

Clarithromycin's specific paediatric formulations are:

- ***Clarithromycin 125 mg/5 ml granules*** for paediatric suspension were first approved on 5<sup>th</sup> May 1991. The original formulation was subsequently replaced with an aqueous formulation, which was first approved in January 1994 (approved in the EU in July 1994, in Denmark). Clarithromycin 125 mg/5 ml granules for paediatric suspension have been approved in over 100 countries around the world.
- ***Clarithromycin 250 mg/5 ml granules*** for paediatric suspension were first approved on 30<sup>th</sup> June 1993. The original formulation was subsequently replaced with an aqueous formulation, which was first approved in May 1995 (approved in the EU in August 1995, in The Netherlands). Clarithromycin 250 mg/5 ml granules for paediatric suspension have been approved in over 80 countries around the world.
- ***ClaroSip®***, ***clarithromycin in a drinking straw***, an innovative formulation introduced by Grünenthal GmbH in 2006 to ensure high compliance, particularly in children. Clarosip is not recommended in children younger than two years or weighing less than 12kg.

**Parenteral formulation** (Clarithromycin Powder for Solution for Injection 500 mg/vial) - at present, there are insufficient data to recommend a dosage regimen for parenteral formulation for routine use in children.

Clarithromycin is nationally approved in most EU countries of which the majority seems to have information on paediatric use specified in sections 4.1 and 4.2 of the SPC. The proportion of paediatric patients is not specified, but can be estimated to be substantial, since macrolide antibiotics are considered a cornerstone in the treatment of common infections in infants and young children. The indications in the different EU countries probably do not generally differ between adults and

paediatric patients, however dosage recommendations for paediatric patients may vary slightly between countries (mainly regarding options of number of daily doses and length of treatment).

#### **Assessor's comment**

The MAH has not provided the product labeling in those European countries where clarithromycin is authorised. Thus, the adequacy of the information provided for the paediatric population cannot be assessed. The MAH is requested to provide the different SmPCs and patient leaflets.

#### **Assessor's comment**

The use of Clarithromycin in infants younger than 6 months was, not addressed within the documentation submitted, with exception of one study (Reference 36). The MAH is requested to address this issue.

## **II.2 Non-clinical aspects**

Stability, toxicity and bioavailability studies were reviewed.

### **II.2.1 Stability**

The submitted **stability study** (reference 43 in Table 2) is related to the manufacturing process and the taste characteristics of clarithromycin pediatric granule formulation without any patient involved and without any clinical endpoint.

- Granulation of Clarithromycin with Carbopo1974, a polyacrylic acid polymer material, has been shown to yield a unique bioavailable formulation with significantly better taste characteristics than the pure drug. The degree of taste masking is measured by the Ether Extractables test which measures the amount of free Clarithromycin in a sample which dissolves in Ether. The smaller this number, the better the taste masking. A specification of 1.5% Ether Extractables has been set for the Pediatric Clarithromycin formulation after PVP granulation. In general it has been found that granulation with Carbopol alone reduces the Ether Extractables to around 2%; this number usually drops to below 1% after PVP granulation.

### **II.2.2 Toxicity**

Three animal toxicity studies (References 44, 45 and 46 in Table 2) have been reviewed, confirming the safety of the clarithromycin pediatric formulations without adding any new data.

- Single dose acute toxicity was assessed in 3-day-old ICRmice, Immature Wistar rats, young adult Sprague-Dawley-derived, CrI:CD@BR rats and 5-month old beagle dogs (Reference 44). Despite an approximate 2-fold reduction in median lethal dosage in young rats and mice, when compared to comparable adult rodents, indicating enhanced risk to overdosage, the median lethal dosage still appears to be over 80 times the maximum recommended daily dosage for children of 7.5 mg/kg BID or 15 mg/kg/day. Furthermore, the repeated daily dosing studies up to 6 weeks in duration indicated comparable or lesser risk to the toxic effects seen in adult animals at comparable dosing. Enhanced hazard for erythrocytic changes and for cutaneous rashes was noted in younger animals, but no other unique hazards could be related to age differences.
- A single oral dose of three ABBOTT-56268 pediatric formulations were evaluated for acute oral toxicity in CD@BR rats, 16 days old at start of treatment. The dose for all rats was 20 ml/kg (i.e., 5 g/kg). Except for one rat considered to have been misdosed, none of the rats died and no signs of toxicity were observed. Also, no gross morphologic changes were found when the rats were killed and necropsied two weeks after treatment. Thus, clarithromycin pediatric

formulations were found to be non-toxic to rats at the technically applicable maximum dose of 5 g/kg (Reference 46)

- Oral dosage of 150 mg/kg/day for six weeks produced slight toxicity in the treated immature rats, as it manifested by slightly decreased body weight gain (approximately 8% less than that of the controls) and increased relative liver weight in the treated immature rats. However, no treatment-related gross or microscopic changes were found. The two lower dosages of 15 and 50 mg/kg/day produced no treatment-related changes. The no-effect dosage was judged to be 50 mg/kg/day. These findings, in general, are consistent with those reported in a six-week oral toxicity study with clarithromycin in immature rats (Reference 45)

### **II.2.3 Bioavailability**

Single-center, single-dose, open-label, balanced, randomized, three-period, crossover bioavailability study bioavailability study in healthy adult male subjects (Reference 4) compared two different clarithromycin granules for suspension formulations in healthy adults (formulation A and B respectively). A single dose of 250 mg clarithromycin (10 ml of Formulation A or B, or one tablet of Formulation C) was administered to each subject orally once in each of the three study periods. One of the formulations had a lower bioavailability profile compared to the reference tablet formulation and a higher incidence of adverse events compared to the other formulations

## **II.3 Clinical aspects**

### **II.3.1 Pharmacokinetic studies**

The pharmacokinetics of clarithromycin has been well established. MAH has not submitted any new kinetic data.

One **Phase I/II pharmacokinetic study** (Reference 31) was reviewed.

- 24 pediatric patients with AIDS received clarithromycin granules for suspension (7.5, 15, or 30 mg/kg/day for 10 weeks). The study revealed some statistically significant effects on pharmacokinetic parameters when clarithromycin was administered in combination with Zidovudine or Dideoxyinosine, in the treatment of disseminated *Mycobacterium Avium Complex* (MAC). However, these changes were minor and unlikely to be of clinical significance. Doses of 15 and 30 mg/kg/day appeared to be superior to a 7.5 mg/kg/day dose in this patient population. However, the small sample sizes made it difficult to detect meaningful clinical differences if they existed. As to safety considerations, Clarithromycin at doses of up to 30 mg/kg/day was well-tolerated in pediatric patients receiving concomitant ZBV or ddl.

Five **Phase II pharmacokinetic studies** (Ref. 2, 3, 12, 24 and 25) are confirming the pharmacokinetic and safety profile of clarithromycin without providing any new data.

Two of the studies compared the absorption of clarithromycin suspension formulations to that of the clarithromycin tablet (References 2 and 3).

- In a single-center, single-dose, open-label, balanced, randomized, four-period, crossover, pharmacokinetic study each of the 23 subjects received a single 250-mg dose (either 10 ml of Formulation 1, 5 ml of Formulation 2, fasting or non-fasting, or one tablet of Formulation 3) on four consecutive occasions separated by a one-week washout period (Reference 2). The rates of absorption for the suspension formulations judged by T<sub>max</sub> were similar to the rate for the reference tablet formulation. Additionally, the extents of absorption, judged by C<sub>max</sub> and AUC, were comparable to the extent of absorption for the reference tablet. Administration of a clarithromycin suspension with food led to a decreased rate but similar extent of absorption.

