



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

19 March 2009  
EMA/743325/2014  
Committee for Medicinal Products for Human Use (CHMP)

**Ketek**

(telithromycin)

Procedure No. EMEA/H/C/000354/P46/038

CHMP assessment report for paediatric use studies  
submitted according to Article 46 of the Regulation (EC)  
No 1901/2006

**Assessment Report as adopted by the CHMP with all information of a commercially  
confidential nature delete**



## Administrative Information

Invented name of the pharmaceutical product	Ketek
Name of the active substance	telithromycin
Pharmacotherapeutic classification (ATC code)	J01FA15
Pharmaceutical form and strength	Film-coated tablet, 400 mg
Centralised Procedure Reference Number	EMA/H/C/354 P46 038
Marketing Authorisation holder	Aventis Pharma SA
Date of first Authorisation/last update	2001-07-09
Marketing authorisation number	2006-07-10
Date of Assessment Report/Last update	2008-12-12
Name of the Rapporteur	Bengt Ljungberg

Medicinal product no longer authorised

# 1. Introduction

Telithromycin, a ketolide antibiotic chemically related to the macrolides, was introduced to the European market 2001. Telithromycin was originally approved for the treatment of community acquired lower and upper respiratory tract infections. Telithromycin exhibits a high *in vitro* activity against *Streptococcus pneumoniae*, irrespective of erythromycin resistance, *Streptococcus pyogenes* and *Haemophilus influenzae*. In June 2007, the CHMP decided to restrict the indication due to safety concerns to:

When prescribing Ketek, consideration should be given to official guidance on the appropriate use of antibacterial agents and the local prevalence of resistance (see also sections 4.4 and 5.1).

Ketek is indicated for the treatment of the following infections:

*In patients of 18 years and older:*

- Community-acquired pneumonia, mild or moderate (see section 4.4)
- When treating infections caused by known or suspected beta-lactam and/or macrolide resistant strains (according to history of patients or national and/or regional resistance data) covered by the antibacterial spectrum of telithromycin (see sections 4.4 and 5.1):
  - Acute exacerbation of chronic bronchitis,
  - Acute sinusitis

*In patients of 12 years and older:*

- Tonsillitis/pharyngitis caused by *Streptococcus pyogenes*, as an alternative when beta lactam antibiotics are not appropriate in countries/regions with a significant prevalence of macrolide resistant *S. pyogenes*, when mediated by ermTR or mefA (see sections 4.4 and 5.1).

Following the somewhat revised benefit/risk evaluation by the CHMP in June 2007, mainly based on safety concerns regarding risk for hepatotoxicity, visual disturbances, transient loss of consciousness as well as potential to increase QT interval, the MAH took the decision to stop the paediatric development program of telithromycin, dated 3 October 2007. On the 13 December 2007 the CHMP adopted the conclusion to support the decision to stop the paediatric development, and committed to assess the clinical study reports when available.

In 2005, the European Medicines Agency (EMA) reminded all Marketing Authorisation Holders in Europe of their legal obligation to submit any information or data collected postauthorization, and in particular, paediatric data (EMA letter of 25 March, 2005, ref EMA/105756/2005).

The study reports of the completed paediatric clinical phase III studies were submitted by sanofi-aventis in June 2008, as per regulation 1901/2006, Article 46. Data included a summary of the telithromycin paediatric data (pharmaceutical, non-clinical and clinical) that supported the initiation of the clinical program and the results of the Phase III telithromycin clinical paediatric studies that were initiated in June 2005 and voluntarily stopped by sanofi-aventis in September 2007.

Sanofi-aventis does not intend to file for a specific paediatric indication or usage.

## 2. Assessment

The clinical paediatric program included several Phase I and Phase II studies, and four Phase III clinical study reports (Studies [EFC6131, EFC6132, EFC6133, EFC6134]) and one case report form from a single patient included in Study [POP6135].

The formulation used in Phase III studies was a 10% powder for oral suspension.

