London, 30 March 2007
Product name: **LEVVIAX**
Procedure No. EMEA/H/C/354/A22/41

SCIENTIFIC DISCUSSION

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1. Origin of regulatory Activities

On 9 July 2001, the European Commission granted Aventis Pharma S.A. a marketing authorisation for Levviax for treatment of the following infections: mild to moderate community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), and acute sinusitis (ABS) in patients of 18 years and older, as well as tonsillitis/pharyngitis caused by Streptococcus pyogenes in adults and adolescents, as an alternative when beta-lactam antibiotics are not appropriate.

Throughout the year 2006, the CHMP has been reviewing relevant safety data on Levviax. The CHMP/EMEA have asked the Marketing Authorisation Holder to submit comprehensive safety reviews, including updated analysis on hepatic adverse reactions, a review of the benefit-risk balance in each of the therapeutic indications and comparative data from clinical trials with telithromycin compared to other antibiotics.

In their meeting in January 2007 the CHMP concluded that the Marketing Authorisation Holder failed to submit a reassuring answer to these questions. The CHMP thus remained concerned regarding the overall benefit-risk balance of Levviax.

Compared to other macrolides, Levviax seems to be associated with a somewhat different risk profile, i.e. adverse reactions as eye disorders, which sometimes are of severe nature, and serious adverse reactions as aggravation of myasthenia gravis, loss of consciousness and acute liver failure. Altogether, these adverse reactions constitute a significant risk which could have impact on the approved therapeutic indications. Furthermore, the CHMP noted the submission of the Risk Management. However, the Marketing Authorisation Holder did not propose Risk Minimisation Activities.

Further to the FDA Joint Advisory Committee meeting held on December 14-15, 2006, the following regulatory steps were advised regarding revision of the US prescribing information; the indications acute bacterial sinusitis (ABS) and acute exacerbation of chronic bronchitis (AECB) should be removed from the labelling, and the safety partss of the labelling should be updated. On the 12 February 2007, FDA authorised a new Levviax labelling, where these issues were implemented, including a contraindication in myasthenia gravis.

During the January 2007 meeting, these concerns were discussed and CHMP requested the responses to the following questions to be provided by the Marketing Authorisation Holder in writing by 12 February 2007 and in an oral explanation at the March 2007 CHMP meeting.

1. The Marketing Authorisation Holder should carry out a benefit-risk evaluation for Levviax in all the authorised indications.
Comparative data from clinical trials with telithromycin compared to other antibiotics (such as erythromycin, clarithromycin, roxithromycin, amoxicillin/clavulanic acid etc…) for which data is available to the Marketing Authorisation Holder should be included in the evaluation.
2. In the context of the identified risks the Marketing Authorisation Holder should propose adequate Risk Minimisation Measures whenever necessary.

1.2. QUESTION 1 ON THE BENEFIT-RISK ASSESSMENT IN THE AUTHORISED INDICATIONS

The MAH has provided:

- A review of current medical need for antibiotics in the treatment of respiratory tract infections (RTIs),
- An overall and by indication summary of the microbiological and clinical efficacy data pertaining to the benefits of telithromycin,
- An overall and by indication summary of the risks associated with telithromycin,
- An overall and by indication comparative evaluation of the Benefit-Risk profile of telithromycin vs. other antibiotics.

1.2.1. Review of the current medical need

The present Benefit-Risk Evaluation includes a review of the current medical need for antibiotics in the treatment of community-acquired RTIs. The key organisms associated with RTI are *Streptococcus pneumoniae* (including penicillin- and/or macrolide-resistant strains), *Haemophilus influenzae* and *Moraxella catarrhalis* (including β-lactamase-producing strains), *Staphylococcus aureus* and *Streptococcus pyogenes*. In addition, atypical and intracellular pathogens such as *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila* represent important causes of CAP. All these pathogens have been shown to be sufficiently covered by the spectrum of telithromycin. Beta-lactam agents and macrolides are commonly used for the treatment of community acquired RTI, but resistance against S. pneumoniae, the most important RTI pathogen, has reached significant levels in several European countries.

1.2.1.1 Clinical impact of antibiotic resistance

S. pneumoniae resistance to antibiotics varies greatly among European countries and remains high in several countries particularly in Southern Europe (Table 1).

Large differences in penicillin non-susceptibility in invasive *S. pneumoniae* isolates are reported among European countries by the European Antimicrobial Resistance Surveillance System (EARSS), varying from 1% in the Netherlands to 36% in France and 39% in Romania in 2005. Several countries reported a significant increase such as Sweden (from 1.5% in 1999 to 3.6% in 2005), Iceland (from 2.1% in 1999 to 8.1% in 2005), and Bulgaria (from 8% in 2002 to 32.6% in 2005). In contrast, Spain (from 32.5% in 1999 to 25.6% in 2005), Ireland (from 19.5% in 2000 to 11.1% in 2005), Belgium (from 13.5% in 1999 to 11.8% in 2005), and the UK (from 7.4% in 1999 to 3.9% in 2005) reported a decrease in the proportion of nonsusceptible strains over the same period.

Erythromycin resistance is generally more prevalent than penicillin resistance in the EU. In 2005, the majority of countries reported between 10% and 25% erythromycin resistance. Belgium, France, Hungary, Italy, Romania and Slovakia reported rates over 30%. Only Estonia, Czech Republic, Sweden, Denmark and Bulgaria still reported antibiotic resistance levels below 10%. Until 2000, The Netherlands, Austria, Norway, Germany and Finland also reported levels below 10%, but the proportion of antibiotic-resistant *S. pneumoniae* in these countries has increased significantly in the last 5 years.

The Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT) – Global study, an international study initiated in 1999 is a longitudinal microbiological surveillance study designed to evaluate the activity of telithromycin against *S. pneumoniae* and other common RTI pathogens and to compare its activity with that of other antibacterial agents. In this study, all isolates (not only invasive isolates) coming from RTIs are collected (Table 1). In many countries, PROTEKT results reports higher resistance rates in comparison with EARSS. This may be explained by the fact that both invasive and noninvasive isolates are collected in the PROTEKT study.

The frequency of the *erm*(B) genotype among macrolide resistant *S. pneumoniae* is higher in Europe compared to the US. This genotype is found in the vast majority of macrolide resistant *S. pneumoniae* in many EU countries (Belgium, France, Hungary, Poland, Portugal, Slovak Republic, Spain, Sweden) and in approximately half of the strains in Italy and Germany. This genotype of resistance is associated with very high MICs, ≥ 64 mg/l for the macrolides (erythromycin, clarithromycin, azithromycin).

Table 1 - Epidemiology of Streptococcus pneumoniae resistance to penicillin and macrolides in Europe

	EARSS 2005			PROTEKT 2003-2004		
Country	**ERSP %**	**PNSP %**	**PRSP %**	**ERSP %**	**PNSP %**	**PRSP %**
Austria	15	5	1	16.9	12.3	6.2
Belgium	31	12	3	30.7	16.2	9.9
Bulgaria	8	33	30	20	20	0
Czeh Rep.	2	4	0	2.9	7	4.1
Germany	17	5	0	22.2	9.4	2.2
Denmark	6	4	1	-	-	-
Estonia	0	2	0	-	-	-
Spain	23	25	9	33.5	40	28.5
Finland	20	7	1	15.9	18.9	4.4
France	41	36	5	51.1	53.4	38.4
Greece	-	-	-	49.4	55	43.6
Croatia	17	17	0	-	-	-
Hungary	37	22	2	43.6	48.7	23.7
Ireland	15	33	8	18	20	16
Iceland	17	8	0	-	-	-
Italy	31	9	5	45.6	17.6	13.2
Luxemburg	24	12	7	-	-	-
Latvia	3	0	0	-	-	-
Netherlands	11	1	0	10.2	3.4	1.7
Norway	16	2	1	-	-	-
Poland	33	33	17	18.2	11.2	9.8
Portugal	19	17	1	6.1	15.1	3
Romania	31	39	22	-	-	-
Sweden	6	4	0	6	12.8	4.5
Slovakia	40	0	0	13.4	38.3	17.2
Slovenia	11	11	2	-	-	-
UK	11	4	2	24.2	9.1	3

ERSP: erythromycin-resistant S. pneumoniae; PNSP: penicillin non-susceptible S. pneumoniae; PRSP: penicillin -resistant S. pneumoniae

Convincing evidence that resistance has an adverse effect on clinical outcomes particularly mortality is sparse, especially in out-patients. However, it has recently been suggested that resistance may need to be reconsidered as an independent predictor of poor clinical response, but interpretation of the studies is difficult due to confounding factors such as comorbidities, severity of illness, and age

[Tleyjeh, 2006]. A recent study using a large claims database found no statistically significant association between *S. pneumoniae* susceptibility and RTI treatment outcomes in AECB and ABS, conditions that are not associated with bacteremia [Furuno, 2006]. On the other hand, four recent studies focusing on patients with pneumococcal bacteremia provide evidence that macrolide-resistant *S. pneumoniae* contributes to an increased risk of treatment failure with macrolides [Lonks et al, 2002; Van Kerkhoven et al, 2003; Danneman et al, 2006; Grant et al., 2006].

1.2.1.2 Current antibiotic treatment

CAP, AECB, and ABS are most often treated empirically with the following antibiotics: β-lactams (eg, penicillin, amoxicillin, amoxicillin-clavulanic acid, oral cephalosporins), macrolides (eg, clarithromycin, azithromycin, and erythromycin), ketolides (telithromycin), and quinolones (eg, levofloxacin, moxifloxacin). To a lesser extent, tetracyclines and trimethoprim-sulfamethoxazole are also used in the treatment of RTIs.

