EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Ketek

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision issued [2] / amended on	Product Information affected [3]	Summary
N/0068	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/02/2017		PL	
PSUSA/2881/ 201507	Periodic Safety Update EU Single assessment - telithromycin	11/02/2016	n/a		PRAC Recommendation - maintenance
N/0067	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/11/2015		PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

IA/0065	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	31/07/2015	n/a		
II/0062	Update of sections 4.4 and 4.8 of the SmPC with new adverse reactions on ventricular arrhythmias, convulsions and tremor following cumulative reviews requested by the CHMP as part of the evaluation of PSUR23/PSU047. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	29/07/2015	SmPC and PL	Based on new safety information requested by the CHMP during the last PSUR review, the MAH has included “tremor”, “convulsions” and “ventricular arrhythmia (including ventricular tachycardia, torsade de pointes) with potential fatal outcome” as adverse reactions in SmPC section 4.8. In addition, the SmPC section 4.4 has been updated with a warning indicating that ventricular arrhythmias (including ventricular tachycardia, torsade de pointes) have been reported in patients treated with telithromycin and sometimes occurred within a few hours of the first dose. The Package Leaflet and RMP have been updated accordingly.
IG/0454	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	17/07/2014	n/a		
PSUV/0060	Periodic Safety Update	20/02/2014	23/04/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)’ for PSUV/0060.
IA/0061	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	04/12/2013	23/04/2014	SmPC, Labelling and PL	
IA/0059/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites	26/07/2013	23/04/2014	SmPC, Annex II and PL	

	A.7 - Administrative change - Deletion of manufacturing sites				
IG/0313	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/06/2013	n/a		
II/0057	Update of sections 4.3 and 4.5 of the Ketek SmPC with information about the administration of telithromycin together with colchicin and calcium channel blockers and with information on the potential of telithromycin to inhibit P-glycoprotein, which could mediate some clinically relevant interactions of telithromycin, based on the additional data provided by the MAH following a request from the CHMP after the assessment of a previous procedure. The package leaflet was updated in accordance. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	18/10/2012	19/11/2012	SmPC and PL	Following requests from CHMP from a previous procedure to include information about the concomitant administration of telithromycin and calcium channel blockers in the SmPC of Ketek (sections 4.3 and 4.5) and to provide additional data to address the potential of telithromycin to inhibit P-glycoprotein, the inhibition of which might mediate some clinically relevant interactions of Ketek, the MAH submitted the current variation to update sections 4.3 and 4.5 of the Ketek SmPC with the requested information. The package leaflet was updated in accordance.
II/0056/G	This was an application for a group of variations - Changes in the manufacturing process of the active substance - Addition of a manufacturing site for the synthesis of the active substance B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The	15/11/2012	15/11/2012		

	proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product				
II/0055	To update sections 4.3, 4.4 and 4.5 of the SmPC in order to complement the safety information concerning the concomitant use of telithromycin and drugs that can prolong the QT interval. The Package Leaflet and Labelling are updated accordingly. Furthermore, the Product Information is being brought in line with the QRD template version 7.3.1 The MAH took the opportunity to make minor editorial changes to the PI and to update the list of the local representatives for Ireland, Portugal and the United Kingdom in the Package Leaflet. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	21/06/2012	23/07/2012	SmPC, Annex II, Labelling and PL	Following the assessment report of PSURs 19 and 20, the CHMP requested the MAH to include additional information concerning the concomitant use of Ketek and drugs that can prolong the QT interval in the Ketek SmPC, i.e. a comprehensive list of drugs known to cause QT interval prolongation. This variation updated sections 4.3, 4.4 and 4.5 of the Ketek SmPC to provide information concerning the concomitant use of telithromycin and drugs that can prolong the QT interval. The Package Leaflet and Labelling are updated accordingly. Furthermore, the PI is being brought in line with the QRD template version 7.3.1 The MAH took the opportunity to make minor editorial changes to the PI and to update the list of the local representatives for Ireland, Portugal and the United Kingdom in the Package Leaflet.
IB/0054	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	13/02/2012	n/a		

IB/0052/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	06/12/2011	21/06/2012	Annex II and PL	
IA/0053/G	This was an application for a group of variations. B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	07/11/2011	n/a		
R/0051	Renewal of the marketing authorisation.	17/03/2011	12/05/2011	SmPC, Annex	At time of last renewal, the CHMP considered that the safety