### Clinical efficacy

#### Dose-finding studies from paediatric program

Eleven (11) Phase I studies in adults and in infants and children, and 4 Phase II studies in infants and children were performed as part of the telithromycin paediatric program. Pharmacokinetic analyses showed that the pharmacokinetic measures C<sub>max</sub> and AUC in plasma were comparable in infants (6 to 24 months of age) and children (2 to 12 years of age). According to the parameter estimates by age group, different dosing regimens were considered not necessary for the two age groups.

An assessment of safety data from Phase II studies led to the conclusion that the safety profile of a 30 mg/kg dose of telithromycin given either once daily or divided into two doses showed a range of adverse events in the upper range of acceptability; the 30 mg/kg dose was not carried forward into a Phase III program. In contrast, the safety profile of the 20 mg/kg dose was favourable, with a low rate of gastrointestinal events. The efficacy response to *S. pneumoniae*, including macrolide-resistant *S. pneumoniae*/penicillin-resistant *S. pneumoniae* infections, was not affected by the difference in dose, whereas the response to *H. influenzae* infection, and the response in subjects <2 years old, was better with the higher dose, but only at the on-therapy visit. Therefore, a decision was made to move forward into Phase III with a dose of 25 mg/kg once daily. Pharmacokinetic modelling demonstrated that the pharmacokinetic profile of the 25 mg/kg dose in children would be similar to that of the 800 mg dose in adults.

#### Assessor's comments:

Pharmacokinetic results of Phase I and Phase II clinical studies indicated that different dosing regimens for infants (6 to 24 months of age) and children (2 to 12 years of age) were not necessary. The efficacy and safety results in Phase II, led to the selection of an oral suspension dose of 25 mg/kg for the Phase III program. However, these data have not been submitted and has therefore currently not been assessed by the rapporteur.

#### Phase III studies

The Phase III telithromycin paediatric program consisted of 5 studies:

- Two studies in acute otitis media in children  $\geq 6$  months and <60 months of age (Study [EFC6131]), and in children  $\geq 6$  months and <72 months of age (Study [EFC6132])
- Two studies performed in tonsillitis/pharyngitis, in children aged 6 months to 12 years (Study [EFC6133]), and in adolescents (children 13 to 18 years of age) and adults (Study [EFC6134])
- One study in community-acquired pneumonia in children aged 6 months to <13 years (Study [POP6135])

## Telithromycin Phase III paediatric studies

Study	Indication	Study title	Safety evaluable	Study timelines
<b>B3001 (EFC6131)</b>	AOM	Multinational, randomized, double-blind, double-dummy, comparative study to evaluate the efficacy and safety of telithromycin 25 mg/kg given once daily for 5 or 10 days depending on age and previous treatment history versus cefuroxime axetil 15 mg/kg, given twice daily for 10 days, in children with acute otitis media	Total 633 - 317 on telithromycin	FPI 27-Jun-2005 LPO 27-Jun-2006 Study terminated September 2007
<b>B3002 (EFC6132)</b>	AOM	Multinational, randomized, double-blind, double-dummy, comparative study to evaluate the efficacy and safety of 5 days of telithromycin oral suspension 25 mg/kg, given once daily, versus 5 days of azithromycin oral suspension, given once as 10 mg/kg followed by 5 mg/kg given once daily for 4 days, in children with acute otitis media	Total 318 – 157 on telithromycin	FPI 30-Jun-2006 LPO 18-Jul-2006 Study terminated September 2007
<b>B3005 (POP6135)</b>	CAP	Multinational, randomized, double blind, double dummy, pharmacokinetic study of telithromycin oral suspension (25 mg/kg once daily for 7-10 days), with secondary assessments of safety relative to azithromycin oral suspension (10 mg/kg once daily for 1 day followed by 5 mg/kg once daily for 4 days) in children with mild to moderate community-acquired pneumonia	Total 1 on telithromycin	FPI 16-May-2006 LPO 1-Jun-2006 Study terminated September 2007
<b>B3004 (EFC6133)</b>	T/P	Multinational, randomized, double-blind, double-dummy, comparative study to evaluate the efficacy and safety of telithromycin oral suspension, 25 mg/kg once daily for 5 days, versus penicillin V oral solution, 13.3 mg/kg three times daily for 10 days, in children 6 months to less than 13 years of age with Streptococcus pyogenes tonsillitis/pharyngitis	Total 305 – 150 on telithromycin	FPI 12-Mar-2006 LPO 15-Aug-2006 Study terminated September 2007
<b>B3006 (EFC6134)</b>	T/P	Multinational, randomized, double blind, comparative study to evaluate the efficacy and safety of telithromycin, 800 mg once daily for 5 days, versus penicillin V, 500 mg three times daily for 10 days, in adolescent and adult subjects equal to or over 13 years of age with Streptococcus pyogenes tonsillitis/pharyngitis	Total 232 (including 154 adults) - 112 on telithromycin	FPI 20-Feb-2006 LPO 1-Sep-2006 Study terminated September 2007

