Procedural steps taken and scientific information after the authorisation

Levviax

MAJOR CHANGES[1]

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
A22/41	Section 4.1 of the SPC was updated to restrict the indications acute exacerbation of chronic bronchitis and acute sinusitis to infections caused by known or suspected beta-lactam and/or macrolide resistant strains covered by the antibacterial spectrum of telithromycin. The indication tonsilitis/pharyngitis was restricted to infections with Streptococcus pyogenes when beta-lactam antibiotics are not appropriate in countries/regions with a significant prevalence of resistant Streptococcus pyogenes, when mediated by ermTR or mefA. In addition, section 4.2 was updated to consider taking Levviax at bedtime, to reduce the potential impact of visual disturbances and loss of consciousness. Section 4.3 was updated to contraindicate Levviax for patients with myasthenia gravis. Section 4.4 was also updated to strengthen the warnings regarding visual disorders, loss of consciousness and to consider intake at bed-time. The paragraph on myasthenia	22/03/2007	31/05/2007	SPC, PL	Please refer to the Scientific Discussion: Levviax-H-355-A22-41-AR

[1] Major changes e.g. Type II variations, Annex II applications, Renewals and Annual Reassessments
[2] SPC (Summary of Product Characteristics), Labelling, PL (Package Leaflet)

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	gravis was revised. Furthermore, section 4.7 was updated to strengthen driving precautions. The PL was updated accordingly. Furthermore the annex 2 was updated to reflect the request from CHMP in November 2006 to present every 6 months Periodic Safety Update Reports.				
II/0040	Update of Summary of Product Characteristics and Package Leaflet To update sections 4.3, 4.4 and 4.8 of SPC to strengthen the information on hepatic safety and to include fatalities in patients with myasthenia gravis. This follows a complete review of available safety data. The PL was updated accordingly. In addition, following CHMP request the PL was revised to better reflect the information included in the SPC. The PL was further updated with the local representatives in Bulgaria and Romania. The contact details for the local representatives Czech Republic, Denmark, Greece, Ireland, Iceland, Portugal, Finland and Sweden, were also updated.	16/11/06	04/01/2007	SPC, PL	A total of 364 spontaneous case reports of hepatic adverse events have been received up to 20 April 2006. The majority represented mild-moderate and reversible hepatic injury. Worldwide a total of 104 reports of acute severe liver injury were identified. This corresponds to a global reporting rate of 4 reports of acute severe liver injury per million exposures. Based on the review of these hepatic reactions, section 4.3 "Contraindications", was revised to include a contraindication in patients with a previous history of hepatitis and/or jaundice associated with the use of telithromycin. Furthermore, in section 4.4 "Special warnings and precautions for use**"** the sentence concerning hepatic safety was updated adding that the post-marketing cases of severe hepatitis and liver failure have generally been associated with serious underlying diseases or concomitant medications. Additionally following CHMP request this warning was updated to include the reporting of fatal cases of severe hepatitis and liver failure as with some of the 7 fatal cases worldwide related to liver injury a causal relationship to telithromycin is at least possible.

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II/0037	Update of Summary of Product Characteristics and Package Leaflet To update section 4.2 and 5.2 of the SPC to introduce pharmacokinetic information related to patients with severe renal impairment and correspondent dose recommendations. Furthermore, in section 4.3 a new contraindication was introduced in patients with severely impaired renal and/or hepatic function and taking concomitant CYP3A4 inhibitors, such as protease inhibitors or ketokonazole. These changes are reflected in section 2 and 3 of the PL.	21/09/2006	26/10/2006	SPC, PL	A study in 36 subjects assessing the pharmacokinetics and the safety of telithromycin in patients with renal impairment after multiple oral administration of 400, 600, and 800 mg once a day for 5 days was the basis for the update of the dosage recommendations in patients with severe renal impairment. The results of the study showed that a daily dose of 400 mg resulted in too low exposure. The results showed a 1.4 fold increase in Cmax,ss and a 2 fold increase in AUC(0-24)ss at the 800 mg dose in the severe renally impaired group (CLcr < 30 ml/min) compared to healthy subjects. No specific safety concerns have arisen but note was given to the small sample size and the fact that patients with severe renal impairment could be inherently more sensitive for side effects of telithromycin. Therefore, it may be necessary to be more cautious and conservative for the dosing in the subjects with severe renal impairment than that for the healthy subjects. The pharmacokinetic study showed that a daily dose of 600 mg is approximately equivalent with the target exposure observed in healthy subjects. Based on simulated data and as the optimal dosage format (600 mg) is not available, an alternating daily dosing regimen of 800 mg and 400 mg in patients with severe renal impairment was shown to give approximately the same AUC(0-48h) as 800 mg daily in healthy subjects. However, 400/800 mg was not considered as optimal and therefore Levviax cannot be

