8 August 2012
EMA/531185/2012
Committee for Medicinal Products for Human Use (CHMP)

Ketek

(telithromycin)

Procedure No. EMEA/H/C/354/A45/39

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

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

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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

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Ketek (telithromycin)

EMEA/H/C/351/P45

Marketing Authorisation Holder: Sanofi aventis Pharma

Rapporteur:	Bengt Ljungberg
Start of the procedure:	2009-04-26
Date of this report:	2009-06-02
Deadline for Rapporteur's AR:	2009-06-02
Deadline for CHMP member's comments:	2009-06-09
Date of the Final report:	**2009-06-16**

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Ketek
INN (or common name) of the active substance(s):	telithromycin
MAH:	sanofi aventis
Currently approved Indication(s)	*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 S*treptococcus 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).
Pharmaco-therapeutic group (ATC Code):	J01FA15
Pharmaceutical form(s) and strength(s):	Film-coated tablet, 400 mg
Rapporteur:	**Bengt Ljungberg**

I. INTRODUCTION

On 10 December 2008, the MAH submitted 35 completed paediatric studies for Ketek, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Ketek and that there is no consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing

II. SCIENTIFIC DISCUSSION

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. 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 S*treptococcus 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 partly 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 an EMEA letter dated 4 December 2008 (ref. EMEA/648008/2008) the MAH was requested to dispatch to the CHMP members and EMEA all existing data/information of telithromycin in paediatric patients, submitted according to Article 45 regulation (EC) No 1901/2006.

The study reports of the completed paediatric clinical phase III studies were previously 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. This article 46 procedure was finalised in March 2009. As it was mutually agreed October 2007 to stop the paediatric development program of telithromycin, neither the MAH nor the CHMP intend to include a paediatric indication. However, as a result of the article 46 procedure the MAH was requested to submit a type II variation addressing the required amendments in sections 4.2, 4.4 and 5.2, related to paediatric use of telithromycin, see below.

In the present submission, a line listing of non-clinical and clinical paediatric studies including study reports is provided, of which the majority are submitted previously (see initial submission date in the table below).

KETEK (telithromycin) – submission of paediatric studies – Article 45 Regulation EC N° 1901/2006

Study Ref.	Location Module	Study TITLE	Study Number	Initial Submission date
1	4	Single-dose toxicokinetic study in neonatal Sprague Dawley rats	DES 2004-1861	11 Jan. 2008
2	4	A 4-week repeated dose toxicity study of HMR3647 administered to young rats	SBL 78-86	11 Jan. 2008
3	4	A 4-week repeated dose toxicity study of HMR3647 administered orally to young Beagle dogs followed by a 4-weeek recovery period	SBL 78-84	11 Jan. 2008
4	4	Exploratory 7-day oral toxicity study in Sprague Dawley juvenile rats (from postnatal day 6)	DSE 2004-1951	11 Jan. 2008
5	4	Telithromycin epidemiological survey in Austria isolates from paediatric patients	A-00-647-683	11 Jan. 2008
6	4	Telithromycin : analysis of prevalence and genotypes of macrolide-resistant streptococci among pediatric patients in Denmark, Luxemburg, The Netherlands and Turkey	NL-00-647-660	11 Jan. 2008
7	4	In vitro activity of telithromycin, including well characterized erythromycin-resistant clinical isolates of S. pneumoniae and S.pyogenes in paediatrics	- SF-00-647-677	11 Jan. 2008
8	4	Telithromycin : epidemiological multicenter study on macrolide resistance of S.pneumoniae and S.pyogenes in the pediatric population in Germany, 2000-2001	D-00-647-667	11 Jan. 2008
9	4	Determination of the susceptibility of isolates of Streptococcus pneumoniae and Streptococcus pyogenes, from paediatric patients, to telithromycin and comparator compounds and identification of the	UK-00-647-669	11 Jan. 2008