ABS = acute bacterial sinusitis; AOM = acute otitis media; CAP = community-acquired pneumonia; FPI = first patient in; LPO = last patient out; T/P = tonsillitis/pharyngitis

Assessments of clinical efficacy and safety were to be carried out at all visits. In paediatric and adolescent subjects, safety alert terms related to cardiac events, hepatic events, and visual disturbances were to be collected throughout the study. An independent data monitoring committee reviewed efficacy and safety data during all paediatric studies and provided advice on the conduct of the studies to the Sponsor.

#### *Study EFC6131*

Subjects with acute otitis media (age range:  $\geq 6$  months and  $< 60$  months) were randomized to either telithromycin oral suspension 25 mg/kg once daily or cefuroxime axetil oral suspension 15 mg/kg twice daily. Subjects randomized to telithromycin could be assigned to treatment for either 5 or 10 days. Subjects  $\leq 24$  months (inclusive) of age who had received antibacterials for acute otitis media within the past 30 days were to receive treatment for 10 days (considered as high risk subjects); all other subjects were to receive treatment for 5 days (considered as low risk subjects). All subjects randomized to cefuroxime axetil were to be given treatment for 10 days.

The primary efficacy variable was the clinical cure rate at the posttherapy/test of cure visit, with the test of cure based on otoscopic evaluation of the tympanic membrane by the Investigator and the subsequent prescription of antibacterials or performance of surgical procedures for acute otitis media.

#### *Study EFC6132*

Subjects with acute otitis media (age range:  $\geq 6$  months to  $< 6$  years of age) were randomized to receive either telithromycin (50 mg/mL) oral suspension 25 mg/kg

once daily for 5 days (not to exceed 1200 mg/day) or azithromycin (40 mg/mL) oral suspension (10 mg/kg) once on Day 1, followed by 5 mg/kg once daily on Days 2 to 5, not to exceed 500 mg on Day 1 and 250 mg/day on Days 2 to 5.

The primary efficacy variables were time to symptom resolution in the INTT population and clinical cure outcome at test of cure in the PPc population.

#### *Study EFC6133*

Subjects aged 6 months to less than 13 years who had *S. pyogenes* tonsillitis/pharyngitis were randomized to receive either telithromycin oral suspension 25 mg/kg once daily for 5 days or penicillin V oral suspension, 13.3 mg/kg 3 times daily for 10 days.

The primary efficacy variable was the bacteriologic outcome at the posttherapy/test-of-cure visit (Visit 3, Day 13-17) in the PPb population.

#### *Study EFC6134*

This study included subjects aged 13 years or older with *S. pyogenes* tonsillitis/pharyngitis. Each subject received either telithromycin tablets 800 mg once daily for 5 days, or penicillin V tablets 500 mg 3 times daily for 10 days. The primary efficacy variable was the bacteriologic outcome at the posttherapy/test-of-cure visit (Visit 3, Day 13-17) in the PPb population.