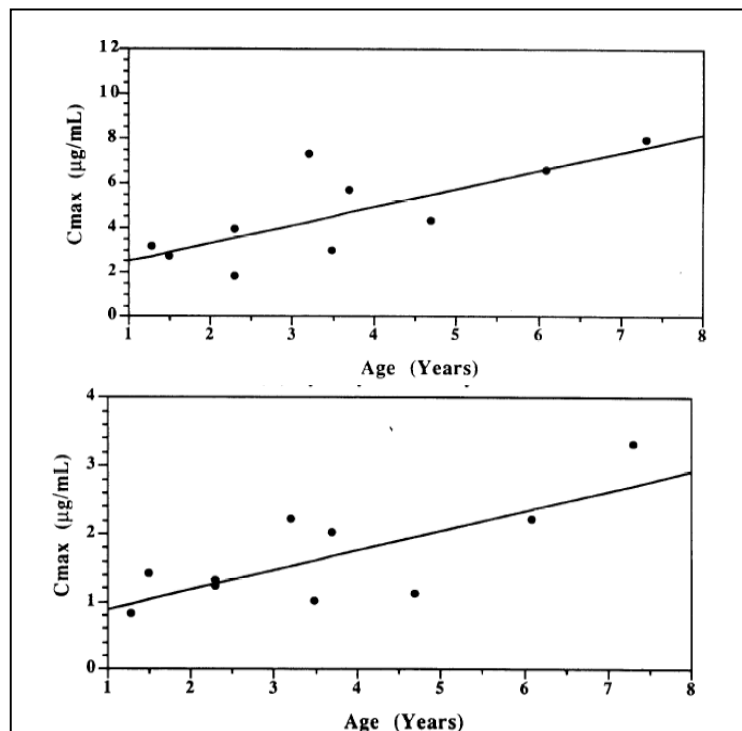
- Single-dose bioavailability of three experimental formulations of clarithromycin granules for suspension versus a tablet formulation was evaluated in twenty healthy adult male subjects participating a phase II, single-center, single-dose, open-label, balanced, randomized, four-period, crossover pharmacokinetic study (Reference 3). A single dose of 250 mg clarithromycin (10 ml of Formulations A, B, or C, or one tablet of Formulation D) was administered to each subject once in each of the four study periods. None of these suspension formulations displayed optimal bioavailability characteristics. Of the three experimental formulations, Formulation A resulted in the best extent of absorption (58%) relative to the reference tablet. However, the serum concentration-time profiles produced by this formulation showed a significant lag time in absorption resulting in no measurable serum concentrations for 2 to 3 hours following the administration of a dose of Formulation A. Formulations B and C did not have the delay in absorption which characterized Formulation A but they did exhibit substantially decreased extents of absorption relative to the reference tablet.

Two other studies evaluated the penetration of clarithromycin through respiratory mucosa and into tonsils, respectively (References 12 and 24).

- Penetration of clarithromycin through respiratory mucosa was evaluated by an open label, single-center study in 31 patients aged 2 to 12 years old with secretory otitis media scheduled for insertion of grommets (Reference 12). All subjects received clarithromycin suspension 7.5 g/kg/dose BID (maximum 500 mg BID) for 7 days. Clarithromycin and its hydroxyl metabolite penetrated into middle ear effusion, and concentrations there were generally twice as high as the corresponding concentrations in serum.
- In the other study evaluating penetration of clarithromycin into tonsils in 2 to 15 years old children undergoing tonsillectomy plasma concentration and microbiologic data were confounded by difficulties experienced in laboratory analyses, therefore no valid conclusions could be drawn (Reference 24).

The last single- and multiple-dose, open-label, single-center study of this category assessed the pharmacokinetics of clarithromycin granules for suspension in 28 children aged 6 months to 10 years, who had an infection for which oral antibiotic treatment was indicated (Reference 25).

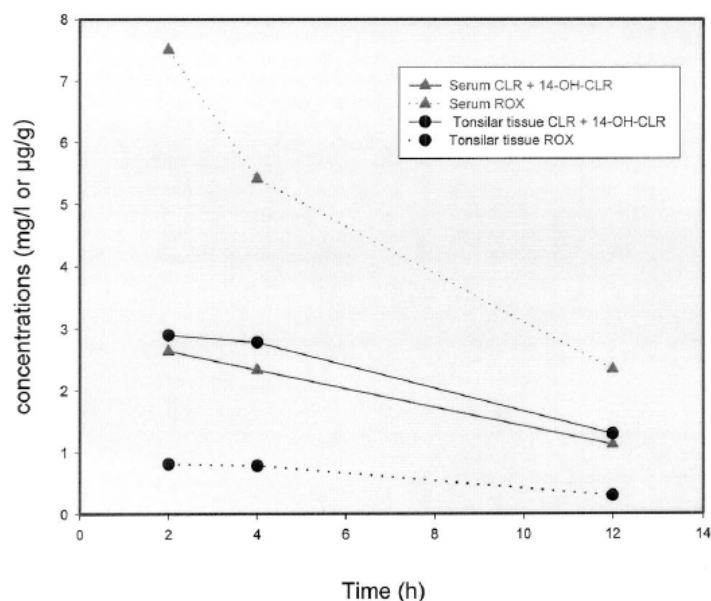
- The subjects in this study received single and multiple oral doses of clarithromycin suspension in a dose of 7.5 mg/kg for 1 to 10 days. After single and multiple administration of clarithromycin suspension to children, there was a short lag time for absorption and for the formation of the microbiologically active metabolite, 14(R)-hydroxy-clarithromycin. The results also indicated rapid and extensive drug absorption in children as demonstrated in adults with the same formulation. Food seemed to have no significant effect on drug absorption or pharmacokinetic profiles in children. The steady state C<sub>max</sub> and AUC showed a tendency to increase slightly with age or weight within the group of patients studied.



**Figure 1.** Steady State Cmax of Clarithromycin (upper panel) and 14(R)-hydroxy-clarithromycin (lower panel) versus Age (reference 25).

The two **Phase IV pharmacokinetic studies** (References 5 and 35) are confirming clarithromycin intratonsil and middle ear fluid pharmacokinetic profile, efficacy and safety profile in pediatric population.

- Diffusion of clarithromycin and roxithromycin into tonsils was evaluated by an open label, multicenter, randomized, pharmacokinetic study without individual direct benefit in 47 patients aged from 3 to 12 years old, requiring tonsillectomy (Reference 5). Children received 6 doses of clarithromycin (7.5mg/kg bid for 3 days) or roxithromycin (3mg/kg bid for 3 days) before tonsillectomy. The results showed superior intra-tonsil pharmacokinetic and anti-bacterial activity of clarithromycin and its active metabolite compared to roxythromycin.
- Another study used acute otitis media as a model to assess penetration of clarithromycin through respiratory mucosa (Reference 35). In this open/label multi-center, randomized study 58 children (6 months to 12 years) with verified acute otitis media received Clarithromycin suspension 7.5 mg/kg/day or 12.5 mg/kg/day BID for 4 days. Throughout the dosing interval, mean middle ear fluid concentrations of both clarithromycin and its metabolite were greater than corresponding plasma concentrations. Ratios of middle ear fluid to plasma concentrations increased over the dosing interval and at 12 hours postdosing were approximately 8 and 4 times greater than the ratios at 2 hours postdosing for clarithromycin and 14(R)-hydroxyclarithromycin, respectively. Both the 7.5 mg/kg and the 12.5 mg/kg BID treatment group dosages were effective in treating otitis media, producing success rates (resolution + improvement) of 86% and 91%, respectively, with no significant differences between groups.



**Figure 2.** Serum and tonsillar tissue concentrations of roxithromycin, clarithromycin and 14-OH clarithromycin (Reference 5)

### II.3.2 Phase II and Phase III clinical studies

One **Phase II clinical study** was provided (Reference 36). It was a double-blind, placebo controlled study of the safety and efficacy of Clarithromycin for the prevention of chronic lung disease in very-low-birth-weight (VLBW) infants colonized with *Ureaplasma urealyticum*.

- 11 infants who had a birth weight of <1255 grams, respiratory distress at birth and a positive culture for *U. urealyticum* received Clarithromycin suspension 15 mg/kg BID or placebo for 10 days. Study was stopped by sponsor due to poor enrollment (100 patients were planned). All five (100%) subjects who received clarithromycin and all six subjects (100%) who received placebo experienced adverse events. No specific safety signal has been identified. One subject in the clarithromycin group experienced life-threatening adverse events of bradycardia and apnea on Study Day 33, which was 21 days after the last dose of the treatment. These events were judged by the investigator to be not related to the study drug. One subject in the placebo group was prematurely withdrawn due to an adverse event of diarrhea. This adverse event started on Study Day 4 that lasted for 5 days and was judged to be possibly related to the study treatment.

A series of twenty-six pediatric **Phase III clinical study** reports (References 13-23, 26-30, 32, 33, 38, 39, 41, 47-51 in table 2) has also been reviewed.

- A single-center, investigator-blind, randomized 1:1 comparative safety and efficacy study of clarithromycin and penicillin V suspensions in the treatment of streptococcal pharyngitis was performed in 34 male (1-16 years of age) and nonchildbearing female (1-12 years of age) pediatric patients diagnosed with streptococcal pharyngitis confirmed by a positive rapid immunoassay test for Group A streptococcal antigen (Reference 13). The subjects received Clarithromycin 7.5mg/kg/dose BID (maximum 250 mg BID) or Penicillin V 250 mg/dose TIP. Clarithromycin 7.5mg/kg/dose (maximum 250 mg) BID for ten days was as safe and effective (success rate in both groups: 100%) as penicillin V 250 mg/dose TID for ten days in the treatment of streptococcal pharyngitis. Only one patient in each treatment groups reported an adverse event considered by the investigator to be possibly related to study medication.