				II, Labelling and PL	profile of Ketek (telithromycin) had to be closely monitored because of safety issues, and that the MAH should submit an additional renewal in 5 years time. Therefore the MAH submitted in November 2011 the second renewal application of Ketek. During the 5-year period several actions has been taken such as scrutinising several safety issues, restriction in 2 of the 3 indications, termination of the paediatric development programme and survey of off-label prescription. Based on the above actions, followed by a decrease in the prescription of telithromycin, the benefit risk profile of Ketek remains positive. No additional safety issues have been identified that require further action. The CHMP was of the opinion that the renewal can be granted with unlimited validity.
II/0050	Update of section 5.1 of the SmPC to harmonise clinical breakpoints of telithromycin with the breakpoints established by EUCAST. In addition the SmPC has been updated according to the QRD template version 7.3. Update of Summary of Product Characteristics	18/02/2010	09/04/2010	SmPC	Following CHMP request adopted on follow-up measure FU2 023.1, this type II variation was submitted to revise section 5.1 of the SPC in order to harmonise clinical breakpoints of telithromycin with those established by EUCAST. Following the evaluation, section 5.1 has been ammended with updated information on clinical breakpoints, a new PK/PD relationship paragraph and additional minor changes which improve and clarify the wording throughot the section. In addition the SmPC has been updated in accordance with QRD template version 7.3 and to incorporate linguistic improvements.
II/0049	To update sections 4.2 and 5.2 of the SPC following CHMP request further to the evaluation of paediatric data in accordance with article 46 of the paediatric regulation. Update of Summary of Product Characteristics	24/09/2009	04/11/2009	SmPC	Following evaluation of data coming from paediatric studies submitted in the frame of the Article 46 of the Paediatric Regulation (EC) No1901/2006, the CHMP requested the MAH to submit a variation to better reflect information available for children. The SPC was revised with minor changes to state that Ketek is not recommended for use in children below 12 years old of age due to limited data on safety and

					efficacy.
II/0048	Update of Summary of Product Characteristics and Package Leaflet To update sections 4.4 "Special warnings and precautions for use" and 4.5 "Undesirable effects" of the SPC on the use of statins. Section 2 of the PL is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	23/04/2009	02/06/2009	SmPC and PL	Following a CHMP request for revision of the information on concomitant use of statins, the MAH conducted a re-evaluation by means of literature research. Use of simvastatin, lovastatin or atorvastatin was already classified as a contraindication due to evidence for pharmacokinetic interaction resulting in high statin blood levels which are connected with risk of adverse reactions. The information was updated for other statins and patients should be carefully monitored for signs and symptoms of myopathy and rhabdomyolysis when co-treated with pravastatin, rosuvastatin and fluvastatin. The information on cerivastatin was removed from the SPC, since this substance is no longer marketed in the EU.
II/0047	Update of Summary of Product Characteristics, Annex II and Package Leaflet To update the SPC sections 4.4 and 4.5 on monitoring rhabdomyolysis with statins, 4.7 to include confusion and hallucination and 4.8 to add the reported adverse reactions anosmia, agueusia, hypersensitivity, arthralgia, myalgia, confusion and hallucination following CHMP request after evaluation of PSUR 12. Section 2 of the PL was updated accordingly. The PL was amended in line with the User Testing and the contact list for the MAH Representatives in Belgian, Spain, France, Ireland, Latvia and Norway was updated. Furthermore, the annex II was revised to update the PSUR submission from every 6 month to once a year as agreed by the CHMP following assessment of PSUR 12.	25/09/2008	18/10/2008	SmPC, Annex II and PL	Following spontaneous reports of anosmia, agueusia, hypersensitivity, arthralgia, myalgia, confusion and hallucination, section 4.8 of the SPC was updated to include these adverse reactions. Two cases of rhabdomyolysis associated with concomitant HMG CoA reductase inhibitor were reported. This co-administration has the potential for interaction via CYP3A4 inhibition by telithromycin leading to increased statin levels. Therefore, the paragraph on statins on section 4.5 was revised and patients should be carefully monitored for signs and symptoms of rhabdomyolysis. Furthermore, a cross-reference to section 4.5 was included in section 4.4 on the paragraph concerning treatment with other products that are metabolised by CYP3A4. Section 4.7 was update to warn about potential confusion or hallucination. Patients should attempt to minimize activities such as driving a motor vehicle, operating heavy machinery or engaging in other hazardous activities during treatment