#### *Study EFC6135*

Only one subject was enrolled in this study on community-acquired pneumonia in paediatric patients, before the study was voluntarily discontinued by the MAH.

### ***Clinical outcome***

All of the Phase III paediatric studies were terminated before reaching the planned sample sizes. Consequently, the intended comparative statistical analyses were not performed, and the efficacy data were summarized using descriptive statistics only.

The EFC6131 study was terminated with 639 out of the target 900 subjects randomized.

Descriptive statistics showed that the primary efficacy assessment of clinical cure rates at posttherapy/test-of-cure for the PPc population was 90.0% (235 of 261 subjects) for telithromycin and 92.7% (240 of 259 subjects) for cefuroxime.

The EFC6132 study was terminated with 321 out of the target 1500 subjects randomized.

Descriptive statistics showed that the primary efficacy assessment of clinical cure rate at posttherapy/test-of-cure for the PPc population was 78.5% (102 of 130 subjects) for telithromycin and 82.7% (115 of 139 subjects) for azithromycin. The median time to symptom resolution in the modified intent-to-treat population was 3.0 days in the telithromycin group and 2.75 days in the azithromycin group.

The EFC6133 study was terminated with 314 out of the target 760 subjects randomized. In the PPb population, the rates of bacteriologic cure based on documented eradication of *S. pyogenes* at the posttherapy/test-of-cure visit (Visit 3, Day 13-17) were 93.7% (89 of 95 subjects) in the telithromycin group and 74.0% (77 of 104 subjects) in the penicillin group.

The EFC6134 study was terminated with 256 out of the target 760 subjects randomized. In the PPb population, the rates of bacteriologic outcome based on documented eradication of *S. pyogenes* at posttherapy/test-of-cure were 93.0% (66 of 71 subjects) in the telithromycin group and 83.3% (70 of 84 subjects) in the penicillin V group.

**Assessor's comments:**

Due to the termination of these studies prior to complete enrolment, as endorsed by the CHMP, only descriptive statistics were provided for the efficacy analyses in the final clinical study reports. No conclusions could be made from the available data.

**Clinical safety**

Safety results were reported by study.

*Study EFC6131*

The safety population included 317 subjects in the telithromycin group and 316 in the cefuroxime group. Median age was 2 years (range 0.5 to 5 years). Treatment-emergent adverse events (TEAEs) were reported in 45.1% of subjects in the telithromycin group and 41.1% in the cefuroxime group. The most frequently reported TEAEs, ie, in  $\geq 3.0\%$  subjects in either treatment group, were diarrhea (telithromycin: 11.7%, cefuroxime: 10.4%), vomiting (telithromycin: 9.1%, cefuroxime: 7.0%), dermatitis diaper (telithromycin: 3.2%, cefuroxime: 4.4%), and pyrexia (telithromycin: 3.5%, cefuroxime: 0.9%).

There were no deaths reported during the study.

A total of 7 subjects (2.2%) in the telithromycin group and 5 subjects (1.6%) in the cefuroxime group experienced serious TEAEs. Two serious TEAEs in each treatment group were associated with the hepatobiliary system. One serious TEAE, "staring," a visual adverse event of special interest, was reported in 1 subject in each treatment group.

The study treatment discontinuations due to TEAEs (telithromycin: 13; cefuroxime: 6) were mostly due to vomiting (8 subjects in the telithromycin group, 3 subjects in the cefuroxime group) or skin disorders (3 subjects in the telithromycin group and none in the cefuroxime group).

For adverse events of special interest, the reporting of hepatic (telithromycin: 4; cefuroxime: 5) and visual events (telithromycin: 1; cefuroxime: 3) was similar between treatment groups, and no cardiac adverse events of special interest were reported. With respect to postbaseline ALT/serum glutamate pyruvate transaminase (ALT/SGPT) elevations  $>3 \times$  upper limit of normal (ULN), 1 was noted in the telithromycin group and 2 in the cefuroxime group. Twenty two of 283 (7.8%) subjects in the telithromycin group and 13 of 280 (4.6%) subjects in the cefuroxime group had platelet values  $\geq 1.5 \times$  ULN at postbaseline.