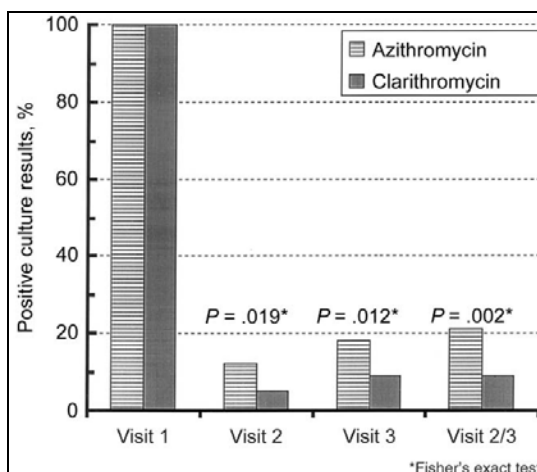
- Another study on treatment of treatment of streptococcal pharyngitis in 77 children with similar experimental design. Almost all of the patients enrolled in this study were not included in the clinical and bacteriologic efficacy analyses in this report due to failure to isolate *S. pyogenes* from the pretreatment throat culture-or due to mistimings of the post-treatment evaluations. The results for this study under the original protocol evaluability criteria demonstrated equivalence of the two treatments ([Reference 16](#)).
- A third multi-center, investigator-blind, randomized 1:1 study comparing safety and efficacy of clarithromycin and penicillin V suspensions in the treatment of streptococcal pharyngitis ([reference 17](#)) involved 197 male or female (1 to 12 years of age inclusive) patients with proven Group A beta-hemolytic streptococcal (*S. pyogenes*) pharyngitis, who were given Clarithromycin 7.5mg/kg/dose BID (maximum 250 mg BID) or penicillin V 250 mg/dose TID for 10 days. A large portion of the patients enrolled were not included in the clinical efficacy analysis due to mistimings of the post-treatment evaluations but 92% (11/12) of the clarithromycin patients and 91 % (10/11) of the penicillin V patients were bacteriologically cured at post-treatment.  
**Safety:** AEs incidence was low and only one SAE (vomiting) occurred in the clarithromycin group.
- A larger safety and efficacy study of clarithromycin and penicillin V suspensions in the treatment of children with streptococcal pharyngitis and/or tonsillitis (multi-center, investigator-blind, randomized 1:1) involved 506 male patients and female patients who had never menstruated and were at no risk of pregnancy, six months to 12 years of age inclusive with pharyngitis and/or tonsillitis of proven Streptococcal pyogenes etiology ([reference 26](#)). Clarithromycin 7.5mg/kg/dose suspension, BID or penicillin V suspension 13.3 mg/kg/dose TID was given for 10 days. Clinical cure rates post-treatment were 86% (152/176) for Clarithromycin and 80% (153/191) for Penicillin V. Clinical success rates post-treatment were 96% (169/176) for Clarithromycin and 94% (179/191) Penicillin V. Twenty-seven patients (14 clarithromycin and 13 Penicillin V) had a clinical recurrence at follow-up. Patient bacteriologic cure rate post-treatment was significantly higher for Clarithromycin than for Penicillin V - 92% 168/183 and 81% (162/199) respectively (p=0.004). Total adverse events consisted of 52% (129/250) in the Clarithromycin group and 46% (117/256) in the Penicillin V group. Adverse events excluding concurrent conditions occurred in 22% (54/250) in the Clarithromycin group and 10% (26/256) in the Penicillin V group (p=0.001). Treatment was discontinued due to adverse events in 4% (10/250) in the Clarithromycin and 2% (4/256) in the Penicillin V group.  
**Comment:** Clarithromycin was statistically more effective than penicillin V in eradicating Group A Streptococcus from the pharynx and tonsils but the database used for this report contained several discrepancies identified after the database and the report were finalized.
- A study of similar design in [Reference 27](#) was conducted as an addendum to protocol the study detailed in reference 26 to evaluate safety and efficacy of clarithromycin suspension in the treatment of children with *M. pneumoniae* pharyngitis No conclusion could be made as to the effectiveness of clarithromycin against *M. pneumoniae* pharyngitis, as none of the patients treated in this study had positive *M pneumoniae* cultures.
- A multi-center, observational study was arranged to observe the patients satisfaction and symptom improvement for Klaricid® XL in Korean patients with acute rhinosinutitis ([reference 38](#)). The study involved 528 patients aged 6 months to 12 years with pharyngitis and/or tonsillitis of proven *S. pyogenes* etiology. Clarithromycin suspension 7.5 mg/kg BID for 5 days or penicillin V suspension 13.3 mg/kg (500 mg max) TID was administered for 5 to 10 days.  
**Efficacy:** Statistically significantly higher bacteriological eradication rates were found in the

patients treated with clarithromycin at the 48-hour post-treatment (94% versus 78%,  $p < 0.001$ ). At the follow-up visit the number of relapses and reinfection were similar.

**Safety:** The incidences of all adverse events, including or excluding concurrent conditions, were similar between the treatment groups with no statistically significant differences observed for the overall incidence of adverse events, the incidence of adverse events grouped by body system, or for any specific adverse event.

- An open, controlled multi-centric study on the efficacy and tolerability of clarithromycin suspension (Klaped®) versus benzathine penicillin, versus cefaclor, and versus amoxicillin treatment in 146 children with streptococcal pharyngo-tonsillitis (Reference 49, published in the Review of Pediatric Infections, Supplement 3:S38-S44, 1991). Patients received 10 days treatment with Clarithromycin suspension 5 mg/kg/dose (maximum of 250 mg/dose) BID, amoxicillin suspension 14 mg/kg/dose (maximum of 500 mg/dose) TID, cefaclor suspension 10 mg/kg/dose (maximum of 300 mg/dose) TID, or benzathine penicillin 1,000,000 UI (for patients >6 years) or 500,000 UI (for patients <6 years) administered as a single dose intramuscularly. Clinical success (cure + improvement) rates during treatment (Study Days 3-5) were in the Clarithromycin group, 99% (75/76). while in the Control Group it consisted of 91% (63/69). Clinical cure rates post-treatment were 97% (74/76) for Clarithromycin and 91% (62/68) for the Control Group. Finally, clinical success rates post-treatment were 100% (76/76) for Clarithromycin and 99% (67/68) for the Control Group. The study did not provided safety information.
- Pharmex provided an investigator blinded parallel-group study in which individuals aged > 12 years with symptomatic pharyngitis and a positive throat culture for *S. pyogenes* were randomized in a 1:1 ratio at each study center (47 clinical centers within the United States) to receive either the recommended 10-day oral course of clarithromycin (250 mg b.i.d., N=260) or the 5- day recommended oral course of azithromycin (500 mg on treatment day 1, followed by 250 mg q.d. for the next 4 days, n=265). (Reference Pharmex 1, published as Kaplan E L, Gooch W. M, Notario, GF, Craft J. Macrolide Therapy of Group A Streptococcal Pharyngitis: 10 Days of Macrolide Therapy (Clarithromycin) Is More Effective in Streptococcal Eradication than 5 Days (Azithromycin), CID 2001:32 (15 June), 1798-1802). Ten days of clarithromycin therapy was more effective than 5 days of azithromycin therapy in eradicating the organism (91% [176/194] vs. 82% [162/198];  $p = 0.012$ ). More than 97% of all streptococcal isolates were macrolide-sensitive.

**Comment:** Whether these bacteriologic eradication rates were the result of the 2 macrolides compared or were due to differences in duration of therapy could not be determined, but the statistically significant difference in eradication of group A streptococci does raise additional questions about shortened courses of macrolide therapy for this common infection.



