Invanz

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)	25/10/2022		Labelling and PL	
IA/0067	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	22/06/2022	n/a		

[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).

WS/2193	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	02/06/2022	n/a		
IB/0066	To update sections 4.4 and 4.8 of the SmPC to implement the signal recommendations on 'Ertapenem – Toxic encephalopathy in patients with renal impairment (EPITT no 19498)' adopted at the 25-28 October 2021 PRAC meeting. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	02/02/2022		SmPC and PL	
IAIN/0064	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	15/02/2021	13/12/2021	Annex II and PL	
IAIN/0063/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same	10/12/2020	n/a		

	pharmaceutical group as the currently approved manufacturer				
II/0062	Update of section 4.8 of the SmPC in order to add 'hypersensitivity vasculitis' to the list of adverse drug reactions (ADRs) with frequency 'Rare', based on post-marketing reports; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, update the PI in line with the Annex to the European Commission guideline on `Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017 Rev.1) regarding sodium content, and bring the PI in line with the latest QRD template version 10.1. The MAH also updated the Package leaflet to add the missing adverse event "injection site induration" with frequency 'Rare'. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	03/12/2020	13/12/2021	SmPC, Annex II, Labelling and PL	For more information, please refer to the Summary of Product Characteristics.
PSUSA/1256/ 202003	Periodic Safety Update EU Single assessment - ertapenem	26/11/2020	n/a		PRAC Recommendation - maintenance
II/0060	To update sections 4.8 and 5.1 of the SmPC to update the safety information with the addition of a new post-marketing adverse reaction term: acute generalized exanthematous pustulosis (AGEP) and to update the breakpoints table withe the most recent	10/10/2019	19/10/2020	SmPC, Labelling and PL	The cumulative review for SCAR events conducted by the MAH identified one new safety signal for the SCAR event of AGEP. The MAH discussed the case report described above and provided the evidence to support a potential causal association between ertapenem and the development of

	EUCAST recommendation (v 9.0, Jan 2019)on clinical breakpoints for ertapenem.Section 4 of the Package Leaflet is updated accordingly. The MAH is also updating the labeling section and the rest of the Product Information according to the latest QRD requirements and is updating List of Local Representatives. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				AGEP, namely the temporal relationship between the onset of symptoms and treatment with ertapenem, the confirmation of AGEP by skin biopsy, and positive skin patch testing. Although pertaining to one single well described case, the potential causal relationship between treatment with ertapenem and the development of AGEP cannot be excluded and, as such, the MAH's proposal update the product information is acceptable.
IA/0059/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	16/05/2019	n/a		
T/0058	Transfer of Marketing Authorisation	20/04/2018	08/05/2018	SmPC, Labelling and PL	
IA/0057/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	30/11/2017	n/a		

	A.7 - Administrative change - Deletion of manufacturing sites				
PSUSA/1256/201703	Periodic Safety Update EU Single assessment - ertapenem	26/10/2017	n/a		PRAC Recommendation - maintenance
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/02/2017	08/05/2018	Labelling	
IB/0054/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	31/03/2016	n/a		
II/0053	Update of section 5.1 to recategorize Bacteroides fragilis group from "commonly susceptible species" to "Species for which acquired resistance may be a problem" following a CHMP recommendation in conclusion to the assessment of LEG 025.	28/01/2016	11/01/2017	SmPC, Annex II, Labelling and PL	In line with the most recent data on the in vitro activity of ertapenem, section 5.1 was updated to include Bacteroides fragilis group in category 2 of the table of organisms.