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					considered as first choice treatment in patients with severe renal impairment. There is limited pharmacokinetic and safety data on increased exposure to telithromycin in patients with impaired renal and liver function, and taking CYP3A inhibitors. Therefore, a conservative approach indicating that telithromycin should not be used in patients with severely impaired renal and/or hepatic function and receiving concomitant administration of strong CYP3A4 inhibitors was considered appropriate until relevant data are available.
R/0034	Renewal of the marketing authorisation	28/06/2006	07/09/2006	SPC, Annex II, Labelling, PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit/risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of Levviax continues to be favourable. Considering the increased awareness of safety issues, especially concerning serious hepatic related adverse reactions the CHMP is of the opinion that one additional five-year renewal on the basis of pharmacovigilance grounds is required. The MAH will submit yearly PSURs, unless otherwise specified by the CHMP.
II/0039	Update of Summary of Product Characteristics To update section 4.8 "Undesirable effects" of the Summary of Product Characteristics (SPC) to introduce "QT/QTc interval	28/06/2006	07/08/2006	SPC	A total of 13 post-marketing cases of QT interval prolongation reported with telithromycin administration have been identified. In 11 of these cases the causality could not be excluded. Based on these data and upon the fact that section 4.4 includes a

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	prolongation" in the reactions reported during post-marketing experience as requested by the CHMP following the assessment of PSURs 7 and 8 (covering the period 10 July 2004 – 9 July 2005)..				warning concerning QT prolongation, the CHMP considered that section 4.8 should be amended to introduce "QT/QTc interval prolongation" in the reactions reported during post-marketing experience.
II/0038	Update of Summary of Product Characteristics To update section 4.4 "Special warnings and precautions for use" and 5.2 "Pharmacokinetic properties" of the Summary of Product Characteristics (SPC) on pharmacokinetic information related to patients with hepatic impairment, based on results of a study of repeated dose in patients with hepatic impairment.	28/06/2006	07/08/2006	SPC	The MAH has submitted within this variation a study of repeated dosing in patients with hepatic impairment. The MAH has shown that there is no significant difference in exposure between healthy volunteers and subjects with hepatic impairment. Higher renal elimination was observed in the hepatically impaired patients. This data suggests that no dose adjustments are required, but because of the limited number of subjects included and because there are very few subjects with possible decreased metabolic capacity of the liver, telithromycin should still be used with caution in this group of patients.
II/0036	Update of Summary of Product Characteristics and Package Leaflet To update section 4.4 and 4.8 of the SPC in order to introduce stronger warnings related to liver disorders and to reflect this change in section 2 and 4 of the PL	23/02/2006	22/03/2006	SPC, PL	Following the evaluation of data of hepatotoxicity from published cases, clinical trials and reported cases in PSURs the CHMP considered necessary to update the SPC introducing stronger warnings related to liver disorders. Alterations in hepatic enzymes have been commonly observed in clinical studies with telithromycin. Postmarketing cases of severe hepatitis and liver failure have been reported. These hepatic reactions were observed during or immediately after treatment and in most cases were reversible after discontinuation of telithromycin. The risk/benefit assessment for telithromycin is currently favourable although the present findings and the proposed revision of safety information implies that all hepatic events have to be thoroughly considered, closely monitored and cumulatively presented in the future PSURs.