**Figure 3.** Positive throat cultures before and after therapy with oral azithromycin (5 days) or oral clarithromycin (10 days). Visit 1 p initial visit, enrollment; visit 2 p 13–19 days; visit 3 p 28–38 days. There were statistically significantly fewer failures to eradicate group A streptococci after 10 days of therapy with clarithromycin. Statistical comparisons were made with Fisher's exact test. (Reference Pharmex 1, published in CID 2001:32 (15 June), 1798-1802)

- A single-center, investigator-blind, randomized 1:1 safety and efficacy comparative study of clarithromycin and amoxicillin suspensions in the treatment of patients with acute otitis media involved 16 male (1-16 years of age) and nonchildbearing female (1-12 years of age) pediatric patients diagnosed with acute otitis media ([Reference 14](#)). Clarithromycin 7.5mg/kg/dose BID (maximum 250 mg BID) for ten days was as safe and bacteriologically effective as amoxicillin 14 mg/kg/dose TID (maximum 500 mg TID) for ten days in the treatment of acute otitis media. No AE was reported in the clarithromycin group.
- Comparative multi-center, investigator-blind, randomized 1:1 study on safety and efficacy of clarithromycin and amoxicillin / clavulanate suspensions in the treatment of patients with acute otitis media was performed on 103 male or female (1 to 12 years of age inclusive) patients, who were treated 10 days for acute otitis media by Clarithromycin suspension 7.5 mg/kg/dose BID (maximum of 250 mg) or amoxicillin/clavulanate suspension 14 mg/kg/dose of the amoxicillin component TID (maximum of 500mg) ([Reference 20](#)). Post-treatment clinical cure rates and clinical success rates were 92% (23/25) and 92% (23/25) for Clarithromycin and 97% (38/39) and 97% (38/39) for AmoxVClav respectively. Adverse events occurred in 8% (4/50) in the Clarithromycin group and in 17% (9/53) in the AmoxVClav group. Discontinuation of treatment due to adverse events was reported in 2% (1/50) in the Clarithromycin group and in 9% (5/53) in the AmoxVClav group.
- Another comparative study on safety and efficacy of clarithromycin and amoxicillin / clavulanate suspensions in the treatment of patients with acute otitis media involved 79 male or female (1 to 12 years of age inclusive) patients with acute otitis media ([Reference 21](#)). Children were given Clarithromycin suspension 7.5 mg/kg/dose (maximum of 250 mg) BID or amoxicillin/clavulanate suspension 14 mg/kg/dose of the amoxicillin component (maximum of 500mg) TID for 10 days. Clinical cure rates post-treatment and clinical success rates post-treatment were 90% (28/31) and 97% (30/31) for Clarithromycin and 90% (28/31) and 100% (31/31) for AmoxVClav respectively. Patient bacteriologic cure rate post-treatment was 2/2 (100%) for Clarithromycin and, 2/2 (100%) for Amox./Clav. Adverse Events were recorded in 3/39 (8%) in the Clarithromycin group and in 6/40 (15%) in the AmoxVClav group. None of the treatments with Clarithromycin was discontinued due to adverse events, while this happened in 2/40 (5%) in the AmoxVClav group.
- A safety and efficacy comparative multi-center, investigator-blind, randomized 1:1 study of clarithromycin and cefaclor suspensions involved 379 male or female (6 months to 12 years of age inclusive) patients with acute otitis media ([Reference 22](#)). Clarithromycin suspension was given in 7.5 mg/kg/dose (maximum of 250 mg) BID or cefaclor suspension in 20 mg/kg/dose BID (maximum of 1000 mg per day) for 10 days. Clinical cure rates post-treatment were 82% (122/149) for Clarithromycin and 86% (113/131) for Cefaclor. Clinical success rates post-treatment were 86% (128/149) for Clarithromycin and 90% (118/131) for Cefaclor. Clinical failures/relapses occurred in thirty-four patients (21 clarithromycin; 13 cefaclor); 38 patients in each treatment group had a clinical recurrence at follow-up. Overall frequency of adverse events was 35% (70/199) for Clarithromycin and 34% (62/180) for Cefaclor. Adverse events excluding concurrent conditions were lower - Clarithromycin 15% (30/199), Cefaclor 17% (31/180). Only a small part of treatments was discontinued due to adverse events (Clarithromycin 3% (5/199) and Cefaclor 1% (2/180)).

**Comment:** In this study, the two major pathogens, *E. influenzae* and *S. pneumoniae*, were more frequently isolated from the clarithromycin-treated patients than the cefaclor-treated ones, a difference that could not be explained entirely by the unequal randomization at one site. This difference could have caused a treatment bias, since patients infected with *H. influenzae* are

more likely to fail. The larger number of *H. influenzae* patients treated with clarithromycin, however, did not appear to affect the outcome since the clinical cure and success rates of the two treatment groups were comparable.

- In another single-center, investigator-blind, randomized 1:1 safety and efficacy comparative study of clarithromycin and amoxicillin suspensions in the treatment of patients with acute otitis media 46 male or female (1 to 12 years of age inclusive) patients with acute otitis media were treated by Clarithromycin suspension 7.5mg/kg/dose BID (maximum of 1000 mg per day) or amoxicillin 14mg/kg/dose TID (maximum of 1000 mg per day) for 10 days (Reference 23). Clinical Cure Rates Post-Treatment was 95% (20/21) for Clarithromycin and 83% (19/23) for Amoxicillin. Clinical Success Rates Post-Treatment was 100% (21/21) for Clarithromycin and 96% (22/23) for Amoxicillin. The overall frequency of adverse events was 4.5% (1/22) for Clarithromycin and 4.2% (1/24) for Amoxicillin. None of the treatments were prematurely discontinued due to an adverse event in the Clarithromycin group, while this occurred in one case in the Amoxicillin group (4.2%, 1/24)
- A safety and efficacy comparative study of clarithromycin and Augmentin® (amoxicillin / clavulanate potassium) suspensions (multi-center, investigator-blind, randomized 1:1) was conducted in 433 children six months to 12 years of age inclusive with acute otitis media (Reference 29). Clarithromycin suspension 7.5 mg/kg/dose (maximum of 500 mg) BID and Amoxicillin/Clavulanate Potassium suspension 13.3mg/kg/dose of the amoxicillin component (maximum of 500 mg) Q8H was given for 10 days. Clinical cure rates post-treatment were 77% (125/163) for Clarithromycin and 81% (145/179) for Augmentin® suspensions. Clinical success rates post-treatment was 84% (137/163) for Clarithromycin and 85% (153/179) for Augmentin®. 52 patients were clinical failures/relapses (26 in each group), 77 patients (34 Clarithromycin and 43 Amox./Clav.) had a clinical recurrence at follow-up. All adverse events noticed in the Clarithromycin group 48% (101/209) and in the Augmentin® group 55% (123/224). Adverse events excluding concurrent conditions were significantly higher in the Augmentin® group (42%, 94/224) as compared to Clarithromycin (29%, 60/209) (p=0.005). Treatment was discontinued due to adverse events in 2 % (5/209) in the Clarithromycin arm and in 4% (9/224), in the Augmentin® group.
- A safety and efficacy comparative study of clarithromycin and Augmentin® (Amoxicillin / Clavulanate Potassium) suspensions in the treatment of children with acute otitis media with tympanocentesis involved 312 children six months to 12 years of age inclusive with a diagnosis of acute otitis media confirmed by tympanocentesis (Reference 32). The subjects received for 10 days Clarithromycin suspension 7.5 mg/kg/dose (maximum of 500 mg) BID or Amoxicillin/Clavulanate Potassium (Augmentin®) suspension 13.3 mg/kg/dose of the amoxicillin component (maximum of 500 mg) Q8H. Clinical cure rates post-treatment were significantly higher for Augmentin® as compared to Clarithromycin (97%, 91/94 and 82%, 80/98 respectively, p<0.001). Similarly, clinical success rates post-treatment were higher for Augmentin® as compared to Clarithromycin (98%, 92/94 and 83%, 81/98). On contrary to this, all adverse events were significantly lower (p<0.001) during treatment with Clarithromycin (44% 68/156) as compared to Augmentin® therapy 64%, 100/156). A similar relationship was noted for adverse events excluding concurrent conditions (p<0.001) - Clarithromycin 28% (44/156) and Augmentin® 50% (78/156).

**Comment:** Amoxicillin/Clavulanate Potassium suspension 13.3mg/kg/dose (maximum 500 mg) Q8H for 10 days was more effective than clarithromycin suspension in the treatment of acute otitis media in pediatric patients in this study but clarithromycin caused fewer gastrointestinal adverse events than Amoxicillin/Clavulanate Potassium.