		mechanism of resistance in erythromycin A-resistant strains		
10	4	In vitro activity of telithromycin (HMR3647) against Streptococcus pyogenes and Streptococcus pneumoniae clinical isolates from paediatric patients in Greece	GR-00-647-679	11 Jan. 2008
11	4	Activity of telithromycin on clinical isolates of Streptococcus pyogenes and Streptococcus pneumoniae from paediatric patients in different regions of Italy	I-00-647-664	11 Jan. 2008
12	4	Activity of telithromycin against erythromycin susceptible and resistant Streptococcus pyogenes and Streptococcus pneumoniae isolates from paediatric origin	E-00-647-675	11 Jan. 2008
13	4	Susceptibility of 1034 Streptococcus pneumoniae and 1039 Streptococcus pyogenes strains from paediatric patients in ten central and eastern European contries to telithromycin, erythromycin A, azithromycin, clarithromycin, clindamycin, levofloxacin, quinupristin/dalfopristin, and penicillin G	USA-00-647-657	11 Jan. 2008
14	4	In vitro activity of telithromycin (HMR3647) against strains of S. pneumoniae and S. pyogenes isolated in Iceland and comparison with other antimicrobials	IS-00-647-651	11 Jan. 2008
15	4	Minimal inhibittory concentrations of telithromycin (Ketek) against Streptococcus pneumoniae, Heamophilus influenzae and Moraxella catarrhalis strains isolated from specimen of young patients (17 years old or less) and from specimen of adults (18 years old and older)	CDN-01-647-704	11 Jan. 2008
16	4	Activity of telithromycin and comparators against paediatric respiratory tract infection (RTI) isolates collected across Canada over the past 3 years (1997-1998, 1998-1999, and 1999-2000)	CDN-00-647-661	11 Jan. 2008
17	4	In vitro activity of telithromycin and multiple comparison antibiotics against recent clinical isolates from children	USA-00-647-674	11 Jan. 2008
18	4	In vitro activity of antimicrobial agents against Streptococcus pyogenes in paediatrics : a Belgian multicenter study	B-00-647-656	11 Jan. 2008
19	4	Pattern of killing of telithromycin and azithromycin against various strains of Streptococcus pneumoniae	USA-02-647-731	11 Jan. 2008
20	4	Experimental studies of otitis media due to Streptococcus pneumoniae treated with HMR3647	USA-96-004-541	11 Jan. 2008
21	4	Evaluation of telithromycin on acute otitis media in an experimental animal model (chinchilla)	USA-02-647-718	11 Jan. 2008
22	4	U.S. Survey of Telithromycin Activity against Streptococcus pyogenes	US-06-S. pyo-592	11 Jan. 2008
23	5	Pharmacokinetics of Telithromycin (HMR3647) in infants and children suffering from bacterial lower respiratory tract infections after single oral administration of 30mg/kg of a telithromycin suspension (50mg/ml)	HMR 3647B/1002	11 Jan. 2008
24	5	Open Study to determine the concentration of telithromycin in middle ear fluid and plasma in infants/children with acute otitis media or otitis media with effusion after single oral administration of 20mg/kg or 30mg/kg of a telithromycin pediatric suspension Report 1004 (PKD6208)	HMR 3647B/1004	11 Jan. 2008
25	5	Open Study to determine the concentration of telithromycin in the extracellular and intracellular compartments of middle ear fluid in children with acute otitis media or otitis media with spontaneous effusion after single oral administration of a telithromycin pediatric suspension - Report 1007 (CPK-P-2003-0108)	HMR 3647B/1007	11 Jan. 2008
26	5	Open Study to determine the concentration of telithromycin in middle	HMR 3647B/1009	11 Jan. 2008

		ear fluid and plasma in infants/children with otitis media with effusion after multiple oral administration of 20mg/kg, once daily for 5 days or 15mg/kg twice daily for 4.5/5 days of telithromycin pediatric suspension - Report 1009 (PKD6210)		
27	5	Multicenter, Phase II, open-label study of the efficacy, safety, acceptability, and pharmacokinetics of telithromycin, after repeated oral administration of either of two doses, once daily, for 5 days or 7 to 10 days, in the treatment of respiratory tracts infections in children of 6 months to 12 years - Report 2001 (F2001CLN0378)	HMR 3647B/2001	11 Jan. 2008
28	5	Multicenter, Phase II, open-label study of the efficacy, safety, acceptability, and pharmacokinetics of telithromycin, following administration of 20mg/kg once daily, for 5 days in the treatment ofacute otitis media in children - Report 2004 (CLN-P-2003-0379)	HMR 3647B/2004	11 Jan. 2008
29	5	Multicenter, Phase II, open-label study of the efficacy, safety, acceptability, and pharmacokinetics of telithromycin, following administration of 15mg/kg twice daily, for 5 days in the treatment of acute otitis media in children - Report 2006 (CLN-P-2003-0085)	HMR 3647B/2006	11 Jan. 2008
30	5	Evaluation of pharmacokinetics, safety, efficacy and acceptability of HMR3647 (20mg/kg and 30mg/kg q.d.) in pediatric patients with infection (a non-blind, randomised, parallel-group comparative study)	HMR 3647B/2101	11 Jan. 2008
Addendum / non-clinical studies				
31	4	Two- to seven-day oral exploratory toxicity study in juvenile rats	DSE 2004-0390	5 Jun. 2008
32	4	4-week oral toxicity study in Sprague Dawley juvenile rats (from postnatal day 5). Comparison of an impurity-enriched batch with standard batch	DSE 2005-0198	5 Jun. 2008
Addendum / Japanese Clinical studies (English translation of the study synopses)				
33	5	Evaluation of the Safety, Pharmacokinetics, Efficacy and Acceptability of HMR 3647 20mg/kg QD for 5-7 Days with Community Acquired Pneumonia (CAP) in children. (Multicenter, open label, non comparative study)	HMR3647B/3101	21 Oct. 2008
34	5	Evaluation of the Safety, Efficacy, Pharmacokinetics and Acceptability of HMR 3647 20 mg/kg QD for 5 Days with Acute Otitis Media in Children(Multicenter, open label, non comparative study)	HMR3647B/3103	21 Oct. 2008
35	5	Investigation of the efficacy, safety and acceptability of HMR 3647 (1-g divided 20% fine granule packets) in paediatric patients with infections (a multi-center collaborative single-group non blinded study)	HMR3647B/3104	21 Oct. 2008