	Update of Summary of Product Characteristics and Package Leaflet				with Ketek.
IA/0046	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	08/05/2008	n/a		
IA/0045	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	08/05/2008	n/a		
IA/0044	IA_09_Deletion of manufacturing site	08/05/2008	n/a		
IA/0043	IA_05_Change in the name and/or address of a manufacturer of the finished product	27/02/2008	n/a		
IA/0042	IA_05_Change in the name and/or address of a manufacturer of the finished product	27/02/2008	n/a	Annex II and PL	
A22/0041	Section 4.1 of the SPC was updated to restrict the indications acute exacerbation of chronic bronchitis, acute sinusitis and tonsillitis/pharyngitis. In addition, section 4.2 was updated to consider taking Ketek at bedtime, to reduce the potential impact of visual disturbances and loss of consciousness. Section 4.3 was updated to contraindicate Ketek for patients with myasthenia gravis. Section 4.4 was also updated to strengthen the warnings regarding visual disorders, loss of consciousness and to consider Ketek at bed-time. The paragraph on myasthenia 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	22/03/2007	31/05/2007	SmPC, Annex II and PL	Please refer to the Scientific Discussion: Ketek-H-354-A22-41-AR

	Reports. Article 22 Review				
II/0040	To update sections 4.3, 4.4 and 4.8 of Summary of Product Characteristics (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 Package Leaflet (PL) was updated accordingly. In addition, following CHMP request the PL was revised to better reflect the information included in the SPC. Furthermore, the MAH completed the list of local representatives in the PL to include the two new Member States (Bulgaria and Romania) and to update the format of the PL according to the latest EMEA/QRD template. The MAH also took the opportunity to update the contact details for Czech Republic, Denmark, Greece, Ireland, Iceland, Portugal, Finland and Sweden. Update of Summary of Product Characteristics and Package Leaflet	16/11/2006	04/01/2007	SmPC and PL	A total of 380 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. Based on a review of cases of fatal myasthenia gravis and the potentially life-threatening nature inherent in aggravating myasthenia gravis, an association of fatal myasthenic crisis with telithromycin can not be ruled out. Five cases of fatal aggravation of myasthenia gravis and plausible temporal relationship to telithromycin treatment were identified. Therefore, section 4.4 "Special warnings and precautions for use" was updated to add reports of death in myasthenic

					patients treated for respiratory tract infections with telithromycin.
II/0037	To update section 4.2 "Posology and method of administration" and 5.2 "Pharmacokinetic properties" of the Summary of Product Characteristics to introduce pharmacokinetic information related to patients with severe renal impairment and correspondent dose recommendations. Furthermore, in section 4.3 "Contraindications" 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 "Before you take Ketek" and 3 "How to take Ketek" of the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	26/10/2006	SmPC and PL	The MAH has submitted this variation to update the pharmacokinetic information related to patients with severe renal impairment and corresponding dose recommendation (in treated patients with alternating daily doses of 800 mg and 400 mg). This update is based on an additional study to assess 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. In order to support a dosage recommendation in patients with severe renal impairment, additional analysis was conducted using population pharmacokinetic (PK) modeling and simulation. The results of the pharmacokinetic study clearly 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 renal impaired group (CLcr < 30 ml/min) compared to healthy subjects. The MAH was requested to discuss the increased exposure in relation to safety data at higher exposures and concludes that telithromycin was well tolerated during these aforementioned PK studies. No specific safety concerns have arisen. However, the CHMP considered that the interpretation of these results may be complicated by small sample size and 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 resulted in approximately the same AUC(0-24)ss in the severe renal impaired group (CLcr < 30 ml/min) compared to 800 mg in healthy subjects. Based on simulated data an alternating daily dosing regimen of 800 mg and 400 mg in patients with severe renal impairment would give approximately the same AUC(0-48h) as 800 mg daily in healthy subjects. Due to compliance concerns on the alternating daily dosing regimen, the MAH had been repeatedly asked during this assessment to further explore the possibilities to formulate dividable 400 mg tablets or a lower strength. According to the MAH 400 mg tablets are film-coated to mask the strong bitter taste of telithromycin and therefore he decided not to formulate dividable 400 mg tablets and expose the patients to the drug bitterness. The MAH is also not in favour of a lower strength because of the claimed difficulties in provision of the 300 mg formulation of Ketek in the EU. As the CHMP did not consider the alternate 400/800 mg optimal, Ketek cannot be considered as first choice treatment in patients with severe renal impairment. There is limited pharmacokinetic and safety data in patients with impaired renal and liver function, and taking CYP3A inhibitors, increasing exposure. 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	SmPC, Annex II, Labelling and 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 Ketek 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 years renewal on the basis of pharmacovigilance grounds is required. The MAH will submit yearly PSURs, unless otherwise specified by the CHMP.
II/0039	To update section 4.8 "Undesirable effects" of the Summary of Product Characteristics (SPC) to introduce "QT/QTc interval 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). Update of Summary of Product Characteristics	28/06/2006	07/08/2006	SmPC	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 warning concerning QT prolongation, the CHMP considered that section 4.8 should be amended introduce "QT/QTc interval prolongation" in the reactions reported during post-marketing experience.
II/0038	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. Update of Summary of Product Characteristics	28/06/2006	07/08/2006	SmPC	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/0035	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	SmPC and 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