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II/0035	Update of Summary of Product Characteristics and Package Leaflet To update section 4.8 of the SPC to introduce “vertigo” as uncommon side effects and to reflect this change in the section 4 of the PL.	23/03/2006	27/04/2006	SPC, PL	Vertigo, as a noted reaction of macrolide antibiotics, may also be expected with telithromycin. Clinical trial data reveals an incidence of vertigo with telithromycin that is comparable to other antibiotics. A review of post-marketing reports revealed the possibility of a drug relationship in a small number of cases. This is supported by positive rechallenge information in a small number of reports and also in some cases by a pattern correlating with Tmax. Therefore, “vertigo” was introduced in section 4.8 of the SPC as an uncommon side effect.
II/0025	Update of Summary of Product Characteristics and Package Leaflet To update section 4.8 of the SPC to introduce "pancreatitis" and "transient loss of consciousness" as rare side effects reported during post-marketing use, following PSUR 5 and PSUR 6. The Marketing Authorisation Holder proposed also to update Section 4.7. Additionally the MAH took the opportunity to update the list of local representatives of the PL.	21/04/2005	03/06/2005	SPC, PL	The Marketing Authorisation Holder proposed to update section 4.8 "Undesirable effects" of the Summary of Product Characteristics (SPC) to introduce "pancreatitis" and "transient loss of consciousness" as rare side effects reported during post-marketing use, following PSUR 5 (covering the period 10/07/2003-07/01/2004) and PSUR 6 (covering the period 08/01/2004-09/07/2004). The Marketing Authorisation Holder proposed also to update Section 4.7 "Effects on ability to drive and use machines" accordingly. Patients should be aware that rare cases of transient loss of consciousness, which may be preceded by vagal symptoms, have been reported and be cautioned about the potential effects of the these events on the ability to drive or operate machinery.
II/0024	Quality changes	20/01/2005	07/03/2005	SPC, Labelling, PL	The Marketing Authorisation Holder applied to replace the currently authorised film-coated tablet for Levviax 400 mg by a reduced-size tablet (from 18mm x 9mm to 13.9mm x 8.5mm). The Marketing Authorisation Holder took the opportunity to update 2 analytical methods for the finished product, to introduce

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					minor linguistics changes in the Estonian, German, Latvian, Lithuanian, Swedish and Spanish labelling and to update the annex II.
II/0022	Update of Summary of Product Characteristics and Labelling	18/11/2004	10/01/2005	SPC, Labelling	To update section 4.5 "Interaction with other medicinal products and other forms of interaction" of the Summary of Product Characteristics (SPC), under the paragraph "Effect of Levviax on other medicinal products", to amend the statement recommending that consideration should be given to monitoring prothrombin times (PT) / International Normalised Ratio (INR) while patients are receiving telithromycin and oral anticoagulants simultaneously. Furthermore, the Marketing Authorisation Holder (MAH) has added to the same section a subheading for oral contraceptives. In addition, the MAH updated the ATC code for telithromycin in order to be in line with the WHO ATC Index of January 2003. The MAH also took the opportunity of this variation to introduce minor linguistic amendments in the Swedish labelling texts.
II/0018	Change(s) to the manufacturing process for the active substance	20/11/2003	24/11/2003		
II/0016	Update of Summary of Product Characteristics	26/06/2003	08/10/2003	SPC	The Marketing Authorisation Holder (MAH) applied for an update of the Summary of Product Characteristics (SPC) sections 5.3 ("Preclinical safety data") to include findings of the re-evaluation of phospholipidosis-associated changes in the five pivotal repeated-dose oral toxicity studies.
II/0015	Update of Summary of Product Characteristics	22/10/2003	27/01/2004	SPC	The MAH applied for an update of the Summary of Product Characteristics (SPC) section 4.8 ("Undesirable effects") to include "very rare cases of hepatitis and very rare cases of angioneurotic oedema, anaphylactic reactions including anaphylactic shock" as undesirable effects, following the CPMP