- An open, randomized, controlled multi-centric study on the efficacy and tolerability was performed in 96 pediatric patients with a diagnosis of acute otitis media. Clarithromycin oral suspension (Klaped®) 7.5 mg/kg/dose (maximum of 250 mg/dose) BID or cefaclor suspension 10 mg/kg/dose (maximum f300mg/dose)TID was given as treatment 10 days (**Reference 47, the study report was published in the Review of Pediatric Infections, Supplement 3:S45-S51, 1991**). Clinical cure rates on Study Days 3-5 were significantly higher in the Clarithromycin group as compared to the Cefaclor treatment (73%, 35/48 versus 38%, 18/47, p=0.007). Clinical success rates on Study Days 3-5 were also higher with Clarithromycin (75% 36/48) than with Cefaclor (45%, 21/47). The side effects attributable to study drug were negligible.
- A Safety and Efficacy Comparative Study of 5-days treatment with clarithromycin and amoxicillin suspensions was conducted in 259 Pediatric patients aged 1-12 years with acute otitis media. In this cases, Clarithromycin suspension 125mg BID (body weight <25 kg) or 250mg BID (body weight >25 kg) or amoxicillin suspension 125mg TID (body weight <25 kg) or 250mg TID (body weight >25 kg) was administered for 5 days. (**Reference 51**).

**Table 3.** Safety and Efficacy Comparative Study of 5-days treatment with clarithromycin and amoxicillin suspensions in 259 paediatric patients aged 1-12 years with acute otitis media (**Reference 51**)

	<b>Clarithromycin</b>	<b>Amoxicillin</b>
Clinical cure rates post-treatment	91/114 (80%)	71/105 (68%)
Clinical success rates post-treatment	110/114 (96%)	101/105(96%)
Clinical recurrences	6	5
Adverse events (All Patient)	2 1/132 (16%)	22/127 (17%)
Adverse events (related to study medication)	4/132 (3%)	8/127 (6%)
Discontinued due to adverse events	0/132	3/127 (2%)

- Comparative study on safety and efficacy of clarithromycin and erythromycin ethylsuccinate suspensions in the treatment of patients with mild to moderate skin or skin structure infection (single-center, investigator-blind, randomized 1:1) involved 41 male (1-16 years of age) and nonchildbearing female (1-12 years of age) pediatric patients diagnosed with mild to moderate skin or skin structure infection, who were given for 10 days Clarithromycin 7.5mg/kg/dose BID (maximum 250 mg BID) or erythromycin ethylsuccinate suspension, 14 mg/kg/dose TID (maximum of 530 mg) (**Reference 15**). Clarithromycin was as safe and effective as erythromycin ethylsuccinate for 10 days in the treatment of mild to moderate skin or skin structure infections in these pediatric patients. Three (15%) of the 20 clarithromycin patients and six (29%) of the 21 erythromycin patients reported at least one adverse event during the study.
- Comparative safety and efficacy of clarithromycin and cefadroxil suspensions in the treatment of children with mild to moderate skin or skin structure infection was assessed in 120 male or female (1 to 12 years of age inclusive) patients receiving Clarithromycin 7.5 mg/kg/dose BID (maximum 250mg BID) or cefadroxil suspension 15 mg/kg/dose (maximum of 500mg) BID for 7 to 10 days (multi-center, investigator-blind, randomized 1:1 study - **Reference 18**). The clinical cure rate at post-treatment was 94% (44/47) in the clarithromycin treatment group and 100% (44/44) in the cefadroxil treatment group. The bacteriologic cure rate and the pathogen eradication post-treatment were 100% for both groups. One adverse effect was noted in the cefadroxil group, none in the clarithromycin group.
- Comparative safety and efficacy of clarithromycin and cefadroxil suspensions in the treatment of children with mild to moderate skin or skin structure infection was also evaluated in another multi-center, open-label, randomized 1:1 study involving 74 Male or female (1 to 12 years of age inclusive) patients who were given Clarithromycin 7.5 mg/kg/dose BID (maximum 250mg

BID) or cefadroxil suspension 15 mg/kg/dose (maximum of 500mg) BID for 10 days (Reference 19) Clinical cure rates post-treatment, clinical success rates post-treatment, patient bacteriologic cure rate posttreatment and pathogen bacteriologic eradication rate were 18/19 (95%), 18/19 (95%), 19/19 (100%) and 19/19 (100%) for Clarithromycin and 26/26 (100%), 26/26 (100%), 26/26 (100%) and 31/31 (100%) respectively.

- A larger study with identical experimental setup was conducted in 231 male or female patients, six months to 12 years of age inclusive with mild to moderate skin or skin structure infections. Clarithromycin suspension 7.5mg/kg/dose BID (maximum of 500 mg BID) or cefadroxil suspension 15mg/kg/dose BID (maximum of 1000 mg BID) for 10 days (Reference 28). The database used for this report contained several discrepancies identified after the database and the report were finalized.
- A comparative study (multi-center, investigator-blind, randomized 1:1) of the safety and efficacy of clarithromycin and EryPed® (erythromycin ethylsuccinate) suspensions in the treatment of 260 male or female children, 3 to 12 years of age inclusive with community-acquired pneumonia who were suitable candidates for oral macrolide therapy (Reference 30). All received Clarithromycin suspension 7.5 mg/kg/dose BID (maximum of 500 mg BID) or erythromycin ethylsuccinate suspension 40 mg/kg/day in two or three equally divided doses BID or TID (maximum of 1600 mg/day) for 10 days (Results are shown in table 3).
- An open-label study was aimed to evaluate the safety and efficacy of clarithromycin suspension in the treatment of children with Chlamydia pneumoniae and asthma. The study was terminated before completion of the proposed enrollment due to the slow rate of accession. Statistical analyses were not performed, since data were available for only 8 patients. No conclusions could be drawn from the results of this study (Reference 33).
- An open, controlled multi-centric study on the efficacy and tolerability of clarithromycin (Klaped®) versus amoxicillin/clavulanate and cefaclor treatment on children with a diagnosis of acute bronchopneumonia involved 99 pediatric patients. Children were treated for 10 days with Clarithromycin suspension (5 mg/kg/dose TID), or amoxicillin/clavulanate suspension 40-50mg/kg/day, or cefaclor 30mg/kg/day (Reference 48, Study report was published in the Review of Pediatric Infections, Supplement 3:S52-S58, 1991). Clinical success (cure + improvement) rates during treatment (Study Days 3-5) were 92% for Clarithromycin and 83% for the Control Group, clinical cure rates post-treatment were 85% (50/59) for Clarithromycin and 69% (25/36) for the Control Group. Clinical success rates post-treatment were 100% (59/59) for Clarithromycin and 100% (36/36) for the Control Group. Due to adverse events were discontinued 3% (2/60) in the Clarithromycin group and 5% (2/39) in the Control Group.
- A single-blind, randomized, comparative, phase III, multi-center study of clarithromycin and cefaclor suspensions in the treatment of children with lower respiratory tract infections was accomplished in 126 male or female children of six months to 12 years of age. All subjects with lower respiratory tract infections received for 5 to 10 days Clarithromycin suspension 7.5mg/kg/dose BID (maximum of 500mg/BID) or cefaclor suspension 20mg/kg/day (40 mg/kg/day in the case of pneumonia, maximum of 1g/day) divided into equal doses, Q8H. (Reference 50). Clinical cure rates post-treatment were 89% (51/57) for Clarithromycin and 91% (49/54) for Cefaclor, while clinical success rates post-treatment were 100% (57/57) for Clarithromycin and 96% (52/54) for Cefaclor. Total adverse events occurred in 21% (13/61) in the Clarithromycin group and in 12% (8/65) in the Cefaclor arm. After the report was completed, additional data lab information was received for one patient with adverse event of elevated liver transaminases.
- Another open, non-comparative, single-center safety and efficacy study of clarithromycin in children involved 39 children with various diagnoses including bacterial tonsillitis / pharyngitis, pneumonia, otitis media, or bacterial infections of the skin and soft tissues. Clarithromycin

suspension was given in 7.5mg/kg/dose Q12H. Clinical cure rate post-treatment was 92% (36/39), while clinical success (cure + improvement) rate post-treatment: was 100% (39/39). In 3 % of cases (1/40) the treatment was discontinued due to adverse events (Reference 41).