	Update of Summary of Product Characteristics and Package Leaflet				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/0036	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. Update of Summary of Product Characteristics and Package Leaflet	23/02/2006	22/03/2006	SmPC and 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.
IB/0033	IB_10_Minor change in the manufacturing process of the active substance	26/01/2006	n/a		
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 notification)	29/07/2005	n/a	PL	
IA/0031	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	09/06/2005	n/a		
II/0025	Update of Summary of Product Characteristics and Package Leaflet	21/04/2005	03/06/2005	SmPC and PL	The Marketing Authorisation Holder proposed to update section 4.8 "Undesirable effects" of the Summary of Product

	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. To update Section 4.7. Additionally the MAH took the opportunity to update the list of local representatives of the PL. Update of Summary of Product Characteristics and Package Leaflet				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 these events on the ability to drive or operate machinery.
IB/0030	IB_10_Minor change in the manufacturing process of the active substance	19/05/2005	n/a		
IB/0029	IB_10_Minor change in the manufacturing process of the active substance	18/05/2005	n/a		
IB/0028	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	11/04/2005	n/a		
II/0024	Quality changes	20/01/2005	07/03/2005	SmPC, Annex II, Labelling and PL	The Marketing Authorisation Holder applied to replace the currently authorised film-coated tablet for Ketek 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 and to introduce minor linguistics changes in the Estonian, German, Latvian, Lithuanian, Swedish and Spanish labelling and to update the annex II.
IA/0027	IA_13_a_Change in test proc. for active substance - minor change	17/01/2005	n/a		

IA/0026	IA_13_a_Change in test proc. for active substance - minor change	17/01/2005	n/a		
II/0022	Update of Summary of Product Characteristics and Labelling	18/11/2004	10/01/2005	SmPC and 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 Ketek 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.
IB/0023	IB_10_Minor change in the manufacturing process of the active substance	01/12/2004	n/a		
IB/0021	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	05/07/2004	n/a		
N/0020	To update the list of local representatives in the Package Leaflet (PL), to include the local representatives of the ten new European Member States and to update the format of the PL according to the latest EMEA/QRD template. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/06/2004	n/a	PL	

IA/0019	IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms IA_36_ b_Change in shape or dimensions of the container/closure - other pharm. forms IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	23/02/2004	23/02/2004	SmPC, Labelling and PL	
II/0015	Update of Summary of Product Characteristics	22/10/2003	27/01/2004	SmPC	Update of the 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 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. These changes are also being reflected in the Package Leaflet.
II/0018	Change(s) to the manufacturing process for the active substance	20/11/2003	24/11/2003		Based on production experience, the MAH applied for a number of changes related to the active substance, one synthetic intermediate and two starting materials.
II/0016	Update of Summary of Product Characteristics	26/06/2003	08/10/2003	SmPC	Update of the SPC section 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/0014	Update of Summary of Product Characteristics and Package Leaflet	26/06/2003	08/10/2003	SmPC and PL	Update of the 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 introduced on 2 April 2003. These changes are also being reflected in the Package Leaflet.
I/0017	15_Minor changes in manufacture of the medicinal product	01/08/2003	20/08/2003		
II/0012	Update of Summary of Product Characteristics	19/03/2003	09/07/2003	SmPC	Update of the 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.
I/0013	13_Batch size of active substance	04/04/2003	09/04/2003		
II/0011	Update of Summary of Product Characteristics	21/11/2002	04/03/2003	SmPC	Update of the 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 Characteristics	21/11/2002	04/03/2003	SmPC	Update of the 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.
I/0007	20_Extension of shelf-life as foreseen at time of authorisation	21/06/2002	22/07/2002	SmPC	
I/0008	12_Minor change of manufacturing process of the active substance	21/06/2002	28/06/2002		

I/0006	20a_Extension of shelf-life or retest period of the active substance	21/06/2002	28/06/2002		
II/0004	Update of Summary of Product Characteristics	21/03/2002	07/06/2002	SmPC	Changes in section 4.4 "Special warnings and special precautions for use" and 4.5 "Interaction with other medicinal products and other forms of interaction" of the Summary of Product Characteristics (SPC) following the CHMP 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.
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/05/2002	20/06/2002	PL	
II/0003	Change(s) to the manufacturing process for the active substance	17/01/2002	26/02/2002		
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/02/2002	26/03/2002	PL	
I/0002	16_Change in the batch size of finished product	28/08/2001	23/10/2001		
I/0001	12_Minor change of manufacturing process of the active substance	28/08/2001	23/10/2001		