1.2.2 Summary of the microbiological data of telithromycin supporting the benefits of the agent

Overall, the antibacterial spectrum of telithromycin is targeted against RTI pathogens. The main pathogens covered by telithromycin are:

-*Streptococcus pneumoniae* (including macrolides and/or penicillin resistant strains)
-*Haemophilus influenzae* (natural intermediate susceptibility; including β-lactamase-positive strains)
-*Moraxella catarrhalis* (including ß-lactamase-positive strains)
-*Streptococcus. pyogenes* (susceptible to macrolides or resistant to macrolides by the presence of *mef*(A)or *erm*(TR) genes, but not high-level erythromycin A resistant *erm*(B) positive strains.
-Atypical and intracellular pathogens *C. pneumoniae, M. pneumoniae,* and *L. pneumophila.*

Streptococcus pneumoniae

S. pneumoniae resistance to telithromycin is less than 1% worldwide, including Europe, and there is currently no trend towards an increase of resistance. In contrast to the macrolides, telithromycin binds tightly to 2 sites on the ribosome, domains II and V of the 23S rRNA on the 50S subunit and is therefore active against bacteria that harbour a macrolide-lincosamide-streptogramin$_B$ (MLS_B)-inducible type of resistance and does not induce MLS_B resistance *in vitro*. Telithromycin is active *in vitro* against *S. pneumoniae* resistant to the macrolides via an efflux mechanism (*mef*(A)) or via methylation (*erm*(B)), including strains with multiple mechanisms of resistance to macrolides, ie, *erm*(B) + *mef*(A). The compound demonstrates concentration-dependent bactericidal activity against *S. pneumoniae* unlike most macrolides.

The activity of telithromycin against *S. pneumoniae* is regularly monitored by the worldwide PROTEKT program. The *in vitro* activity of telithromycin and other antibiotics commonly prescribed for RTIs on *S. pneumoniae* of various phenotypes of resistance is described in Table 2.

Table 2 - PROTEKT Global: Antibiotic activity against *Streptococcus pneumoniae*, 2003-2004

	all SP	PEN-R SP	ERY-R SP	MDRSP	XDR SP
Number of strains	7083	1696	2638	2833	727
TEL					
MIC_{90} (mg/L)	0.25	0.5	0.5	0.5	0.5
TEL-R, %	0.1	0.4	0.3	0.3	0.6
AZI					
MIC_{90} (mg/L)	≥128	≥128	≥128	≥128	≥128
AZI-R, %	37.1	77.7	99.3	82.6	99.3
AMC					
MIC_{90} (mg/L)	2	≥ 8	4	≥ 8	≥ 8
AMC-R, %	4	16.9	8.4	10.1	25.4
CEF					
MIC_{90} (mg/L)	8	≥ 16	8	8	≥ 16
CEF-R, %	28.7	99.9	60.2	70.5	100
LEV					
MIC_{90} (mg/L)	1	1	1	1	1
LEV-R, %	0.9	1.7	1.6	1.8	3.9

SP=*Streptococcus pneumoniae*; PEN-I=penicillin intermediately-resistant; PEN-R=penicillin-resistant; ERY-R=erythromycin-resistant; TEL-R=telithromycin-resistant; AZI-R=azithromycin-resistant; AMC-R=amoxicillin-clavulanic acid-resistant; CEF-R=cefuroxime-resistant; LEV-R=levofloxacin-resistant. MDRSP=multidrug-resistant *S. pneumoniae* (resistance to ≥antibacterial classes, with penicillin, cefuroxime, erythromycin, tetracycline, cotrimoxazole, and levofloxacin being the class representatives); XDR=extended drug resistance (ie, *S. pneumoniae* isolates that are resistant to 5 or 6 classes of antibacterials).

Haemophilus influenzae

Telithromycin has been shown to have moderate activity against *H. influenzae*. There is no signal of an increase in the prevalence of strains with high-level resistance. Telithromycin activity is not affected by β-lactamase production or other resistance mechanisms of resistance to β-lactams.

Table 2 - PROTEKT Global: Antibiotic activity against *Haemophilus influenzae*, Year 5

	Year 1	Year 2	Year 3	Year 4	Year 5
No. of *Haemophilus influenzae*	2986	3133	4294	4457	2834
TEL					
MIC_{90} (mg/L)	2	2	2	2	2
AZI					
MIC_{90} (mg/L)	2	2	2	2	2
AMC					
MIC_{90} (mg/L)	1	1	1	2	2
CEF					
MIC_{90} (mg/L)	2	2	2	2	4
LEV					
MIC_{90} (mg/L)	0.015	0.015	0.015	0.03	0.03

Year 5=2003-2004.

Streptococcus pyogenes

Telithromycin has been shown to have a good activity against *S. pyogenes.* Cross-resistance occurs between telithromycin and high-level erythromycin A resistant strains carrying the *erm*(B) gene, which represents 0 to 14% of the macrolide resistant genotypes in Europe.

Prevalence of *S. pyogenes* resistant to penicillin, macrolides and telithromycin in European countries that participated to Protekt Global year 5

Country	Ery R	Azi R	Clari R	Tel R
Austria	0.00%	0.00%	0.00%	0.00%
Belgium	16.13%	16.13%	16.13%	9.68%
Bulgaria	16.67%	16.67%	16.67%	0.00%
Czech Republic	7.89%	7.89%	7.89%	5.26%
Finland	0.00%	0.00%	0.00%	0.00%
France	18.18%	18.18%	18.18%	13.64%
Germany	8.45%	8.45%	8.45%	1.41%
Greece	6.06%	6.06%	6.06%	0.00%
Hungary	12.50%	12.50%	12.50%	8.33%
Ireland	0.00%	0.00%	0.00%	0.00%
Italy	48.15%	48.15%	48.15%	27.78%
Netherlands	0.00%	0.00%	0.00%	0.00%
Poland	0.00%	0.00%	0.00%	0.00%
Portugal	0.00%	0.00%	0.00%	0.00%
Slovak Republic	18.75%	18.75%	18.75%	6.25%
Spain	26.92%	26.92%	26.92%	1.92%
Sweden	0.00%	0.00%	0.00%	0.00%
United Kingdom	0.00%	0.00%	0.00%	0.00%

Ery : erythromycin, Azi : azithromycin, Clari : clarithromycin, Tel : telithromycin

Telithromycin's weak *in vitro* activity against enteric Gram-negative flora makes it less likely than fluoroquinolones or β-lactams to contribute to the development of clinically significant antibiotic resistance among enteric pathogens of concern.

Discussion:

Decreased susceptibility to beta-lactam and macrolide agents in *S. pneumoniae* and *H. influenzae* may complicate the treatment of CAP, AECB and ABS, although resistance rates vary substantially between different European countries. This is of particular importance in the indication CAP, where the benefit of antibiotic treatment is undoubtedly demonstrated, and in countries and regions where resistance rates are high. Notably, although susceptibility rates among clinical *S. pneumoniae* strains to telithromycin remain very high in the European countries and that *in vitro* and clinical data indicate that telithromycin should overcome erythromycin resistance in *S. pneumoniae*, there seems to be a significant although week cross-resistance with the macrolides. MIC_{90} for the EryS phenotypes have previously been estimated to 0.03 mg/l, compared to 0.5 mg/l for the EryM and MLSB phenotypes, indicating a mechanism of cross-resistance, although additional genetic events seem to be required for clinically significant resistance to telithromycin to occur. In vitro results have shown that telithromycin is affected by the erythromycin *erm*(B) and *mef*A related resistance mechanisms but to lesser extent than erythromycin. While exposure to telithromycin can select for pneumococcal mutants with increased MICs, the MICs seem to remain within the proposed susceptibility range. There is no cross- or co-resistance between telithromycin and beta-lactam resistance in *Streptococcus pneumoniae*.

Telithromycin exhibits a natural intermediate *in vitro* activity against clinical *H. influenzae* strains, and clinical efficacy has been demonstrated for susceptible strains in the approved indications. A certain degree of cross-resistance between telithromycin and erythromycin has been shown, as telithromycin resistant strains are most often also resistant to erythromycin. Beta-lactamase production or ampicillin resistance per se in *H. influenzae* clinical strains has no impact on the telithromycin MIC distribution.

Tonsillitis/pharyngitis is commonly treated with penicillin, due to 100% susceptibility among *S. pyogenes*, unless beta-lactams are considered inappropriate due to hypersensitivity. For *S. pyogenes*, cross-resistance occurs between telithromycin and high-level erythromycin A resistant strains carrying the *erm*(B) gene**.**

Many antimicrobial agents, including telithromycin, macrolides and several beta-lactam agents, reach significantly concentrations in the intestines and may consequently have an impact on the normal microflora and select for resistant strains and resistance genes. Telithromycin has been shown to cause moderate quantitative disturbances and selection of resistant Bacteroides spp in the normal intestinal microflora comparable to those associated with clarithromycin administration. In contrast to clarithromycin, telithromycin was not associated with selection of highly resistant oral streptococci, intestinal Enterobacteriaceae or Enterococcus spp. during the administration period, indicating a more favourable ecological profile of telithromycin, most probable associated with its more narrow antibacterial spectrum.

According to *in vitro* susceptibility data and current knowledge about resistance rates and resistant mechanisms, telithromycin may offer an advantage to conventional macrolides in the treatment of respiratory tract infections when resistance against conventional macrolides in *S. pneumoniae* is suspected and when beta-lactams are not the drugs of choice due to resistance or hypersensitivity.

1.2.3 Summary of clinical efficacy data of telithromycin supporting the benefits of the agent

Sixteen Phase III studies were conducted world-wide which supported the 4 EU-approved indications; 12 double-blind comparative trials and 4 open label noncomparative trials. The pivotal active-comparator, noninferiority study designs were consistent with regulatory guidelines. For all comparative studies the primary efficacy analysis was based on clinical outcome (cure) at the post-therapy/test of cure visit (TOC, Visit 3) in the per protocol (PPc) population, except in tonsillitis-pharyngitis where the main analyses were the bacteriological outcome at TOC. In all Phase III studies, telithromycin was administered as an oral dose of 800 mg once daily. The prespecified noninferiority margins were consistent with the available FDA guidances, accepting a delta of 15 % in the comparative studies for CAP, AECB, ABS, and T/P. In addition, the guidance for T/P included a minimal cure rate of 85 % for success. The final data for all studies, except two, had a lower bound of the confidence interval above -10 %. The two exceptions were Study 3009 for CAP, which was terminated early due to safety considerations for the comparator (trovafloxacin) and Study 3004 for T/P that was intended to be supportive to the larger study 3008 for the T/P indication.