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					assessment of the clinical study comparing telithromycin with Amoxicillin/Clavulanic acid and the Periodic Safety Update Reports covering the period of 10 January - 9 July 2002 and 10 July 2002 - 9 January 2003. Furthermore, the MAH took the opportunity to update section 4.7 ("Effects on ability to drive and use machines") and section 4.8, to further strengthen the warning on the occurrence of visual effects, further to the CPMP assessment on the safety data.
II/0014	Update of Summary of Product Characteristics and Package Leaflet	26/06/2003	08/10/2003	SPC, PL	The MAH applied for an update of the Summary of Product Characteristics (SPC) sections 4.4 ("Special warnings and special precautions for use") and 4.8 ("Undesirable effects") to include information on the aggravation of myasthenia gravis, further to an USR for telithromycin (Levviax) introduced on 2 April 2003. These changes are also being reflected in the Package Leaflet.
II/0012	Update of Summary of Product Characteristics	19/03/2003	09/07/2003	SPC	To update the Summary of Product Characteristics (SPC) sections 4.4 ("Special warnings and special precautions for use") and 4.5 ("Interaction with other medicinal products and other forms of interaction") to update the information about the in vivo interaction of telithromycin with CYP2D6 substrates, following the CPMP assessment of an interaction study with metoprolol. In addition, the MAH proposes linguistic changes to the German and Finnish language version of the SPC.
II/0011	Update of Summary of Product Characteristics	21/11/2002	03/03/2003	SPC	To update the Summary of Product Characteristics (SPC) section 5.2 ("Pharmacokinetics") to include information on sinus concentration of telithromycin based on the results of a new pharmacokinetic study.
II/0010	Update of Summary of Product	21/11/2002	03/03/2003	SPC	To update the Summary of Product

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	Characteristics				Characteristics (SPC) section 4.8 ("Undesirable Effects") to provide better guidance to prescribers in the differential diagnosis of visual disturbances in telithromycin-treated patients, following the CPMP assessment of a clinical follow-up measure.
II/0004	Update of Summary of Product Characteristics	21/03/2002	07/06/2002	SPC	Changes in section 4.4 , 4.5 (SPC) following the CPMP assessment of a clinical follow-up measure, namely an interaction study between telithromycin and rifampicin. In addition, to introduce linguistic changes in the French and Swedish version of the SPC.
II/0003	Change(s) to the manufacturing process for the active substance	17/01/2002	26/02/2002		

MINOR CHANGES[3]

No	Scope	Product Information affected[2]	Date[4]
IB/0033	10_Minor change in the manufacturing process of the active substance		26/01/2006
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	PL	29/07/2005
IA/0031	11_a_Change in batch size of active substance or intermediate - up to 10-fold		09/06/2005
IB/0030	10_Minor change in the manufacturing process of the active substance		19/05/2005
IB/0029	10_Minor change in the manufacturing process of the active substance		18/05/2005
IB/0028	14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site		11/04/2005
IA/0027	13_a_Change in test proc. for active substance - minor change		17/01/2005
IA/0026	13_a_Change in test proc. for active substance - minor change		17/01/2005
IB/0023	10_Minor change in the manufacturing process of the active substance		01/12/2004
IB/0021	13_b_Change in test proc. for active substance - other changes (replacement/addition)		05/07/2004
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	PL	25/06/2004
IA/0019	29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	SPC,	23/02/2004

[3] Minor changes e.g. Type I variations and Notifications
[4] Date of entry into force of the change

No	Scope	Product Information affected[2]	Date[4]
	36_a_Change in shape or dimensions of the container/closure - sterile ph. forms/biologicals 41_a_01_Change in pack size - change in no. of units within range of appr. pack size	Labelling, PL	
I/0017	Minor changes in manufacture of the medicinal product		01/08/2003
I/0013	Batch size of active substance		04/04/2003
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	PL	31/05/2002
I/0008	Minor change of manufacturing process of the active substance		21/06/2002
I/0007	Extension of shelf-life as foreseen at time of authorisation	SPC	21/06/2002
I/0006	Extension of shelf-life or retest period of the active substance		21/06/2002
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	PL	05/02/2002
I/0002	Change in the batch size of finished product		28/08/2001
I/0001	Minor change of manufacturing process of the active substance		28/08/2001