	Furthermore, the PI is brought in line with the latest QRD template version 9.1. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
PSUV/0051	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
II/0052	Update of section 4.8 of the SmPC in order to include the adverse event term 'teeth staining' following relevant post-marketing cases. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	08/10/2015	SmPC and PL	Cumulative review of the MAH's safety database on the identified post-marketing safety reports of 'tooth discoloration' in association with exposure to ertapenem sodium has been conducted by the MAH. Cases have been identified with temporal association to the use of ertapenem sodium, which support the addition of the term 'teeth staining' as new ADR, with not known frequency, to the SmPC. The Package leaflet has been updated accordingly.
II/0050/G	This was an application for a group of variations. To change the vial size and remove the logo in the caps, and to make a minor change to the manufacturing process. B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products 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 originally approved batch size	25/09/2014	27/10/2014	SmPC	

	B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information				
II/0048	Update of section 4.8 of the SmPC in order to update the safety information with the adverse event term "depressed level of consciousness", following the identification of "depressed level of consciousness" as a new signal. The Package Leaflet is updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 9. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/11/2013	27/10/2014	SmPC and PL	A total of 12 ertapenem sodium reports from healthcare professionals (HCPs) were identified from market introduction (30 March 2001) through 14 February 2013 which contained the preferred term ' depressed level of consciousness '. In the majority of the reports, depressed level of consciousness was reported with one or more terms currently listed for ertapenem under the Psychiatric or Nervous system SOC. The time to onset for the 12 cumulative reports ranged for 1 to 24 days with median of 7 days. The event of depressed level of consciousness occurred with a similar time to onset as several other events within the Psychiatric and Nervous system SOC. These results support the addition of the adverse event term "depressed level of consciousness" to section 4.8 of the Invanz SmPC, under the Nervous system disorders SOC. The Package Leaflet (Section 4) was updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 9.
IG/0366	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	08/11/2013	n/a		

	PSMF location				
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/07/2013	27/10/2014	PL	
II/0045	To introduce a change in the manufacturing process of the finished product. B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	17/01/2013	17/01/2013		
IA/0046	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	15/11/2012	n/a		
IA/0044/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	26/10/2012	n/a		
IG/0182	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/08/2012	n/a		
IA/0042	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished	12/07/2012	n/a		

	product, including quality control sites (excluding manufacturer for batch release)				
II/0040	To update section 4.8 of the SmPC by adding the term "gait disturbance" in the postmarketing experience section under the "Nervous system disorders" SOC and section 9 of the SmPC with the date of the latest renewal. The Package Leaflet sections 4 and 6 were updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives for Italy, the Netherlands and Malta in the Package Leaflet (PL). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/05/2012	27/06/2012	SmPC and PL	A total of 11 Invanz reports (9 with clinically evaluable information; 8 serious and 1 non-serious) were identified from market introduction which contained the preferred term 'gait disturbance'. Analysis of the 8 serious evaluable reports suggests a temporal relationship between ertapenem sodium initiation and onset of gait disturbance. These results support the addition of the preferred term "gait disturbance" to section 4.8 of the Invanz SmPC, under the "Nervous System Disorders" SOC; the Package Leaflet sections 4 and 6 were updated accordingly. Section 9 of the SmPC with the date of the latest renewal. In addition, the list of local representatives for Italy, the Netherlands and Malta in the Package Leaflet (PL) was updated.
IB/0041	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	04/05/2012	n/a		
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/02/2012	27/06/2012	PL	
R/0036	Renewal of the marketing authorisation.	20/10/2011	22/12/2011	SmPC, Annex II and PL	During the renewal period no major change to the manufacture of Invanz was implemented. No change in the efficacy of Invanz was observed in clinical trials conducted since initial marketing authorisation. With respect to safety data, a cumulative review on muscular weakness was submitted by the MAH at the request of CHMP and this adverse reaction was added in section 4.8 of the Invanz

					SmPC as unknown frequency under SOC "Musculoskeletal and connective tissue disorders" and under "Possible Side-effects" in the Patient Leaflet. No other new specific safety concern was raised in a number of clinical trials conducted with Invanz. The safety results provided in the PSURs and overall safety bridging report do not indicate any other new safety signal or new adverse events, which are not covered in section 4.8 of the SmPC. 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 Invanz continues to be favourable. Therefore, CHMP has recommended that the renewal can be granted with unlimited validity. The product information (PI) has been updated according to the latest QRD template. Finally, the list of local representatives for Belgium, Bulgaria, Czech Republic, Germany, Estonia, Luxemburg, Malta, Netherlands, Greece, Portugal, Island, Italy, Cyprus, Slovak Republic, Sweden and the UK has been updated.
IAIN/0038	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	02/12/2011	n/a		
IB/0035	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	24/06/2011	n/a		