Community-Acquired Pneumonia (CAP)

The effectiveness of 800 mg of telithromycin administered once daily for 7-10 days in the treatment of CAP, evaluated in 4 Phase III double blind and 4 Phase III open label clinical studies, are summarised in Table 3:

Table 3 - CAP: Clinical cure rates by study for telithromycin and comparator(s) at posttherapy/test of cure

	Telithromycin			Comparator(s)			Difference95% CI[a]
	N	n	(%)	N	n	(%)	
PPc population							
Study A3001	149	141	(94.6)	152	137	(90.1)	4.50% [-2.1; 11.1]
Study A3006	162	143	(88.3)	156	138	(88.5)	-0.19% [-7.8; 7. 5]
A3009 *	80	72	(90.0)	86	81	(94.2)	-4.19% [-13.9; 5.2]
Study A4003 TEL 7 d	159	142	(89.3)	146	134	(91.8)	-2.47% [-9.7; 4.7]
Study A4003 TEL 5 d	161	143	(88.8)	146	134	(91.8)	-2.96% [-10.18; 4.26]
Comparative CAP pooled [b]	*552*	*499*	*(90.4)*	*540*	*490*	*(90.7)*	*-0.34%* [-4.0; 3.3]
Study A3000	197	183	(92.9)				
Study A3009OL	187	175	(93.6)				
Study A3010	357	332	(93.0)				
Study A3012	723	646	(89.3)				
All CAP studies TEL 7 to 10 d	*2016*	*1835*	*(91.0)*				

Population definitions: mITT=modified intent-to-treat; PPc=clinically evaluable per protocol; bmITT=bacteriologically evaluable modified intent-to-treat; PPb=bacteriologically evaluable per protocol; N=number of subjects; n=number clinically cured.
a 95% confidence interval of the difference in cure rates between the treatment groups.
b Excluding the 5-day treatment group.
* Study terminated early.
Comparators: A3001 amoxicillin, A3006 clarithromycin, A3009 trovafloxacin, A4003 clarithromycin.

In addition, 3 Phase IV studies confirmed the high clinical efficacy of telithromycin in CAP, with a trend for superior efficacy in one study, where telithromycin was tested against the locally prescribed regimen in countries with high levels of antibiotic resistance:

Table 4 - Clinical cure rates at posttherapy/test of cure – Superiority study A4015

mITT population	Telithromycin			Comparator group (usual care)			95% CI[a]
	N	n	(%)	N	n	(%)	
CAP Study A4015	242	208	86.0%	240	189	78.8%	[0.4; 14.0]*[f]

[a] 95% confidence interval of the difference in cure rates between the treatment groups;
* statistically significant difference Chi_2=4.301 p=0.0381

Acute exacerbation of chronic bronchitis
The result of 3 Phase III studies on clinical effectiveness of 800 mg of telithromycin administered once daily for 5 days in the treatment of AECB are shown in Table 5:

Table 5 - AECB: Clinical cure rates by study for telithromycin and comparator(s) at posttherapy/TOC, PPc population

	Telithromycin			Comparators			95% CI[a]
	N	n	(%)	N	n	(%)	
PPc population							
Study A3003	115	99	(86.1)	112	92	(82.1)	[-6.4; 14.3]
Study A3007	140	121	(86.4)	142	118	(81.1)	[-5.8; 12.4]
Study A3013	225	193	(85.8)	231	206	(89.2)	[-9.9; 1.1]
All AECB	480	413	(86.0)	485	416	(85.8)	[-4.3; 4.9]

N=number of subjects; n=number clinically cured
[a]95% confidence interval of the difference in cure rates between the treatment groups.
Comparators: A3003 amoxicillin-clavulanic acid, A3007 cefuroxime, A3013 clarithromycin

In addition, four controlled Phase IV studies confirmed the clinical efficacy of telithromycin for the treatment of AECB in adults. In one of these, the results showed that the rate of patients who were carriers of a penicillin or macrolide-resistant *S. pneumoniae* (penicillin- or erythromycin-resistant *S. pneumoniae* [PERSp]) at the TOC visit was significantly lower in the telithromycin group than in the azithromycin group but not different from cefuroxime.

Table 6 - Primary endpoint: Percentage of patients harboring a PERSp at test of cure visit among patients with Streptococcus pneumoniae at inclusion - Stringent Sp mITT population

Stringent Sp mITT population	Telithromycin			Azithromycin			Cefuroxime			Telithromycin versus Azithromycin	Telithromycin versus Cefuroxime
	N	n	(%)	N	n	(%)	N	n	(%)		
PERSp at test of cure	177	23	12.99%	106	30	28.30%	130	17	13.08%	Adjusted test = 0,0142 Significant difference	Adjusted test = 0,6117

Furthermore, it was also shown that in vitro resistance to macrolides was associated with a worse clinical outcome in AECB patients treated with a macrolide (azithromycin).

Acute bacterial sinusitis

The clinical and bacteriologic effectiveness of 800 mg oral telithromycin administered once daily for 5 or 10 days in the treatment of ABS was evaluated in 3 comparative studies.

Table 7 - ABS: Clinical cure rates by study at posttherapy/ test of cure, PPc population

	Telithromycin						Comparators			Difference	95% CI[a]
	5-day			10-day			10-day				
	N	n	(%)	N	n	(%)	N	n	(%)		
PPc population											
Study A3005	146	110	(75.3)	140	102	(72.9)	137	102	(74.5)	0.89%	[-9,9;11.7][a]
Study A3011	189	161	(85.2)	NA			89	73	(82.0)	1.16%	[-7.1;13.4]
All ABS randomized controlled studies	*335*	*271*	*(80.9)*				*226*	*175*	*(77.4)*	*3.46%*	[-3.8; 0.7]
Study A3002	123	112	(91.1)	133	121	(91.0)	NA				

Comparators= 5- vs. 10-days duration of telithromycin (A3002), amoxicillin-clavulanic acid (Study A3005), and cefuroxime axetil (Study A3011).
NA=not applicable; ABS=acute sinusitis; N=number of subjects; n=number of clinically cured.
[a] Pair wise comparison between 5-day telithromycin regimen and 10-day comparator regimen.

In 3 Phase IV randomized controlled studies performed in the ABS indication in adults, it was shown that telithromycin was non-inferior to moxifloxacin, high dosage amoxicillin-clavulanic acid (875/125 mg bid) and amoxicillin-clavulanic acid (500/125mg tid). Time to symptom resolution, which was evaluated in two of the studies using a 5-item symptom score, was shown to be similar between telithromycin and moxifloxacin, and shorter with telithromycin than high-dose amoxicillin-clavulanic acid (median time 4.0 vs. 5.0 days).

Tonsillitis/Pharyngitis in adults and adolescents

Two Phase III studies demonstrated the effectiveness of oral telithromycin 800 mg administered once daily for 5 days for the treatment of Group A β-hemolytic streptococcal (GABHS) T/P infection in adults, relative to 10 days of therapy with penicillin or clarithromycin.

Table 8 - Tonsillitis/pharyngitis: Satisfactory bacteriological outcome by study for telithromycin and comparator(s) at posttherapy/test of cure

Study	Telithromycin			Comparators			95% CI [a]
	N	n	(%)	N	n	(%)	
PP population							
Study 3004	115	97	(84.3)	119	106	(89.1)	[-14.3; 4.8]
Study 3008	150	137	(91.3)	135	119	(88.1)	[-4.6; 11.0]
Combined	265	234	(88.3)	254	225	(88.6)	[-6.2; 5.6]

Comparators= 10-days duration of penicillin (A3004) or clarithromycin (Study A3008).
a95% confidence interval of the difference in cure rates between the treatment groups

Very limited data have been obtained in subjects with *S. pyogenes* resistant to erythromycin in these studies. The limited data do not allow correlation between bacteriological outcome and a particular type of resistance gene at TOC, 3 subjects treated with telithromycin were bacteriologically eradicated and 8 persisted, presumed persisted or recurred. At Late Posttherapy Visit (LPTV) 6/11 were eradicated. This compared to 8/9 eradicated at TOC and LPTV for penicillin and 0/4 at TOC and LPTV for clarithromycin.

No phase IV clinical trial has been conducted in T/P.

Discussion:
The clinical efficacy of telithromycin in the treatment of mild to moderate CAP, AECB and ABS in adults has been clearly demonstrated in a number of Phase III clinical trials. These studies were the basis for the original approval of these indications. Efficacy was also observed in limited subpopulations at risk, such as elderly adults, patients with pneumococcal bacteremia in CAP, as well as in subjects with penicillin- or macrolide-resistant *S. pneumoniae* or multidrug-resistant *S. pneumoniae* (ie, resistant to ≥2 or more classes of antibacterial agents). In addition, the clinical efficacy of telithromycin for the treatment of CAP was confirmed in 3 Phase IV studies. One of these demonstrated a trend for superior efficacy of telithromycin, where the study drug was tested against the locally prescribed regimen in countries with high levels of antibiotic resistance. In addition, the efficacy of telithromycin, as a second line treatment, for T/P in adolescents and adults was sufficiently demonstrated in one pivotal study (vs. clarithromycin) and in one supportive study (vs. penicillin).