**Table 4.** A comparative study (multi-center, investigator-blind, randomized 1:1) of the safety and efficacy of clarithromycin and EryPed® (erythromycin ethylsuccinate) suspensions in the treatment of 260 male or female children, 3 to 12 years of age inclusive with community-acquired pneumonia (Reference 30)

	<b>Clarithromycin</b>	<b>Erythromycin</b>
Clinical cure rates post-treatment	84% (104/124)	76% (84/110)
Clinical success rates post-treatment	98% (121/124)	95% (105/110)
Radiologic resolution rates post-treatment	93% (103/111)	84% (82/98)
Radiologic success rates post-treatment	98% (109/111)	94% (92/98)
Overall bacteriologic eradication rate post-treatment	83% (34/41)	90% (37/41)
Total adverse events	62% (82/133)	65% (82/127)
Adverse events excluding concurrent conditions	28% (37/133)	32% (40/127)
Discontinued due to adverse events	2 % (3/133)	4% (5/127)

- A randomized, controlled, single-blind, parallel-group, multi-center study assessed the safety and efficacy of clarithromycin versus erythromycin estolate in the treatment of children with pertussis. 153 children between 1 month and 16 years of age, inclusive, with a clinical syndrome of pertussis were enrolled. Children received Clarithromycin granules for suspension 7.5 mg/kg/dose BID (maximum dose: 500 mg BID) for 7 days or erythromycin estolate 13.3mg/kg/dose TID (maximum dose: 333 mg TID) for 14 days.  
**Comment:** Subject enrollment was ended prematurely with 153 subjects (30 Reference 39, the study was published in the *Pediatric Infectious Diseases Journal* Volume 20(12), December 2001, pp 1149-11540 planned) due to the removal of the erythromycin estolate formulation from distribution by the manufacturer. This discontinuation was for non-medical reasons unrelated to therapeutic efficacy or safety concerns.

### II.3.3 Efficacy studies

Because of its activity against important Gram-positive and Gram-negative pathogens and its pharmacokinetic profile, cefixime has been used in a wide range of bacterial infections. In the available clinical studies (see above), no new efficacy or safety data have been identified. Three of this studies have been previously published (References 39, 47, 48, 49).

- A randomized, controlled, single-blind parallel-group, multi-center study assessed the safety and efficacy of clarithromycin versus erythromycin estolate in the treatment of children with pertussis. The study population made up by 153 children between 1 month and 16 years of age, inclusive, with a clinical syndrome of pertussis. The treatment consisted of Clarithromycin granules for suspension 7.5 mg/kg/dose BID (maximum dose: 500 mg BID) for 7 days or erythromycin estolate 13.3mg/kg/dose TID (maximum dose: 333 mg TID) for 14 days. (Reference 39, published in the *Pediatric Infectious Diseases Journal* Volume 20(12), December 2001, pp 1149-1154). Subject enrollment was ended prematurely with 153 subjects (300 planned) due to the removal of the erythromycin estolate formulation from distribution by the

manufacturer. This discontinuation was for non-medical reasons unrelated to therapeutic efficacy or safety concerns.

- An open, randomized, controlled multi-centric study on the efficacy and tolerability was performed in 96 pediatric patients with a diagnosis of acute otitis media. Clarithromycin oral suspension (Klaped®) 7.5 mg/kg/dose (maximum of 250 mg/dose) BID or cefaclor suspension 10 mg/kg/dose (maximum of 300 mg/dose) TID was given as treatment 10 days (**Reference 47, the study report was published in the Review of Pediatric Infections, Supplement 3:S45-S51, 1991**). Clinical cure rates on Study Days 3-5 were significantly higher in the Clarithromycin group as compared to the Cefaclor treatment (73%, 35/48 versus 38%, 18/47, p=0.007). Clinical success rates on Study Days 3-5 were also higher with Clarithromycin (75%, 36/48) than with Cefaclor (45%, 21/47). The side effects attributable to study drug were negligible.
- An open, controlled multi-centric study on the efficacy and tolerability of clarithromycin (Klaped®) versus amoxicillin/clavulanate and cefaclor treatment on children with a diagnosis of acute bronchopneumonia involved 99 pediatric patients. Children were treated for 10 days with Clarithromycin suspension (5 mg/kg/dose TID), or amoxicillin/clavulanate suspension 40-50mg/kg/day, or cefaclor 30mg/kg/day (**Reference 48, Study report was published in the Review of Pediatric Infections, Supplement 3:S52-S58, 1991**). Clinical success (cure + improvement) rates during treatment (Study Days 3-5) were 92% for Clarithromycin and 83% for the Control Group, clinical cure rates post-treatment were 85% (50/59) for Clarithromycin and 69% (25/36) for the Control Group. Clinical success rates post-treatment were 100% (59/59) for Clarithromycin and 100% (36/36) for the Control Group. Due to adverse events were discontinued 3% (2/60) in the Clarithromycin group and 5% (2/39) in the Control Group.
- An open, controlled multi-centric study on the efficacy and tolerability of clarithromycin suspension (Klaped®) versus benzathine penicillin, versus cefaclor, and versus amoxicillin treatment in 146 children with streptococcal pharyngo-tonsillitis (**Reference 49, published in the Review of Pediatric Infections, Supplement 3:S38-S44, 1991**). Patients received 10 days treatment with Clarithromycin suspension 5 mg/kg/dose (maximum of 250 mg/dose) BID, amoxicillin suspension 14 mg/kg/dose (maximum of 500 mg/dose) TID, cefaclor suspension 10 mg/kg/dose (maximum of 300 mg/dose) TID, or benzathine penicillin 1,000,000 UI (for patients >6 years) or 500,000 UI (for patients <6 years) administered as a single dose intramuscularly. Clinical success (cure + improvement) rates during treatment (Study Days 3-5) were in the Clarithromycin group, 99% (75/76). While in the Control Group it consisted of 91% (63/69). Clinical cure rates post-treatment were 97% (74/76) for Clarithromycin and 91% (62/68) for the Control Group. Finally, clinical success rates post-treatment were 100% (76/76) for Clarithromycin and 99% (67/68) for the Control Group. The study did not provided safety information.

Two additional studies provided by Pharmex (**References Pharmex 2 and 3**) dealt with efficacy and tolerability of Clarithromycin in the treatment of children with Helicobacter pylori infection.

- One of the studies aimed to evaluate the effectivity of combined 1 week treatment (clarithromycin 250 mg twice daily, omeprazole 20 mg twice daily, and tinidazole 500 mg twice daily), which has been shown to be highly tolerable and effective, achieving a success rate of >90% in the adult population. (**Reference Pharmex 2 published in Pediatrics 1998 <http://www.pediatrics.org/cgi/content/full/102/1/e14>**). The study group consisted of 35 boys and girls with a mean age of 15.9 years (range, 10 to 19) referred for evaluation of dyspeptic symptoms. They all underwent upper gastrointestinal endoscopy, in which *H pylori* infection was confirmed by rapid urease test and/or histologic staining. Therapeutic efficacy was assessed by a 13C-urea breath test performed 4 weeks after completion of treatment. No major side effects were recorded. It was concluded, that one-week clarithromycin/omeprazole/tinidazole

triple therapy is highly tolerable and effective (*H pylori* resolution 88.9%) for treating *H pylori* in the pediatric age group, but previous treatment failure diminishes the likelihood of success

- The aim of the second study from Brasil was to investigate Helicobacter pylori (Hp) eradication rate using a short regimen (7 and 10 days) of triple therapy with clarithromycin (30 mg/kg/day - maximum dose 500 mg bid), amoxicillin (50 mg/kg/day - maximum dose 1g bid) and omeprazole (0.6 mg/kg/day - maximum dose 20 mg bid). In twenty-five Hp positive patients who presented severe epigastralgia (Reference Pharmex 3 published in Arq Gastroenterol 2001, 38, 203-206). After 2 months, clinical symptoms were evaluated and gastric biopsies were taken to test Hp eradication. Overall eradication rate was achieved in 16/25 patients (64% - IC (95%) = 45-83%), in 11/15 (73% - IC (95%) = 51-95%) patients who used 10 days therapy course and in 5/10 (50% - IC (95%) = 19-81%) who used 7 days therapy course. Eradication drugs were well accepted and adverse effects were reported in two patients (8%). The authors concluded, that this triple therapy regimen had moderate efficacy (64%). The data suggests that 10 days therapy course achieves better eradication rate (73%) than 7 days course (50%) to treat Hp infection in the study population.

#### II.3.4 Phase IV clinical studies

Four **phase IV clinical** studies have been reviewed. One of them (Reference 37) have been prematurely discontinued due to low enrolment (6 patients enrolled instead of 80 patients planned). No new data has been identified for the three other phases IV studies.