#### *Study EFC6132*

The safety population included 157 subjects in the telithromycin group and 161 in the azithromycin group. Median age was 2.2 years (range 0.5 to 6 years). Treatment-emergent adverse events were reported in 37.6% of subjects in the telithromycin group and 36.6% in the azithromycin group. The most frequently reported TEAEs, ie, in  $\geq 3.0\%$  subjects in either treatment group, were diarrhoea (telithromycin: 6.4%, azithromycin: 5.0%), otitis media (telithromycin: 5.7%, azithromycin: 5.0%), cough (telithromycin: 3.2%, azithromycin: 4.3%), vomiting (telithromycin: 2.5%, azithromycin: 3.1%), and gastroenteritis viral (telithromycin: 1.3%, azithromycin: 3.1%). There were no deaths reported during the study. There was 1 serious TEAE (viral infection) reported during the study in the telithromycin group which resolved without sequelae. The Investigator determined the event was unrelated to study treatment. Treatment-emergent adverse events led to treatment discontinuation in 1.3% of telithromycin subjects and 1.2% of azithromycin subjects.

For adverse events of special interest, there were no hepatic or cardiac events in either group. There was 1 subject (1014/2041) in the telithromycin group that reported a visual TEAE of blepharospasm. The TEAE manifested 1 hour after the first dose of study medication. The event resolved without sequelae. The Investigator assessed the event to be nonserious, of mild intensity, and possibly related to study medication. The pattern of postbaseline hepatic enzyme levels were similar across the treatment groups and the majority of abnormalities in laboratory analytes were similar between the 2 treatment groups. Eight of 130 (6.2%) subjects in the telithromycin group and 2 of 132 (1.5%) subjects in the azithromycin group had platelet values  $\geq 1.5 \times$  ULN at postbaseline.

#### *Study EFC6133*

The safety population included 150 subjects in the telithromycin group and 155 in the penicillin group. Treatment-emergent adverse events were reported in 32.0% of subjects in the telithromycin group and 37.4% of subjects in the penicillin group. The most frequently reported TEAEs, ie, in  $\geq 3.0\%$  of subjects of either treatment group, were vomiting (telithromycin: 7.3%, penicillin: 3.2%), cough (telithromycin: 4.7%, penicillin: 3.2%), otitis media (telithromycin: 0.7%, penicillin: 3.2%), and headache (telithromycin: 0.7%, penicillin: 3.9%).

There were no deaths reported during the study. One subject (0.7%) in the telithromycin group reported a serious TEAE associated with study medication overdose, and recovered without any clinical intervention. No other adverse events were reported in this subject. Treatment-emergent adverse events leading to discontinuation of subjects were reported by 6% of subjects in the telithromycin group and 3.2% of subjects in the penicillin group. Vomiting was the most frequently reported TEAE that led to discontinuation in the telithromycin group.



With respect to adverse events of special interest, 1 hepatic event (elevated baseline ALT) was reported in the telithromycin group. The subject had an elevated baseline ALT value that returned to normal after treatment. There were 2 visual events (blurred vision) reported, 1 in each treatment group. In both cases the events resolved without sequelae. There were no subjects with postbaseline ALT or aspartate aminotransferase (AST) values  $>3 \times \text{ULN}$ . No subject had postbaseline bilirubin values  $>2 \times \text{ULN}$ .

#### *Study EFC6134*

The safety population included 112 subjects (36  $<18$  years of age) in the telithromycin group and 120 (42  $<18$  years of age) in the penicillin group.