II.1 Non-clinical aspects

The non-clinical paediatric development for telithromycin consisted of studies carried out in juvenile animals, to specifically address potential toxicity in these animals. Single and repeat dose studies were performed in young rats and young dogs. See list of non-clinical studies above.

Oral administration of a standard and an impurity-enriched batch for 2 days at doses of 50 or 150 mg/kg/day to juvenile rats (dosing starting on postnatal Day 5) induced mortality at 150 mg/kg/day (15/20 and 19/20 pups, respectively, within 2 days). The death of a single pup at 50 mg/kg/day with the impurity-enriched batch was considered most likely incidental and not related to compound administration. Daily oral administration of standard batches to juvenile rats at 50 mg/kg/day for 7 days produced no deaths, no clinical signs and no body weight changes. Therefore, under these study conditions, the dose level of 150 mg/kg/day given as a solution was a lethal dose and the dose of 50 mg/kg/day was a No-Observed Effect Level, based on clinical endpoints. There was no clear difference in the toxicity profile between the standard and the impurity-enriched batches.

In a 4 week rat study there were no compound-related changes in organ weights, and no compound-related macroscopic observations. There were no compound-related microscopic changes in rats treated with the

impurity-enriched batch. Very minimal compound-related microscopic changes, consisting of very minimal foamy alveolar macrophage collections in the lungs or minimal epithelioid macrophages in the medullary cords and paracortex of the mesenteric lymph node, were observed in occasional rats treated with the standard batch at 25 and 75 mg/kg/day. These observations were consistent with changes observed in previous studies in adult rats.

Data from these studies do not provide any new information that raises any further need for SPC amendments regarding paediatric use of Ketek.

II.2 Clinical aspects

See list of clinical studies above. The phase 1 and phase 2 clinical studies are all previously assessed in the article 46 procedure for Ketek (EMEA/H/C/354 P46 038; Rapporteur's AR submitted 2008-12-12). In addition, the MAH now submitted study synopsis for three Japanese open label phase 3 clinical studies. Data from these studies do not provide any new information that raises any further need for SPC amendments regarding paediatric use of Ketek, except the minor amendment currently discussed in the ongoing article 46 procedure.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **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 an overall by indication safety assessment by the CHMP leading to restricted indications in June 2007 due to a partly 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. The submitted study synopsis of the three open-labeled Japanese studies did not raise any additional concerns.

Across all of the submitted non-clinical and 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 and as a second line indication tonsillitis/pharyngitis in patients of 12 years of age and older, that would warrant a change of the safety information or other information concerning paediatric patients in the SPC of Ketek.

However, as already discussed during the article 46 procedure for Ketek (EMEA/H/C/354 P46 038; AR submitted 2008-12-12), 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.

As a result of article 46 procedure for Ketek (EMEA/H/C/354 P46 038, the CHMP adopted the following conclusions on 19 March 2009:

Due to the overall safety profile of telithromycin, the CHMP 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 CHMP 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 MAH should update sections 4.2 and 4.4 of the SPC as follows:

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.

2. The current statement in section 5.2 of the SPC 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.

The MAH was requested to submit a type II variation by 10 July 2009 addressing these conclusions.

➢ 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 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. Necessary amendments in sections 4.2, 4.4 and 52 will be addressed in the requested type II variation which is expected in July 2009. No further action is considered required in relation to the present procedure (EMEA/H/C/354/P45).

☒ Fulfilled

No further action required.