- Open label, multi-center study involved 1558 patients aged from 3 to 10 years old with a confirmed (strip test) *S. streptococcus* tonsillitis, who were treated with clarithromycin granules (15 mg/kg bid) during 5 days. (Reference 6). This study confirmed clarithromycin efficacy for treating *S. streptococcus* tonsillitis according to routine medical practices (97.5% efficacy). The incidence of adverse effects was low; they consisted of mainly GI disorders.
- Another open label, multi-center, study with 340 patients aged from 3 to 10 years old diagnosed with a lower respiratory tract infection, who needed treatment with clarithromycin granules (15 mg/kg bid) for 7 to 10 days (Reference 7). This study confirmed clarithromycin efficacy for lower respiratory tract infection (acute exacerbation of chronic bronchitis or atypical pneumopathy) according to routine medical practices (95.5% efficacy). No severe adverse effects were reported, the incidence of adverse effects was low, and they consisted of mainly GI disorders.
- A randomized, investigator blind, multi-center comparative study of the safety and efficacy of clarithromycin and Augmentin® (Amoxicillin / Clavulanate) suspensions in the treatment of paediatric patients with acute bronchitis involved 194 pediatric patients with acute bronchitis who were suitable candidates for oral antibiotic therapy (Reference 34). They received for 7 days Clarithromycin suspension 7.5 mg/kg/day BID (maximum of 500 mg BID) or 13.3mg/kg of the amoxicillin component of Augmentin® TID (maximum dose of 250 mg TID). Overall clinical cure rates were: 92% for clarithromycin and 85% for amoxicillin/clavulanate. One or more adverse effects were noted in 13% of the Clarithromycin group and in 18% subjects of the Augmentin® arm.

#### II.3.5 Post-marketing clinical studies

Six **post-marketing observational studies** (PMOS) were identified and reviewed (Ref. 1, 8, 9, 10, 11, 40). One PMOS study report from Korea (Ref. 11) is not mentioning the patient's age or age profile but according to the study endpoints ("Observational study on *impact of smoking* to *H.pylori* eradication rate in Korean patients who has duodenal ulcer disease") no pediatric population is expected to have been enrolled.

No new clinical or safety data have been identified from these post-marketing studies involving a large population (29,158 patients enrolled).

Three studies, one phase II (Ref.36), one phase III (Ref. 33) and one phase IV (Ref. 37) have been prematurely discontinued due to low enrollment. Importantly, these discontinuations were not linked to any safety signal.

- Multi-center, non-comparative, post-marketing observational study enrolled 1,487 adults and adolescent (>12 years) patients with pharyngitis/tonsillitis ([Reference 1](#)). The subjects were treated with filmtablet coated of clarithromycin 500mg, once daily for 7 days. The recommended dosage of one 500mg tablet once a day has shown good and excellent efficacy and safety within all patients independently from body weight (body weight <70kg for 703 patients=47% of the study population).
- A multi-center, open label, post-marketing surveillance study to obtain further findings in the safety of Klaricid® XL therapy in patients with upper or lower respiratory tract infections involved 4,834 patients who were prescribed clarithromycin 500mg once-a-day as directed in the package insert and treated for a period of at least 7 days with a 30-day follow-up to collect the adverse events ([Reference 8](#)). This study confirmed clarithromycin once-a-day efficacy for upper and lower respiratory tract infections (94.6% efficacy). Overall adverse event rate was low (2.1 %), no severe adverse effects were reported.
- A multi-center, open label post-marketing surveillance study to obtain further findings in the safety of Klaricid® XL therapy in patients with upper or lower respiratory tract infections involved 11,383 subjects,, of them 11,099 were less than 10 years old (97.62%). Patients were prescribed clarithromycin granules 500mg once-a-day as directed in the package insert and treated for a period of at least 7 days with a 30-day follow-up to collect the adverse events ([Reference 9](#)). This study confirmed clarithromycin granules once-a-day efficacy for upper and lower respiratory tract infections (96.4% efficacy). Overall adverse event rate was low (2.16%), no severe adverse effects were reported.
- A multi-center, post-marketing surveillance study was designed to obtain further findings in the safety of Klaricid® DR therapy in 7,455 patients with upper or lower respiratory tract infections ([Reference 10](#)). Patients (3% less than 9 years old and 9.5% between 10 and 19 years old) were prescribed clarithromycin tablets as directed in the package insert and treated for a period of at least 7 days with a 30-day follow-up to collect the adverse events. The study confirmed clarithromycin efficacy for upper and lower respiratory tract infections (97.1% efficacy). Overall adverse event rate was low (1.18%), no severe adverse effects were reported.
- A multi-center, observational study was performed to observe the patients satisfaction and symptom improvement for Klaricid®XL in 2114 over 12 year-old Korean patients with acute rhinosinutitis and with coexistence of acute rhino-sinusitis asthma ([Reference 40](#)). Klaricid® XL (Clarithromycin) had 91.10% (1863/2045) of high patients' satisfaction and 96.53% (1974/2045) of high improvement in symptom as a treatment of acute rhino-sinusitis patients. No adverse event resulted in dose reduction or permanent withdrawal. No serious adverse event occurred.
- A post-marketing observational study was designed to evaluate the on impact of smoking to *H. pylori* eradication rate in 1885 Korean patients who has duodenal ulcer disease and positive to *H. pylori* test ([Reference 11](#)). Patients' age profile is not mentioned in the report but according to the study endpoints, no pediatric population is expected in the patients population observed here. Non-smoking was effective on increasing *H.pylori* eradication rate for standard therapy and ulcer symptom improvement was higher for non-smoking group with statistically significance only in ITT analysis. Incidence rate of adverse event did not differ statistically between non-smoking and smoking groups.

**Postmarketing surveillance studies on ClaroSip®** were also performed by Grunenthal GMBH in order to obtain information on the efficacy of the innovative antibiotic formulation ClaroSip® in community-acquired ENT and respiratory tract infections in a large number of children under routine conditions in a non-selective population and to determine its the acceptance by parents and children (Reference Grunenthal 1-4).

- 2073 patients diagnosed as having pharyngitis, tonsillitis, otitis media or community-acquired pneumonia of 456 physicians were enrolled (Reference Grunenthal 1-2). A further prerequisite was the ability to use a drinking straw (from about the age of two years). ClaroSip® made up by premeasured doses of 125 mg, 187.5 mg and 250 mg tasteless clarithromycin granules encased in a drinking straw to be taken with a suitable beverage. The innovative formulation via the drinking-straw simplifies handling, solves the problem of incorrect dosing, cooling the product is no longer necessary, and an easy check can be made as to whether the whole dose has been taken. The dosage for the individual patient and the duration of treatment was determined by the physician. Of the 2073 patients treated with ClaroSip® 8.59% were younger than the specified minimum age of three years, 632 (30.49%) had 3-4 years and 846 (40.81%) 5 to 8 years. The mean duration of treatment was seven days and 99.23% of the patients took the dosage prescribed by the physician. Treatment was terminated in 1.11% on account of the lack of clinical efficacy and in 2.03% due to poor tolerability. 11.24% of the patients terminated treatment for other reasons, mainly concerning the taste of ClaroSip®. After ClaroSip® treatment 69.13% of the patients were classified as cured, 17.90% had improved, and ClaroSip® therapy failed in only 1.98%. No data were recorded in 11.00% of the patients. The overall assessment of ClaroSip® by the physicians was very positive. The assessed individual aspects (concept of the system, handling, single-dose packaging, free choice of beverage, premeasured single dose, administration control, suitability for children) were considered to be good by 87.36 - 98.02%. Most parents considered the taste to be good and handling to be very simple. With increasing age handling was considered to be easier. A large percentage of both groups were prepared to take or prescribe ClaroSip® again. Also the selected beverage, duration of treatment, age of the child and the indication did not greatly affect the acceptance of ClaroSip®. Only 0.26% changed their attitude from voluntary administration to refusal, and after initial refusal 0.12% voluntarily took ClaroSip®. The cure rate was similar in all durations of therapy. When the duration of treatment was five days or less, administration frequency and acceptance were much lower than in other treatment durations. Also frequency of administration and acceptance of ClaroSip® in the group below the age of three years were lower than in the other age groups. The duration of treatment had no effect on the frequency of administration. The cure rate was very high (82.78%) when ClaroSip® was taken completely over the period of treatment prescribed by the physician. The selected beverage, source of information used to instruct the patient on how to take ClaroSip®, and the indication had no effect on the frequency of administration, acceptance or assessment of the taste and handling. However, whether the information was supplied by the physicians themselves or the nurses had an effect on the assessment of the handling of the drinking straw

### **III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATIONS ON DAY 89**

Macrolide antibiotics, particularly the prototypical macrolide, Erythromycin have been widely used since the 1950s in the management of pediatric infections and represent a common alternative in the empirical treatment of respiratory tract infections. Within the group of the second d generation

macrolides, clarithromycin has proven to be versatile in a variety of uses; due to this fact it is largely promoted for its antibacterial spectrum and high rates of clinical and bacteriological efficacy reflected in the medical literature. Clarithromycin is more stable, better absorbed and better tolerated than erythromycin. Excellent tissue and intracellular penetration may contribute to its clinical efficacy. In children clarithromycin is indicated for acute otitis media caused by *Streptococcus pneumoniae*, *H. influenzae* and *Moraxella catarrhalis*, for pharyngitis/tonsillitis caused by *Streptococcus pyogenes* and for acute maxillary sinusitis, uncomplicated skin and skin structure infections, and pneumonia. Clarithromycin is associated with a lower incidence of gastrointestinal side effects, a low rate of drug discontinuation caused by side effects and a low potential for interaction with other drugs. In addition, it has to be taken into account that its oral administration constitutes an important benefit for the paediatric population.