1.2.4 An overall and by indication summary of the risks associated with telithromycin

The estimated worldwide-marketed exposure to telithromycin through December 2006 is approximately 30.05 million courses of treatment.
The risk profile of telithromycin, including rare events of concern with antibiotics approved in the same indications, has been thoroughly examined with clinical trials, intensified monitoring, and postmarketing surveillance. Changes have been made to the safety sections of Levviax labelling in Europe in 2006. They were either proposed by Sanofi-Aventis or requested by the EMEA/CHMP in the course of reviewing the 5-year renewal application and/or other procedures (eg, labelling variations, Periodic Safety Update Reports, Follow-up Measures, requests for additional information). Changes to the safety parts of the European Summary of Product Characteristics (SmPC) made in 2006 included information related to hepatic adverse events (AEs), exacerbation of myasthenia gravis, vertigo, and QT/QTc prolongation.
During the course of clinical development, several safety topics were identified as potential adverse events of special interest (AESIs) based upon consideration of known effects of the related macrolide class of drugs and review of preclinical, clinical pharmacology and/or clinical data. The combination of recognized macrolide class drug effects and preclinical findings led to close monitoring of hepatic and cardiac adverse events during clinical trials and the execution of specific clinical pharmacology investigations. Visual effects were identified during the comparative clinical trials, leading to the subsequent performance of targeted preclinical and clinical pharmacology investigations. In addition, in the postmarketing phase, association of telithromycin with exacerbation of myasthenia Gravis and syncope were reported.

1.2.4.1 Pooled Phase III studies
The adverse event (AE) profile of telithromycin has been examined in 4780 telithromycin-treated (2702 from comparative studies and 2078 from open label studies) and 2139 comparator-treated subjects in Phase III pivotal efficacy and safety studies. In addition, 12,159 subjects in the telithromycin treatment group of Study A3014 were evaluated for safely. Study A3014 was submitted and reviewed by the CHMP in 2002 in the context of a clinical Follow-Up Measure.
The vast majority of treatment emergent adverse events (TEAEs) associated with telithromycin were of mild to moderate intensity and are related to the gastrointestinal tract, with diarrhoea being the most common AE. The incidence of serious adverse events (SAEs) was similar in both telithromycin and comparator treated groups.

Hepatic adverse events
Evaluation of hepatic effects in all Phase III studies included detailed review of hepatic laboratory values and hepatic AEs. Hepatic laboratory values (such as combined total bilirubin and ALT increases and clinically noteworthy abnormal laboratory values for ALT and AST) were balanced between telithromycin and comparators, and the incidence of hepatic AEs was similar between treatment groups. No cases of drug-related fulminant hepatitis, hepatic failure, liver transplant, or primary hepatic death were observed in Phase III investigations.

Cardiac adverse events
Extensive ECG and AE analyses in Phase I and Phase III studies demonstrated no significant difference from comparators. At therapeutic dose, electrocardiographic analyses in the clinical development program revealed a minimal increase of 1.5 milliseconds in the QTc interval (corrected for heart rate by the Bazett formula). QTc outlier values were uncommon and similar in frequency to those seen with clarithromycin and non-macrolide antibiotics. No excess in risk for significant QTc interval prolongation was noted, including at-risk populations. Similarly, cardiac AEs and death rates are also comparable between telithromycin and comparators.

Visual adverse events
During clinical trials, the review of clinical AE data in controlled studies revealed the incidence of visual TEAEs was higher in the telithromycin-treated than in the comparator-treated groups (1.1% vs. 0.4%). Blurred vision was the most commonly reported visual AE and was generally mild or moderate in severity, transient, and reversible. The effect typically had a short duration (2 to 3 hours). This AE was further evaluated through 2 clinical pharmacology studies to investigate potential mechanisms. These 2 clinical trials were reported in the initial MAA. Based on the clinical descriptions and objective findings from these 2 studies, the mechanism for the reported blurred vision is most consistent with a transient effect on the ciliary body delaying relaxation of the lens and hence accommodation. Importantly, potentially more serious and irreversible causes, such as retinal toxicity or angle closure glaucoma, have been excluded.

Syncope
There were 6 syncope cases in Phase III studies which were balanced between telithromycin and comparator groups. None was considered related by the Investigator.

1.2.4.2 Pooled Phase III studies by indication

Treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) derived from 12 controlled Phase III studies as well as open label studies are shown by indication in the table 9 below.

Table 9 - Treatment-emergent adverse events and serious adverse events by indication

	TEAEs			SAEs		
	TEL n (%)	Comp n(%)	Open label n (%)	TEL n (%)	Comp n (%)	Open Label
CAP	484 (52.8)	352 (48.7)	624 (35.8)	34 (3.7)	38 (5.3)	65 (3.7)
AECB	248 (40.7)	301 (48.1)	0	13 (2.1)	16 (2.6)	0
AS	392 (52.3)	182 (49.7)	114 (34.2)	7 (0.9)	2 (0.5)	4 (1.2)
T/P	224 (52.5)	200 (47.2)	0	5 (1.2)	5 (1.2)	0

Adverse effects of special interests (AESI) (hepatic, cardiac, visual events and syncope) were collected and pooled by indication and are outlined in the following tables 10 and 11.

Hepatic events occurred more frequently (in both treatment groups) in patients treated for CAP vs. other indications. Of note, there was a slightly higher incidence of hepatic events in the telithromycin group for the AS indication (1.7% vs. 0.5%). A majority of these events were reported as liver function abnormalities and none were serious.

Table 10 - Adverse events of special interest by indication: Hepatic adverse events

	TEL N n (%)	Comparators N n (%)	Open label N n (%)
CAP	N: 916	N: 723	N: 1745
	45 (4.9)	33 (4.6)	50 (2.9)
AECB	N: 609	N: 626	0
	9 (1.5)	12 (1.9)	
AS	N: 750	N: 366	N: 333
	13 (1.7)	2 (0.5)	14 (4.2)
T/P	N: 427	N; 424	0
	7 (1.6)	12 (2.8)	

Cardiac AESIs were balanced between telithromycin and comparators within each indication. There was no cardiac AE case in the T/P indication.

Table 11 - Adverse events of special interest by indication: Cardiac adverse events

	TEL N n (%)	Comparators N n (%)	Open label N n (%)
CAP	N: 916	N: 723	N: 1745
	4 (0.4)	3 (0.4)	1 (0.1)
AECB	N: 609	N: 626	0
	1 (0.2)	3 (0.5)	
AS	N: 750	N: 366	N: 333
	0	1 (0.3)	2 (0.6)
T/P	N: 427	N: 424	N: 0
	0	0	0

The incidence of visual AEs was generally higher in the telithromycin treated groups.

Table 12 - Adverse events of special interest by indication: Visual adverse events

	TEL N n (%)	Comparators N n (%)	Open label N n (%)
CAP	N: 916	N: 723	N: 1745
	11 (1.2)	4 (0.6)	9 (0.5)
AECB	N: 609	N: 626	0
	1 (0.2)	2 (0.3)	
AS	N: 750	N: 366	N: 333
	9 (1.2)	3 (0.8)	1 (0.3)
T/P	N: 427	N:424	0
	9 (2.1)	0	

None of the syncope AE cases in Phase III studies was considered related to study drug by the Investigator.

Table 13 - Adverse events of special interest by indication: Syncope/loss of consciousness

	TEL N n (%)	Comparators N n (%)
CAP	N: 916	N: 723
	2 (0.2)	2 (0.3)
AECB	N: 609	N: 626
	1 (0.2)	0
AS	N: 750	N: 366
	0	1 (0.3)
T/P	N: 427	N: 424
	0	0

1.2.4.3 Pooled Phase IV studies by indication

Overall, Phase IV safety data did not reveal any new safety signals as compared to Phase III studies.

Table 14 - Treatment-emergent adverse events and serious adverse events by indication in 10 Phase IV controlled studies

	TEAEs				SAEs			
	Telithromycin		Comparator		Telithromycin		Comparator	
indication	n/N of patients	%	n/N of patients	%	n/N of patients	%	n/N of patients	%
CAP	168/404	41.6	179/398	45.0	27/404	6.7	33/398	8.3
AECB	323/2132	15.2	321/2802	11.5	34/2132	1.6	28/2802	1.0
ABS	149/565	26.4	145/579	25.0	2/565	0.4	2/579	0.3

Comparator: amoxicillin, amoxicillin/clavulanic acid, azithromycin, cefaclor, cefixime, cefpodoxime, cefuroxime, clarithromycin, gatifloxacin, levofloxacin, moxifloxacin, roxithromycin, sultamycillin/tosylate

The incidence of **hepatic AEs** was similar between treatment groups and more frequent in the CAP studies, as expected. No cases of drug-related fulminant hepatitis, hepatic failure, liver transplant, or primary hepatic death were observed in Phase IV studies.

Table 15 - Adverse events of special interest by indication in phase IV controlled studies: Hepatic adverse events

	Telithromycin		Comparator	
indication	n/N of patients	%	n/N of patients	%
CAP	12/404	3.0	13/398	3.3
AECB	1/2132	0.0	0/2802	0.0
ABS	0/565	0.0	1/579	0.2

Five **cardiac AEs** were recorded in Phase IV studies, 4 in telithromycin treated patients, evenly distributed among indications (CAP n=2; AECB n=1; ABS n=1) and 1 in a CAP patient in the comparator group.

As in phase III, **visual AEs** were more frequently reported in the telithromycin group. Blurred vision was the most commonly reported visual AE and was reversible, transient and generally mild or moderate in severity.

Table 16 - Adverse events of special interest by indication in phase IV controlled studies: Visual adverse events

	Telithromycin		Comparator	
indication	n/N of patients	%	n/N of patients	%
CAP	3/404	0.7	0/398	0.0
AECB	9/2132	0.4	4/2802	0.1
ABS	7/565	1.2	1/579	0.2

The number of syncopal events reported in Phase IV was numerically higher for telithromycin than the number reported for the comparators, although few in number. Syncopes were all of mild or moderate intensity and all subjects recovered without sequelae.