Treatment-emergent adverse events were reported in 41.1% of patients in the telithromycin group and 31.7% in the penicillin group. The most frequently reported TEAEs, ie, in  $\geq 3.0\%$  subjects in either treatment group, were diarrhoea (telithromycin: 9.8%, penicillin V: 1.7%), nausea (telithromycin: 4.5%, penicillin: 4.2%), vomiting (telithromycin: 3.6%, penicillin: 1.7%), and headache (telithromycin: 4.5%, penicillin: 0.8%).

There were no deaths reported during the study. One adolescent subject in the telithromycin group reported a serious TEAE associated with serum sickness and liver function abnormality, and recovered without sequelae. One subject (0.8%) in the penicillin group also reported a serious TEAE of visual tracking test abnormality and acute sinusitis, but recovered without sequelae. The frequency of TEAEs leading to discontinuation of subjects was 6.3% in the telithromycin group and 5.0% in the penicillin group.

There were 5 subjects in the telithromycin group and 2 subjects in the penicillin group who reported hepatic adverse events of special interest. The elevation of ALT in 1 subject in the telithromycin group was reported as a serious TEAE. In the telithromycin group, 4 subjects had elevated levels of ALT. In these 4 subjects, 2 subjects ALT  $>5 \times \text{ULN}$  and 2 subjects had ALT within  $>3 \times$  and  $\leq 5 \times \text{ULN}$ . In the subjects with  $>5 \times \text{ULN}$ , 1 subject also had elevated level of AST within  $>3 \times$  and  $\leq 5 \times \text{ULN}$ . One subject in the telithromycin group had elevated level of bilirubin (1.7  $\times \text{ULN}$  at Visit 1 and 1.5  $\times \text{ULN}$  at Visit 3). In the penicillin group, 1 subject had elevated level of ALT within  $>3 \times$  and  $\leq 5 \times \text{ULN}$  and 1 subject had elevated level of AST (4.1  $\times \text{ULN}$ ). All subjects recovered without sequelae.

There were 3 subjects in each treatment group who reported visual adverse events of special interest. In all the cases the events resolved without sequelae, except for 1 adult subject (with a mild event of blurred vision) in the telithromycin group who had blurred vision with small print and was reported as ongoing. The event was attributed to the aging process and reported as not related to the study medication.

#### *Study EFC6135*

No adverse events were reported for the one subject in the POP6135 study, who completed treatment with telithromycin oral suspension 25 mg/kg once daily for 10 days.

### **Platelet evaluation**

A slight increase in post-baseline platelets was observed in the telithromycin groups compared to comparator drug groups in 2 studies, EFC6131 (7.8% vs. 4.6%) and EFC6132 (6.2% vs. 1.5%). Therefore, an analysis was performed of baseline to post-baseline changes in platelets in subjects with post baseline values available. None of the subjects in either study had post-baseline platelet elevation  $\geq 2.5 \times \text{ULN}$ .

The observation of a trend in post-baseline platelet elevation with telithromycin was not seen in older subjects, including adults. These limited data, with uncertain significance in children <72 months with acute otitis media, indicate that no change is warranted in the labeling for adults with respect to the platelets.

Assessor's comments on safety:

A total of 1420 paediatric subjects (age range 6 months to 18 years) were exposed to telithromycin in the paediatric program (Phases I = 200, II = 637, and III = 583). Of the 474 enrolled in the two acute otitis media Phase III studies, approximately 50% were below the age of 2 years. The results of the safety evaluation of all subjects who received telithromycin as an oral suspension at a dose of 25 mg/kg once daily for 5 or 10 days, or as an oral tablet of 800 mg once daily for 5 days, were consistent with the known safety profile of telithromycin. The limited data from the analysis of baseline to post-baseline changes in platelets in studies EFC6131 and EFC6132, which are of uncertain significance in children <72 months with acute otitis media, indicate that no change is warranted in the labeling for adults with respect to the platelets.

Due to the overall safety profile of telithromycin, the Rapporteur considers that the overall benefit/risk ratio for the use of Ketek in children with benign indications such as acute otitis media and tonsillitis/pharyngitis, is negative. Accordingly, the Rapporteur concurs with the MAH that a specific paediatric indication besides the already approved tonsillitis/pharyngitis in adolescents above 12 years of age, is not supported.