The appropriateness of clarithromycin in the treatment of whooping cough (Altunaiji et al. Antibiotics for whooping cough (pertussis) Cochrane Database Syst Rev. 2007 Jul 18; (3):CD004404, Gregory DS. Pertussis: a disease affecting all ages, Am Fam Physician. 2006 Aug 1; 74(3):420-6. MMWR Recomm Rep. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines 2005 Dec 9; 54(RR-14):1-16) as well as infections caused by *Toxoplasma gondii* (Klein JO History of macrolide use in pediatrics. *Pediatr Infect Dis J.* 1997 Apr; 16(4):427-31. , Peters DH, Clissold SP. Clarithromycin. A review of its antimicrobial activity, pharmacokinetic properties and therapeutic potential. *Drugs.* 1992 Jul; 44(1):117-64) or Mycobacterias (Jenkins PA et al. Clarithromycin vs ciprofloxacin as adjuncts to rifampicin and ethambutol in treating opportunist mycobacterial lung diseases and an assessment of *Mycobacterium vaccae* immunotherapy. *Thorax.* 2008 Jul; 63(7):627-34. Epub 2008 Feb 4, Lindeboom JA, et al. Surgical excision versus antibiotic treatment for nontuberculous mycobacterial cervicofacial lymphadenitis in children: a multicenter, randomized, controlled trial. *Clin Infect Dis.* 2007 Apr 15; 44(8):1057-64. Epub 2007 Mar 2.) in the paediatric population should be further addressed. The MAH is asked to provide additional clarifications for the use of clarithromycin for these indications.

Clarithromycin is available for oral as well as parenteral administration:

- For oral administration, the dose recommendations are supported by the reviewed clinical trials. The safety review done by the MAH has not revealed any new concerns about using clarithromycin in the paediatric population above 6 months of age.
- The safety of clarithromycin during pregnancy and breast feeding of infants has not been established. Clarithromycin should thus not be used during pregnancy or lactation unless the benefit is considered to outweigh the risk. Some animal studies have suggested an embryotoxic effect, but only at dose levels which are clearly toxic to mothers. Clarithromycin has been found in the milk of lactating animals and in human breast milk.
- At present, there are insufficient data to recommend a dosage regimen for parenteral formulation for routine use in children.

**Overall conclusion:** It is agreed with the MAH that the reviewed data lend support to the current state, but does not support the addition of any new paediatric information in the SmPC. However, the precise wording of national SmPCs may differ in different EU countries and this information was not provided by the MAH. According to the CMDh best practice guide on article 45-Paediatric regulation (September 2008), *“the aim of Article 45 procedure is to make the information on the use of medicines in the paediatric population available for all healthcare professionals and patients (or parents). After finalisation of the assessment of the data recommendations for the text to be included*

*in the SmPC and PL will be published on the CMDh website. This information should be included in all SmPC's/PLs of products with the same active substance and pharmaceutical form within 90 days of publication of Public assessment report.*” Therefore, it is suggested that a common wording for indications and dosage of clarithromycin in paediatric patients is implemented.

#### **Recommendation:**

- It is suggested that within the EU a common wording of national SmPCs for indications and dosage of clarithromycin in paediatric patients is implemented.
- The appropriateness for the paediatric population of indications such as treatment of infections caused by *Toxoplasma gondii* or *Mycobacterias* should be further specified. The MAH is asked to provide additional clarifications for the use of clarithromycin for these indications.

## **IV. MAH RESPONSE TO THE PRELIMINARY PDAR ON DAY 89**

The MAH submitted a response to the Preliminary PdAR, dated 11/12/2009.

The Abbott Laboratories (the MAH) responded to rapporteur’s Preliminary Assessment Report and request for supplementary information. The MAH has also provided a response to the question from the Norwegian Ministry of Health member state.

On the Rapporteur’s comment 1 the MAH has provided product labeling incorporating SmPC and PIL, from various EU countries where clarithromycin is currently marketed –Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovakia, Spain, Sweden, UK.

To the Rapporteur’s comment 2 the MAH responded, that it had conducted clinical trials using Clarithromycin in children with an age range of 6 months to 12 years old. The only clinical trial (ref. M95-326) conducted in infants less than 6 months old was stopped prematurely due to low enrollment resulting in no specific safety or efficacy conclusions to be drawn. Therefore, Abbott cannot recommend the use of clarithromycin for treating patients less than 6 months old.

The Rapporteur’s comment 3 was, that MAH should provide a proposal for harmonisation of the paediatric information in accordance with the draft guideline of the SmPC (particularly chapters 4.1. and 4.2) and the Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95 rev1). The MAH in its response provided that Abbott has conducted a comprehensive review of the paediatric history for clarithromycin, which included review of currently-approved SmPCs and PILs within the EU.

Abbott intends to make the following recommendations to all EU SmPCs and PILs and will target implementation to coincide with the completion of the Core Safety Profile, currently being reviewed under the PSUR Work Sharing Project procedure number (IE/H/PSUR/0020/001):

1. The following statements will be added to Section 4.1 Therapeutic Indications of all clarithromycin SmPCs considering The Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95 rev1) and The Proposal for a Revision of the European Commission Guideline on Summary of Product Characteristics (EMA/299527/2007):
  - a. “Consideration should be given to official guidance on the appropriate use of antibacterial agents.”

- b. “Clarithromycin is indicated in adults and children 12 years and older.” (adult only formulations, e.g. tablets, IV)
  - c. “Clarithromycin is indicated in children, 6 months to 12 years.” (Paediatric Oral suspension).
2. The following headers and information will be added to Section 4.2 Posology and Method of Administration of all SmPC.
  - a. “Children younger than 12 years: Use of clarithromycin (proposal to add: “TABLET/IV”) is not recommended for children younger than 12 years. Use clarithromycin Paediatric Suspension.”
  - b. “Children older than 12 years: As for adults.”
3. In addition, Abbott will add a statement regarding duration of treatment based on the review of clarithromycin labeling:
  - a. “The usual duration of treatment is 6 to 14 days.” (adult only formulation)
  - b. “The usual duration of treatment is 5 to 10 days.”

Regarding the Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95 rev1), Abbott will ensure that subsection of 5.1 Pharmacodynamic Properties of all clarithromycin SmPCs contain current breakpoint information as well as required wording as stated in the guidance to preface the resistance table for clarithromycin. Abbott has already harmonised the Clarithromycin Ireland and UK SmPC to accommodate the proposals including those on breakpoints as set out in CPMP/EWP/558/95 rev1.

The Norwegian Medicines Agency had additional comments on treatment of *Haemophilus influenzae* as an important causative pathogen in upper and lower respiratory infections such as community-acquired pneumonia and sinusitis infections. Based on additional data addressing the mode of action clarithromycin and its active metabolite 14-OH-clarithromycin, and their PK/PD relationship for *H. influenzae* infections, the MAH did not consider it to be necessary to re-evaluate the efficacy of clarithromycin for treating *H. influenzae* infections. Consequently, there is no need to add any specific information related to *H. influenzae* infections in section 4.4 Special Warnings and Precautions of the SmPC.

## **V. RAPPORTEUR’S OVERALL CONCLUSION AND RECOMMENDATIONS**

Overall the proposed changes in the SmPC and PIL as by the Applicant are agreed as follows:

### **4.1 Therapeutic indications:**

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

Clarithromycin is indicated in adults and children 12 years and older. (Adult only formulations, e.g. tablets, IV)

Clarithromycin is indicated in children, 6 months to 12 years. (paediatric Oral suspension).

#### **4.2 Posology and method of administration:**

Children younger than 12 years: Use of clarithromycin (proposal to add: “TABLET/IV”) is not recommended for children younger than 12 years. Use clarithromycin Paediatric Suspension.

Children older than 12 years: As for adults.

The usual duration of treatment is 6 to 14 days. (Adult only formulation)

The usual duration of treatment is 5 to 10 days. (paediatric suspension formulation)