Table 17 - Adverse events of special interest by indication in phase IV controlled studies: Syncope/Loss of consciousness

	Telithromycin		Comparator	
indication	n/N of patients	%	n/N of patients	%
CAP	0/404	0.0	1/398 [a]	0.2
AECB	4/2132 [b]	0.1	1/2802 [c]	0.0
ABS	0/565	0.0	0/579	0.0

[a] mild syncope not related to ciprofloxacin

[b] 2 were moderate lipothymia possibly related to telithromycin and 2 were mild syncopes considered not related to telithromycin by the investigtor, of which one occured in a context of sub acute-bacterial endocarditis of aortic valve & microemboli

c severe vasovagual syncope possibly related to azithromycin

1.2.4.4 Postmarketing safety data

Postmarketing safety data from an estimated marketed exposure to telithromycin of 30.05 million courses of treatment (as of December 31, 2006), including approximately 14 million courses in Europe support the safety profile observed in clinical trials and have detected very rare or rare adverse events. Particular attention has been given to the evaluation of postmarketing reports of hepatic, cardiac, and visual AEs throughout the post-marketing period. Among the most commonly reported AEs were gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, abdominal pain), visual events, headache, dizziness, and allergic events (eg, rash, urticaria).

Exacerbations of myasthenia gravis

The postmarketing data identified exacerbation of myasthenia gravis as an important and rare AE in patients treated with telithromycin. Exacerbations of myasthenia gravis have also been reported in association with several other classes of drugs, including the macrolides, β-lactams, fluoroquinolones, and aminoglycosides. Given the severity of some of the exacerbation reported, a warning was added to the telithromycin labelling in April 2003 in the context of an urgent safety restriction procedure. The MAH proposed to contra-indicate telithromycin in this patient population (see 3.2 Proposals for Risk Minimisation Measures).

Discussion:
The CHMP endorses the proposed contraindication of patients with myasthenia gravis. Consequentially, the statement concerning this population in section 4.4 should be revised accordingly.

Syncope
Reports of syncope (reported primarily in Japan) led to another product information update. Detailed analysis of the reports suggested that some of the reports could be linked to a secondary vasovagal mechanism occurring in conjunction with gastrointestinal AEs, which were the most common AE noted in clinical trials. There was no evidence for a cardiac arrhythmic aetiology for syncope, consistent with prior clinical study QTc analyses.

Discussion:
The MAH proposed to update sections 4.4 and 4.7 regarding the risks for loss of consciousness. This updated is endorsed by the CHMP.

Other rare events added to the labelling in the post-marketing period
Other adverse drug reactions (ie, angioedema, anaphylaxis, pancreatitis, and palpitations) have been reported and have been added to the labelling for telithromycin.

Hepatic adverse events
There have been several changes made to the SPC regarding the hepatic safety of telithromycin, including multiple revisions in 2006. Among the 16 cases of acute liver failure reported worldwide (as of 15 September 2006): 12 cases have been reported in the US (most of them in 2006), 2 in France (one in 2002 and one in 2005, both unlikely/unrelated to the use of Levviax) and 2 in Japan (both in 2004, unlikely related to the use of Levviax) raising the question of causality and the stimulating effect of the publication in *Annals of Internal Medicine* of January 20, 2006 on the reporting rates especially in the US. Notably, no new cases of acute liver failure (ALF) have been reported in neither Europe nor Japan since the date of this article. In the vast majority of the cases, when the relevant information was available, it was not possible to establish a causal relationship between the ALF and the administration of telithromycin, the cases being confounded by an underlying disease involving the liver, like sepsis, severe circulatory failure, or cardiac failure.
A spontaneous reporting rate analysis was also conducted using the FDA AERS database via Freedom of Information (FOI). The reporting rate of hepatic events appeared to be higher following telithromycin use than those following other antibiotics use. These differences might be partly explained by secular trend of increased spontaneous AE reporting in recent years, the inherent limitations of the AERS database, and the known Weber effect following the publication in Annals of Internal Medicine in early 2006. Nonetheless, this analysis generated a hypothesis that required further evaluation. Therefore, 2 epidemiologic studies were proposed and performed in order to better evaluate the risk of severe hepatic injury among telithromycin users comparing to those following use of comparator antibiotics with similar indications. These 2 epidemiologic studies were based on the independent data sources, the PHARMetrics Integrated Outcome Database and the Ingenix proprietary research database, representing data from over 24 million individual subscribers enrolled in the respective health plans. Each study included more than 100,000 telithromycin patients with a total of more than 227,000 patients. The results of the two independent epidemiologic studies indicate that the risk of severe hepatic injury associated with telithromycin use is comparable with that experienced by other antibiotics with similar indications. The cases of severe hepatic injury identified from the Ingenix database were further validated by medical record review. Following validation, the study confirmed that the risk of severe liver injury is very rare, with no case of ALF identified within 60 days following prescription of telithromycin, whereas there were two cases of ALF following clarithromycin use. Based on the review of currently available clinical and epidemiologic data, including the 2 epidemiologic studies, there is no evidence that the risk of hepatotoxicity with telithromycin is more frequent or more severe than that with other marketed antibiotics used in the treatment of RTIs, including macrolides.

Discussion:
The CHMP considered that these statements are in line with the assessment of FUM 026.6 on hepatic safety, November 2006, in which data on hepatic related adverse events from 11 Phase III studies, one additional large safety study, six post marketing randomized controlled trials, and preliminary data from four ongoing studies, were assayed for each individual comparator. Safety data concerning treatment emerging adverse events in the MedDRA primary SOC "Hepatobiliary disorders," High Level Term (HLT) "Liver function analyses," and Preferred terms (PTs) "Blood alkaline phosphatase increased," and "Blood lactate dehydrogenase increased" were identified and reported. Two SAEs were identified for telithromycin in phase III studies, both recorded as 'Hepatocellular damage'. Both events were judged to be possibly related to study medication and subjects recovered without sequaelae. There was a numerically higher rate of Hepatocellular disorders SOC adverse events reported for telithromycin compared to comparators, 8 (0.3%) vs. 2 (0.1%), but the numerators were very small. Events related to liver related events in Laboratory Investigation SOC were similar between telithromycin and comparators 54/2 702 (2.0%) vs. 41/2 139 (1.9%). No specific liver-related AEs that were markedly more common for telithromycin treated subjects compared to comparator treated subjects could be identified. The CHMP came to the conclusion for this clinical FUM that the submitted data indicated that the risk for liver related adverse events for telithromycin is comparable to that of other macrolides, like clarithromycin. According to pooled data from the double-blinded phase III studies, hepatic safety profile could be graded regarding liver-related TEAEs as follows: cefuroxime (0.3%), amoxi-clavulanate (1.0%), trovafloxacin (1.8%), clarithromycin (2.0%), telithromycin (2.0%), penicillin (4.6%) and amoxicillin (7.3%). Caution should be exercised when interpreting these figures due to relatively small numerators and denumerators in some of the studies. Notably, there was a numerical difference concerning serious liver related adverse events in total.

Cardiac adverse events
"QT/QTc interval prolongation" was added to the post-marketing subsection of the undesirable effects in the European SPC in the context of a type II variation (II/39) adopted in 2006 for sake of consistency with Warnings and Precaution section and not due to a new post-marketing safety signal.

Discussion:
No new signals for cardiac adverse events, requiring an update in the SPC, were identified. This issue should continue to be monitored within the PSURs.

Visual adverse events
Postmarketing surveillance has identified isolated reports of transient blindness or amaurosis; however, with the exception of an unrelated temporal arteritis case, these reports were not confirmed on expert ophthalmology examination, and all of these unconfirmed reports were fully reversible.

Discussion:
The MAH proposed to update sections 4.4 and 4.7 of the SPC regarding the risks for visual disturbances. This proposal is endorsed by the CHMP.

1.2.5 CHMP's overall assessment on possible risks associated with telithromycin:

The MAH has submitted an analysis of adverse events in general and of adverse events of special interest (hepatic, cardiac and visual adverse events and syncope) by indication, collected in Phase III studies. The safety profile of Levviax, based on adverse events recorded from study data, has previously been assessed by the CHMP, in connection with the renewal, type II variations (35, 36, 39 and 40) and clinical follow-up measures (FUM 026) during 2006 and earlier. In all these procedures, the benefit-risk balance of Levviax has been judged positive by the CHMP in the approved indications. According to the presently submitted analyses of Phase III studies, treatment emergent hepatic adverse events in general were similar between telithromycin treated patients and the comparator group 2.74% vs. 2.76%. Cardiac adverse events and syncope were well balanced between the treatment groups. Notably, the incidence of visual adverse events, mainly blurred vision, was higher in the telithromycin treated groups in pooled Phase III studies, most evident for patients with T/P, where it was recorded in 9 of 427 patients (2.1%) vs. 0 of 424 in the comparator treated group. Analyses of pooled Phase IV studies mainly confirmed the findings in Phase III studies. No case of

drug-related fulminant hepatitis, hepatic failure, liver transplant or primary hepatic death was observed in the Phase IV studies. In accordance with the Phase III studies, visual adverse events were more common among telithromycin treated patients, most prominent for the indications ABS (1.2%) and CAP (0.7%). Two reports of possible related syncope/loss of consciousness were reported for telithromycin patients with AECB, vs. in one azithromycin treated patient with AECB.

Post-marketing safety data identified new important safety information. Exacerbation of myasthenia gravis, also including fatal outcomes, was reported for patients treated with telithromycin. This information has previously been added to section 4.4 of the SPC, and the MAH now proposes that telithromycin should be contraindicated in this patient population. In light of the severity of this condition, this addition to section 4.3 is endorsed. Syncope/loss of consciousness is currently listed as a rare adverse event in section 4.8. However, no additional warning, except for in section 4.7 is currently stated in the SPC. Concerning post-marketing data on hepatic adverse events, these have been continuously assessed during FUM26 (1-6) and the type II variation no. 40, resulting in SPC changes in sections 4.3, 4.4 and 4.8. The two epidemiological studies based on the PHARMetrics Integrated Outcome Database and the Ingenix proprietary research database, focusing hepatic safety do not indicate that telithromycin is more associated with severe hepatic injury compared to other agents used for the corresponding indications. No new signals regarding severe liver injury have been identified since the beginning of2007. Post-marketing data concerning cardiac safety and visual adverse events do not add any additional concerns not already identified in clinical studies.