### Summary of product's characteristics (SPC)

Although the presently submitted documentation on paediatric patients does not support a specific paediatric indication or recommendation for use in children besides the currently approved second-line indication tonsillitis/pharyngitis caused by *S. pyogenes* in patients of 12 years and older, the SPC should be updated in sections 4.2, 4.4 and 5.2 based on the new data.

The current statement in section 5.2 regarding subjects below the age of 12 years is no longer correct. MAH is requested to present available PK data and to suggest valid concise information concerning this population, to be stated in section 5.2.

Current information regarding paediatric patients in the SPC with proposed amendments/additions by the Rapporteur in bold italics:

#### Section 4.2

##### In children:

Ketek is not recommended for use in children below 12 years of age due to lack of **limited** data on safety and efficacy (see section **4.4 and 5.2**).

#### Section 4.4

***The paediatric program was terminated before the planned number of subjects was randomised, based on the overall benefit/risk balance for adults. Limited data in patients from 6 months of age with acute otitis media or tonsillitis/pharyngitis, receiving telithromycin oral suspension, indicate a safety profile consistent with that of adults.***

## Section 5.2

*Assessor's comment:*

*This section requires further amendments depending on the MAH's response to the LoQ:*

-Paediatric patients

~~The pharmacokinetics of telithromycin in paediatric population less than 12 years old have not yet been studied.~~ Limited data, obtained in paediatric patients 13 to 17 years of age, showed that telithromycin concentrations in this age group were similar to the concentrations in patients 18 to 40 years of age (**see section 4.4**).

### **Assessor's overall conclusion**

Sanofi-aventis initiated a paediatric program aimed to evaluate the efficacy and safety of telithromycin oral suspension 25 mg/kg once daily in the treatment of acute otitis media, tonsillitis/pharyngitis and community-acquired pneumonia. Following a safety assessment by the CHMP leading to restricted indications in June 2007 due to a somewhat revised benefit/risk evaluation, the MAH decided to terminate all ongoing and planned studies in the paediatric program. This decision was supported by the CHMP in December 2007.

The Phase III clinical program was terminated before the planned number of subjects could be randomized. Thus, the study populations were limited (a total of 471 patients aged from 6 months to 12 years received telithromycin 25mg/kg once daily in Phase III studies), and consequently the efficacy data were summarized using descriptive statistics only. No definitive efficacy conclusions can be drawn from these studies.

Across all of the Phase III clinical studies, the results of the safety evaluation of telithromycin were consistent with the known profile of the product. Regarding the new data presented in this submission, there is no new safety signal identified in the studied paediatric population compared to the approved labeling for use of telithromycin in adults that would warrant a change of the safety information.

However, the new information gained from the interrupted paediatric clinical program, renders a need for updating the sections 4.2, 4.4 and 5.2 in the SPC. It is of importance that the prescribers are informed of the reason for absence of a specific paediatric indication, as well as of the current PK and safety information for this group of patients.

### **3. Conclusion and Recommendation**

Due to the overall safety profile of telithromycin, the Rapporteur considers that the overall benefit/risk ratio for the use of Ketek in children with benign indications such as acute otitis media and tonsillitis/pharyngitis, is negative. Accordingly, the Rapporteur concurs with the MAH that a specific paediatric indication besides the already approved second-line indication for tonsillitis/pharyngitis in adolescents above 12 years of age, is not supported. However, based on the available data on patients 6 months to 12 years, some amendments in the SPC are required.

**List of Questions:**

1. The applicant should update sections 4.2 and 4.4 according to the Rapporteur's proposal.
2. The current statement in section 5.2 regarding subjects below the age of 12 years is no longer correct. MAH is requested to present available PK data and to suggest valid concise information concerning this population, to be stated in section 5.2.

Medicinal product no longer authorised