The analyses of adverse events reported during Phase III and Phase IV studies, and additional information of post-marketing safety data from an estimated marketed exposure of more that 30 million courses of telithromycin treatment reveals important safety information that must be taken into consideration. Although the incidence of adverse events in general does not seem to differ significantly to the commonly used agents in RTIs, the reports of exacerbations of myasthenia gravis including fatal cases, severe hepatic events, and an imbalance in incidences of visual disturbances and cases of syncope are of concern. Several of these issues are already implemented in sections 4.3, 4.4 and 4.8 of the SPC but additional restrictions in the SPC are recommended. The available data indicate that the use of telithromycin is associated with increased risks compared to conventional macrolides and beta-lactam agents. A restriction in the recommended use of Levviax is therefore suggested, particular for the indications AECB, ABS and T/P were the anticipated benefits of telithromycin in terms of extended activity is not considered outweigh the risks in patients infected with pathogens susceptible to macrolides and/or beta-lactams.

1.2.6 Benefit-risk profile of telithromycin compared to other antibiotics

1.2.6.1 Risks associated with other groups of antibiotics

According to a recent study, antibiotics represent 18.2% of the adverse drug events treated in emergency departments in the US. Beta-lactams, particularly amoxicillin-containing agents are the most frequently involved, followed by quinolones, sulfonamide-containing agents and macrolides (Budnitz, 2006), not adjusted for the consumption of these agents.
Similarly, a review of the product information for other antibiotics used in the same indications in the EU and of available information from the FDA AERS database shows that each antibiotic has a specific benefit-risk profile with specific rare and serious associated AEs.

Beta-lactams are known to be associated with serious anaphylactic shocks, hepatotoxocity with amoxicillin-clavulanic acid, and *C. difficile* infections for the cephalosporins.

Quinolones have been associated with serious anaphylaxis, QTc prolongation, tendon rupture, seizures and pseudomembranous colitis.

Macrolides with QTc prolongation, serious liver injury, ear toxicity; adverse effects linked to CYP3A4-related drug-drug interactions (clarithromycin and erythromycin).

Besides treatment emergent adverse events, there are other risks to take into account when comparing antibiotics indicated for similar types of infections. The risks of infection-related complications due to lack of efficacy against respiratory tract pathogens, may be important, especially in regions where the

levels of resistance among RTI pathogens is significant. Furthermore, the risk for selection and enrichment of antibiotic resistance strains, both target pathogens and non-respiratory tract potential pathogens such as members of the normal microbiota. Overall, it is currently stated by several scientific bodies that shorter antibiotic regimens is recommended, in order to minimize the risk for selection of resistance.

1.2.6.2 Comparative benefit–risk profile by indication

The use of antibiotics in the various EU countries is directed by local medical practices, country-specific clinical practices guidelines for antibiotic use, often guided by the local levels of antibiotic resistance. A benefit-risk evaluation of telithromycin was provided for each of the approved indications with respect to the RTI itself and to other antibiotics approved for the treatment of these RTIs.

Community-acquired pneumonia
Community-acquired pneumonia is a RTI associated with a significant morbidity and mortality. Approximately 1 out of every 5 cases requires hospitalisation [American Thoracic Society, 2001]. The mortality rate in patients with CAP varies with the severity of disease. In the US, the mortality rate in patients with CAP is <1% in outpatients, reaching 10% in the most severe cases requiring hospitalisation. Clinical trials have provided evidence for the efficacy of telithromycin in CAP in the adult population including in a limited number of patients with risk factors such as pneumococcal bacteraemia or age over 65 years. Telithromycin is effective against the most frequent pathogens encountered in this indication, in particular *S. pneumoniae* including resistant strains and atypical pathogens.
According to the MAH, telithromycin offers an advantage versus:
Beta-lactams, by exerting activity against atypicals, *Legionella pneumophila* and multidrug resistant *S. pneumoniae*. The overall risk of telithromycin is considered to be balanced by the potential risk of lack of efficacy of this class of compounds against atypical pathogens and the safety risk of this class of compound mentioned above (anaphylaxis, hepatotoxicity, antibiotic associated diarrhoea).
Macrolides, by efficacy against *S. pneumoniae* resistant to macrolides, whatever the mechanism of resistance. The overall risk of telithromycin is considered to be balanced by the potential risk of lack of efficacy of this class of compounds against *S. pneumoniae*, the pathogen most frequently associated with morbidity and mortality and the safety risk of this class of compound mentioned above (QTc-prolongation, severe liver injury, ear toxicity and drug-drug interactions).
Quinolones by having a similar effect against antibiotic-resistant *S. pneumoniae*. The overall risk of telithromycin is considered to be balanced by the safety risk of quinolones. In addition, overuse of quinolones in the outpatients setting carries the risk of increase resistance of gram negatives to quinolones (*E. coli*, *Klebsiella spp.*) and the safety risk of this class of compound mentioned above (QTc-prolongation, tendon rupture, seizures and possible *C. difficile* infection).

Resistance of *S. pneumoniae* to tetracyclines and co-trimoxazole parallel the resistance to macrolides.

Discussion:
Community-acquired pneumonia is associated with a significant morbidity and mortality, thus the importance of appropriate treatment is evident since the risk for clinical failure may seriously affect the outcome for the patient. In light of the enhanced activity of telithromycin compared to conventional macrolides and the increasing prevalence of decreased susceptibility in the primary pathogen *S. pneumoniae*, especially to macrolides and beta-lactams, the CHMP considers that no new safety concern have been identified supporting a restriction of the current wording of this indication. Thus, telithromycin should generally remain an equal alternative to macrolides, beta-lactam agents and quinolones in CAP which do not require IV route treatment, and national official guidelines should be considered when prescribing Levviax for this indication.
The CHMP discussed the restriction of telithromycin for CAP to situations in which penicillin is contraindicated, penicillin and/or macrolide resistance is likely or atypical organisms may be the cause. Since the majority of the CHMP members considered sufficient to refer to the application of national or regional guidelines to inform the use of telithromycin in CAP this indication was not

restricted. The CHMP members that do not considered sufficient to refer to the application of national or regional guidelines to inform the use of telithromycin in CAP expressed their divergent position.

Acute exacerbation of chronic bronchitis

The curative role of antibiotics in this indication has been a matter of scientific debate. A Cochrane review of antibiotics in acute exacerbation of COPD concludes to a reduction of the short-term mortality of 77%, and a decrease of treatment failure by 53%. However, the authors mentioned that the results of the analysis should be interpreted with caution, given the lack of homogeneity of the material reviewed principally [Ram, 2006]. *S. pneumoniae* is among the most frequent pathogens observed in the early stage of this disease, compared to Gram negative bacilli *(Pseudomonas, Enterobacteriaceae)* more frequently observed at a later stage in patients with severe bronchial obstruction.

Clinical trials have provided evidence of the clinical efficacy of telithromycin in AECB, including efficacy in the most vulnerable outpatients (patients with risk factors, patients with significant bronchial obstruction).

According to the MAH, telithromycin offers an advantage versus:

Beta-lactams by exerting activity against *S. pneumoniae* resistant to penicillin and *H. influenzae* beta-lactamase producing strains (resistant to amoxicillin). The overall risk of telithromycin appears to be balanced by the potential risk of lack of efficacy of this class of compounds against these pathogens and the safety risk of this class of compound mentioned above.

Macrolides through efficacy against *S. pneumoniae* resistant to macrolides. Preliminary data obtained in this indication documents that resistance of *S. pneumoniae* has a clear impact on the clinical efficacy of a macrolide, azithromycin. The overall risk of telithromycin appears to be balanced by the potential risk of lack of efficacy of this class of compounds against *S. pneumoniae*, and the safety risks associated with this class of compounds. This is particularly true in patients with risk factors for infection due to antibiotic-resistant *S. pneumoniae*, which is common in countries with high levels of resistance to macrolides.

Telithromycin has not been compared to **quinolones** in AECB. Quinolones are highly effective drugs in this disease, but should be reserved to patients at risk for severe Gram negative infections such as patients with high degree of obstruction. Indeed, since quinolones have broad antibacterial spectrum, overuse of quinolones in the outpatients setting may promote quinolone resistance in Gram negatives and perhaps a higher risk for severe *C. difficile* infection.

Discussion:

The role of antibiotic treatment in the indication acute exacerbation of chronic bronchitis is not as evident as for the indication CAP. Several studies support the use of antibiotics for this indication but diagnosis criteria and thus the external validity in these studies are not always clear. Nevertheless CHMP can not exclude a satisfactory action of antibiotics. Telithromycin efficacy is not in question where microbiology is a concern. Considering the identified risks for telithromycin compared to those of conventional macrolides, of which the risks for serious exacerbation of myasthenia gravis and visual disturbances and possible loss of consciousness seem to be associated with an imbalance in disadvantage of telithromycin, while an increased risk for serious hepatic injury can not be excluded, a restriction in this indication is recommended.

The CHMP considers that the benefit of using telithromycin in this indication only outweighs the risks when treating infections caused by known or suspected beta-lactam and/or macrolide resistant strains covered by the antibacterial spectrum of telithromycin.

Furthermore, the CHMP considers that the prescription of this antibiotic in AECB remains of interest but should be further guided to help Healthcare Professionals to use telithromycin in situations where the benefit-risk balance is optimal. Therefore, the "history of patients" is important to consider especially regarding the recent administration of antibiotics. In fact there are several predictive factors to acquire infections due to *S. pneumoniae* with a decreased susceptibility to penicillin, specifically described for lower respiratory tract infections: prescription of beta-lactams and/or hospitalisation within three previous month period, chronic diseases (eg chronic pulmonary disease), previous medical history in respiratory disease. Moreover, the mention of "national/regional resistance data" should be added in the therapeutic indication wording, to indicate that the conditions of prescription

are related to local epidemiology. Even if AECB infections are not generally microbiological documented in clinical practice, it should be of interest to underline the reasons of the restricted therapeutic indications.

Acute bacterial sinusitis

Complications of acute sinusitis are considered to be rare, but can be serious (eg, brain abscess, meningitis).

Two recent reviews have been performed evaluating the effects of antibiotics vs. placebo in ABS, both showing some trends of better efficacy in antibiotic-treated patients, but also concluding that other studies were needed, given the insufficient documentation of the diagnosis used to enroll patients [Gwaltney et al., 2004; Williams, 2003]. The information in patients with documented bacterial infection, patients with at least 7 days of symptoms, and patients diagnosed with severe infections is scarce. Antibiotic treatment is still currently indicated in most of the ABS guidelines worldwide to prevent complications [Klossek JM, 2005].

Clinical trials have provided evidence of the clinical efficacy of telithromycin in ABS including efficacy in 5 days compared to 10 days of treatment with a variety of antibiotics – including cephalosporins, amoxicillin-clavulanic acid (normal and high-dose), and fluoroquinolone (moxifloxacin) – in the most vulnerable outpatients (subjects with documented pathogens at entry, subjects with at least 7 days of symptoms, and subjects with severe disease as per Investigators' assessment). By using a patient-related outcome (time to symptom resolution), telithromycin was shown to be non-inferior to moxifloxacin, and yielded better results than amoxicillin-clavulanic acid in 1 study. In addition, telithromycin showed a good diffusion in sinus tissue.

According to the MAH, telithromycin offers an advantage in the treatment of ABS versus:

Beta-lactams by exerting activity against *S. pneumoniae*, highly prevalent in ABS due to bacteria including those resistant to penicillin and against beta-lactamase producing *H. influenzae* strains (which are resistant to amoxicillin). The overall risk of telithromycin appears to be balanced by the potential risk of lack of efficacy of this class of compounds against these pathogens and the safety risk of this class of compound mentioned above.

M*acrolides* by activity against *S. pneumoniae* resistant to macrolides. The overall risk of telithromycin appears to be balanced by the potential risk of lack of efficacy of this class of compounds against *S. pneumoniae* and the safety risk of this class of compound mentioned above. This is particularly true in patients with risk factors of infection due to resistant *S. pneumoniae*, which is common in countries with high level of resistance to macrolides.

Quinolones by showing similar efficacy as a quinolone, moxifloxacin in clinical trial. Quinolones are highly effective drugs in this disease. However, they should be reserved to patients in case of failure of other antibiotics or in patients with risk factors of complications to avoid their overuse which may promote increased resistance. Therefore, telithromycin may play a role in sparing the overuse of quinolones in patients with ABS, particularly in those countries with high levels of *S. pneumoniae* resistance, where macrolides are not recommended by clinical practice guidelines for antibiotic use, and where alternatives to β-lactams and telithromycin are limited to fluoroquinolones (the use of which would increase in use if only β-lactams were available).

Discussion:

As for AECB, the role of antibiotic treatment in the indication acute bacterial sinusitis is not uncontroversial, since information in patients with documented bacterial infection, patients with at least 7 days of symptoms, and patients diagnosed with severe infections is scarce. Considering the identified risks for telithromycin compared to those of beta-lactam agents and of conventional macrolides, of which the risks for serious exacerbation of myasthenia gravis and visual disturbances and possible loss of consciousness seem to be associated with an imbalance in disadvantage of telithromycin, while an increased risk for serious hepatic injury can not be excluded, a restriction of this indication is recommended. The CHMP considers that the benefit of using telithromycin in ABS only outweigh the risks when treating patients where beta-lactam antibiotics are not appropriate, due to hypersensitivity or suspected beta-lactam resistance, with infections caused by known or suspected macrolide resistant strains covered by the antibacterial spectrum of telithromycin. The same considerations from AECB to introduce the "history of patients" and to mention of "national/regional resistance data" also apply.

Tonsillitis/pharyngitis

Complication of T/P due to *Streptococcus pyogenes* can be extremely serious, but are very rare in developed countries, because of the use of appropriate antibiotic treatment leading to eradication of *S. pyogenes*. Therefore it is agreed that T/P due to *S. pyogenes* should be treated with antibiotics.

In vitro, telithromycin has a better efficacy against *S. pyogenes* than conventional macrolides. Contrary to macrolides, it is active against some strains of *S. pyogenes* resistant to erythromycin, with high *in vitro* efficacy against *erm*(TR) and *mef(*A) genotypes (approximately 10% and 40% of all erythromycin resistant strains in EU, respectively), but lacks activity against *erm*(B) positive strains (2004 study report).

Telithromycin has shown efficacy in clinical trials in 5 days of treatment vs 10 days for the comparator used. In the EU trials vs. penicillin, telithromycin was numerically inferior to penicillin (but within a 15% delta in PPP, 10% delta in mITT), essentially due to lack of eradication of erythromycin resistant strains with *erm*(B) genotype. In clinical trials telithromycin appears to have a potential advantage over clarithromycin for the eradication of some strains of S. *pyogenes* resistant to macrolides although the numbers are to low to draw definitive conclusion. This is in line with a much better *in vitro* efficacy for telithromycin versus clarithromycin or azithromycin mostly on *erm*(TR) and to a lesser extend *mef*(A) erythromycin resistant strains.

Telithromycin is approved for the indication tonsillitis/pharyngitis, as an alternative, when beta-lactam antibiotics are not appropriate, such as in patients with allergy to beta-lactams. The only antibiotics used in this latter case are currently macrolides, clindamycin or telithromycin. According to the MAH, telithromycin offers an advantage in the treatment of T/P versus:

Macrolides by offering an advantage of *in vitro* efficacy against approximately half of the strains of *S. pyogenes* resistant to macrolides with *erm*(TR), and *mef*(A) genotype representing respectively 10% and 41% of macrolide resistant strains in EU (PROTEKT GLOBAL year 5). Against clarithromycin, telithromycin has the additional advantage of being effective in 5 days, which could result in a better compliance, critical to consider in young patients. The overall risk of telithromycin appears to be balanced by the potential risk of lack of efficacy of this class of compounds against *S. pyogenes* in countries with significant prevalence of *erm*(TR), and the safety risk of this class of compound mentioned above. Telithromycin has not been associated with a lower eradication rate compared to azithromycin used in 3 days treatment duration.

Telithromycin is less active than **clindamycin** against *mef*(A) strains, but has documented efficacy in 5 days and should carry less risk of *C. difficile* infections, classically linked to the use of clindamycin.

Discussion:

The rationale to use antibiotics in tonsillitis/pharyngitis is quite clear: rapid disappearance of symptoms, eradication and decrease of *S. pyogenes* spreading to the entourage, prophylaxis of rheumatic fever.

Telithromycin is currently only indicated for the treatment of T/P when beta-lactam antibiotics are not appropriate. Telithromycin efficacy though clinical trials is always considered as acceptable. In the EU trial vs. penicillin, telithromycin was numerically inferior to penicillin (but within a 15% delta in PPP, 10% delta in mITT), essentially due to lack of eradication of erythromycin resistant strains with the *erm*(B) genotype.

Considering the identified risks for telithromycin compared to those of conventional macrolides, of which the risks for serious exacerbation of myasthenia gravis and visual disturbances and possible loss of consciousness, seem to be associated with an imbalance in disadvantage of telithromycin, while an increased risk for serious hepatic injury can not be excluded, a further restriction in this indication is recommended in countries/ regions with a significant prevalence of macrolide resistance. Furthermore, telithromycin is always active against *mefA* and *ermTR S. pyogenes* although conventional macrolides can be ineffective in infections due to these bacteria.

Other antibiotic such as oral clindamycin can be active in tonsillitis due to macrolide resistant *S. pyogenes* when resistance is mediated by *mefA*, but this antibiotic is not commonly used for this indication in European countries, due to the risk for *C. difficile* infections. Consequently keeping telithromycin in this therapeutic indication is considered relevant. Thus accurate information regarding resistance data, included in the therapeutic section, should be of interest.

The CHMP considers that the benefit of using telithromycin in T/P only outweighs the risks when treating patients where beta-lactam antibiotics are not appropriate, in countries with a significant prevalence of macrolide resistant *S. pyogenes*, when mediated by *erm*(TR) or *mef*A.

1.2.7 CHMP's comments and conclusions of overall benefit-risk evaluation

The MAH has submitted a comprehensive overview of the benefits and risks of telithromycin compared to relevant alternative classes of antibiotics, and discussed these issues for each of the currently approved indications. Efficacy and safety data from clinical trials (Phase III and Phase IV) and additional safety data from two epidemiologic studies and post-marketing data, based on approximately 30 million courses of treatment through December 2006, were reviewed.
A clear benefit of telithromycin over conventional macrolides is that according to recent *in vitro* data from European surveillance studies, telithromycin still displays a high *in vitro* efficacy against *S. pneumoniae* including activity against bacteria that harbour a macrolide-lincosamide-streptogramin$_B$ (MLS_B)-inducible type of resistance and does not induce MLS_B resistance *in vitro*. Telithromycin exerts clinical relevant activity against bacteria resistant to the macrolides via an efflux mechanism (*mef*A) or via methylation (*erm*(B)), as well as against strains with multiple mechanisms of resistance to macrolides, ie, *erm*(B) + *mef*A. The compound demonstrates concentration-dependent bactericidal activity against *S. pneumoniae* unlike most macrolides. According to EARSS data from 2005, macrolide resistance in *S. pneumoniae* exceeds 20% in 10 European countries, up to 41% in France. Thus the expanded activity of telithromycin is a clear advantage in regions/countries with high resistance levels, when macrolide-related compounds are considered appropriate. Like conventional macrolides, telithromycin only exerts a moderate activity against *H. influenzae*. There is no signal of an increase in the prevalence of strains with high-level resistance. Telithromycin activity is not affected by beta-lactamase production or other resistance mechanisms of resistance to beta-lactams. Although not as active as penicillin against *S. pyogenes*, telithromycin displays a good activity against these species (susceptibility rate 96% according to the PROTECT surveillance study 2003-2004, vs 86% macrolide susceptibility). Telithromycin shows activity against low-level macrolide resistant *S. pyogenes* isolates, mediated by *mef*A, *erm*(A), and *erm*(TR), while the majority (90%) of high-level macrolide resistant strains positive for *erm*(B) (incidence 4.3%) are resistant to telithromycin.
Thus, according to *in vitro* susceptibility data and current knowledge about resistance rates and resistant mechanisms, telithromycin may offer an advantage to conventional macrolides in the treatment of respiratory tract infections when resistance against conventional macrolides is suspected and when beta-lactams are not the drugs of choice.

The clinical efficacy of telithromycin in the treatment of mild to moderate CAP, AECB and ABS in adults has been clearly demonstrated in a number of Phase III clinical trials. These studies were the basis for the original approval of these indications. Efficacy was also observed in limited subpopulations at risk, such as elderly adults, patients with pneumococcal bacteremia in CAP, as well as in subjects with penicillin- or macrolide-resistant *S. pneumoniae* or multidrug-resistant *S. pneumoniae*. In addition, one Phase IV study in CAP patients demonstrated a marginal superior efficacy of telithromycin, where the study drug was tested against the locally prescribed regimen in countries with high levels of antibiotic resistance, whereas the results of one Phase IV study in AECB patients showed that the rate of patients who were carriers of a penicillin or macrolide-resistant *S. pneumoniae* at the TOC visit was significantly lower in the telithromycin group than in the azithromycin group, but not different from cefuroxime. In addition, the efficacy of telithromycin, as a second line treatment, for T/P in adolescents and adults has been sufficiently demonstrated in one pivotal study (vs. clarithromycin) and in one supportive study (vs. penicillin). However, in the latter study there was a trend towards inferiority of telithromycin to penicillin.

The safety profile of Levviax, based on adverse events recorded from clinical study data, epidemiological studies and post-marketing reports, has previously been assessed by the CHMP, in connection with the 5 year renewal as well as during several type II variations and follow-up measures during 2006 and earlier. In Phase III trials, overall AE rates, serious AEs and discontinuation rates were similar to those observed with comparators. Most side effects are related to the gastrointestinal tract. However, the analyses of adverse events reported during Phase III and Phase IV studies, and

additional information of post-marketing safety data from an estimated marketed exposure of more than 30 million courses of telithromycin treatment reveal important safety information that must be taken into consideration. Specific adverse events have been reported with the use of telithromycin of which some may be serious: exacerbation of myasthenia gravis, which may be life-threatening, severe hepatic events reported during the post-marketing period, rare syncope, uncommon mild to moderate reversible visual events, rarely severe, and minor QTc prolongation, with no evidence of increased cardiac risk, as well as adverse effects linked to drug-drug interactions. Although the incidence of adverse events in general does not seem to differ significantly to the commonly used agents in RTIs, the reports of exacerbations of myasthenia gravis including fatal cases, severe hepatic events, and an imbalance in incidences of visual disturbances and cases of syncope are of concern. Several of these issues are already implemented in sections 4.3, 4.4 and 4.8 of the SPC but additional restrictions in the SPC are recommended. Available data indicate that the use of telithromycin may be associated with increased risks compared to conventional macrolides and beta-lactam agents, and a thorough assessment of the benefit–risk balance for each of the approved indications is justified.

Assessment per indication:

Community-acquired pneumonia is associated with a significant morbidity and mortality, thus the importance of appropriate treatment is evident since the risk for clinical failure may seriously affect the outcome for the patient. In light of the enhanced activity of telithromycin compared to conventional macrolides and the increasing prevalence of decreased susceptibility in the primary pathogen *S. pneumoniae*, especially to macrolides and beta-lactams, the CHMP considers that no new safety concern has been identified supporting a restriction of the current wording of this indication. Thus, **the indication community-acquired pneumonia is not suggested to be restricted.** Treatment should be guided by national official guidelines as already stated in section 4.1.

Regarding the indications acute exacerbation of chronic bronchitis and acute bacterial sinusitis, the role of antibiotic treatment is not as evident as for the indication CAP. Several studies support the use of antibiotics for these indications but diagnosis and inclusion criteria and thus the external validity in the studies are not always clear. The identified risks associated with telithromycin compared to those of conventional macrolides, of which the risks for serious adverse events such as exacerbation of myasthenia gravis, risk for visual disturbances and loss of consciousness, while an increased risk for serious hepatic injury can not be excluded, indicate an imbalance in disadvantage of telithromycin, thus a restriction in these indications is recommended. The CHMP considers that **the benefit of using telithromycin in the indications acute exacerbation of chronic bronchitis and acute bacterial sinusitis only outweigh the risks when treating infections caused by known or suspected beta-lactam and/or macrolide resistant strains covered by the antibacterial spectrum of telithromycin**. Furthermore, prescription should be guided and "history of patients" and mention of national/regional resistance data is considered important.

Telithromycin is currently only indicated for the treatment of tonsillitis/pharyngitis when beta-lactam antibiotics are not appropriate. In the EU trial vs. penicillin, telithromycin was numerically inferior to penicillin but non-inferior to clarithromycin, essentially due to lack of eradication of erythromycin resistant *S. pyogenes* strains with the *erm*(B) genotype. The identified risks associated with telithromycin compared to those of conventional macrolides, of which the risks for serious adverse events such as exacerbation of myasthenia gravis, as well as an increased risk for visual disturbances and loss of consciousness, while an increased risk for serious hepatic injury can not be excluded, indicate a disadvantage of telithromycin, thus a restriction in this indication is recommended. The CHMP considers that **the benefit of using telithromycin in tonsillitis/pharyngitis only outweigh the risks when treating patients where beta-lactam antibiotics are not appropriate, in countries/regions with a significant prevalence of macrolide resistant *S. pyogenes*, when mediated by *erm*(TR) or *mef*A.**

In conclusion, the benefit-risk profile of telithromycin is still considered positive for the indication CAP, due to increasing resistance rates to macrolides which may lead to serious complications for this population. However, the anticipated benefits of telithromycin in terms of extended antibacterial activity is not considered to outweigh the risks in the commonly non-complicated indications AECB, ABS and T/P, unless used only in patients infected with pathogens with known or suspected resistance against macrolides and/or beta-lactams. Thus restrictions in these indications are recommended.

1.3 Question 2 on risk minimisation measures

MAH proposal for risk minimisation measures

The MAH proposes the following Risk Minimisation Measures that will be included in a revised Risk Management Plan. These Risk Minimisation Measures are focused on:

1) Strengthening specific safety sections of the approved SPC

    a. Upgrade of the Warning for exacerbation of myasthenia gravis to a contraindication for patients with myasthenia gravis.

    b. Revision of the "Warning and Precautions" section with addition of the following AEs (currently described in the Undesirable effects section): loss of consciousness and visual disturbances and proposal could be considered to take telithromycin at bedtime to try and minimise the risk of the possible consequences of these adverse events.

    c. Strengthening of driving precaution for patients who experience visual disturbances or loss of consciousness.

2) Further highlight in the Product information the importance of the appropriate use of antibiotic for bacterial infections and the importance of considering guidelines and local resistance rates when prescribing telithromycin.

3) Establishing a communication strategy of these changes in Europe to inform Healthcare Professionals and specific group of patients (i.e., those with myasthenia gravis) wherever possible.

Discussion and conclusions for risk minimisation measures

The CHMP agrees with the proposals from the MAH on the above changes proposed to the SPC and PL together with the restriction of the indications as mentioned above.

Concerning the communication plan the MAH committed (see letter of undertaking - attachment 5) to prepare a Direct Healthcare Professional Communication including relevant changes to the product information, to inform myasthenia gravis patient associations and to revise the communication material.

A comprehensive RMP according to guidelines was submitted by the MAH and is under evaluation. The RMP may need further revision after the ongoing evaluation of the benefit risk balance requested by the CHMP. This revision should be done within the scope of a pharmacovigilance follow-up measure.

2. CHANGES TO THE PRODUCT INFORMATION

Summary of the Product Characteristics

Section 4.1 "Therapeutic indications"
The indications AECB and ABS were restricted for treating infections caused by known or suspected beta-lactam and/or macrolide resistant strains.
The indication T/P was further restricted in countries/regions with a significant prevalence of macrolide resistant *S. pyogenes*, when mediated by *erm*TR or *mef*A
In addition the importance of appropriate use of antibiotic and considering guidelines / local resistance rates when prescribing telithromycin was further highlighted.

This section is updated as follows:
"When prescribing Levviax, 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).

Levviax 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)."***

Section 4.2 "Posology and method of administration"
Introduction of a sentence
to consider taking Levviax at bedtime, to reduce the potential impact of visual disturbances and loss of consciousness

Section 4.3 "Contraindications"
Introduction of a contraindication for patients with myasthenia gravis. This was previously introduced as a warning.

Section 4.4 "Special warnings and precautions for use"
Introduction of warnings regarding visual disorders, loss of consciousness; and of a recommendation to take telithromycin at bedtime to minimise risk of possible consequences of loss of consciousness and visual disturbances.
Revision of the paragraph on myasthenia gravis.

Section 4.7 "Effects on ability to drive and use machines"
Strengthening the recommendations for patients who experience visual disturbances or loss of consciousness.

Package Leaflet
Sections 2 "Before you take Levviax", 3 "How to take Levviax" and section 4 "Possible side effects" of the Product Leaflet was updated to reflect the SPC amendments

Annex II

Annex II was updated to reflect the request from CHMP to present every 6 months Periodic Safety Update Reports for telithromycin, following the evaluation of PSUR covering the period 10/07/05 - 09/07/06 as requested in the Outcome fax dated 22 November 2006.

3. CONCLUSION

On 22 March 2007 the CHMP considered the data submitted to be acceptable and agreed by majority of 22 out of 28 on the amendments to be introduced in the Product Information. The CHMP members divergent position is appended to the Opinion.