IA/0034/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	24/05/2011	n/a		
IG/0027/G	This was an application for a group of variations. C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	10/11/2010	n/a	Annex II	
IB/0033	Change in the manufacturing process of the finished product B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	07/10/2010	n/a		
II/0032	Update of section 4.8 of the SmPC to include Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome) as undesirable effect following a post-marketing safety report. Sections 2 and 4 of the PL have been updated accordingly.	24/06/2010	28/07/2010	SmPC and PL	The MAH submitted this type II variation to update the Product Information to add Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome) in the "Undesirable effects" section. The proposal was based upon a safety report received by Merck & Co., Inc., and reported in the

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				literature, the first case in connection with ertapenem, and for which there was evidence of a temporal and de-challenge/re-challenge relationship to the administration of the product. It concluded with the update of section 4.8 of the SmPC and sections 2 and 4 of the PL.
II/0031	Update of sections 4.4 and 4.5 of the SPC and the PL to reflect a carbapenem class effect drug-drug interaction between carbapenem antibiotics and valproic acid. The MAH also updated contact details of some local representatives. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	23/10/2009	SmPC and PL	Following the assessment of the result of an open-label, single-sequence, drug-drug interaction study of doripenem co-administered with oral VPA, section 4.4 and section 4.5 of the SPC for doripenem was updated to indicate that the concomitant use of doripenem and valproic acid/sodium valproate is not recommended. The interaction is believed to be a class effect for carbapenems. Hence, the CHMP proposed to initiate a class review on the interaction between carbapenems and valproate. As a consequence, this type II variation II/31 was submitted to update the wording of section 4.4 and section 4.5 of the SPC for ertapenem with information on the drug-drug interaction between carbapenem antibiotics including ertapenem and valproic acid.
II/0030	Update of section 4.8 of the SPC to include "aggression, delirium, disorientation, mental state changes, dyskinesia & myoclonus" as result of the post-marketing surveillance. Section 4 of the PL has also been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	28/08/2009	SmPC and PL	This application is based on the safety reports received by the MAH and entered into their database (Worldwide Adverse Experience System (WAES) database). The WAES database was queried: - from market introduction to 29-Mar-2008 for reports for ertapenem with the preferred terms: mental status changes, delirium and aggression. - from 30-Mar-2001 to 15-Jan-2009 for reports for ertapenem containing the preferred term 'disorientation'. - from market introduction to 27-Jan-2009 for serious reports from health care providers within the post

					marketing environment containing the preferred terms myoclonus, dyskinesia and tremor. The submitted safety data provide some evidence of a temporal association with the use of ertapenem, even though in several cases concomitant drugs and conditions were present to confound the association and there was a lack of information on re-challenge in many of cases. Nevertheless, overall, the above data and the plausible precedent of other undesirable effects on mental state and the nervous system already listed individually in the SPC suggests that "aggression, delirium, disorientation, mental state changes, dyskinesia & myoclonus" should be included as undesirable effects observed from post marketing experience.
II/0029	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Annex II has been updated to reflect the version number of the DDPS. Update of DDPS (Pharmacovigilance)	25/06/2009	23/07/2009	Annex II	The MAH updated its DDPS and submitted therefore this type II variation. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements and is considered acceptable.
IB/0028	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	20/04/2009	n/a		
II/0026	Update of section 4.8 of the SmPC to include "altered mental status" as result of the post-marketing surveillance. Section 4 of the PL has been updated accordingly. The MAH took the opportunity to update the contact details of the local representative in Ireland in section 6 of the PL.	20/11/2008	22/12/2008	SmPC and PL	This update to the product information is based on a review of spontaneously-reported cases of altered mental status as found in the MAH's database. In the documentation submitted, a total of 14 reports with the preferred term, mental status changes (MSC) were reported in temporal association with the use of ertapenem for the period from market introduction to 29 March 2008.

	Update of Summary of Product Characteristics and Package Leaflet				Of 13/14 reports, the onset time of MSC after start of ertapenem sodium was provided in 6/13 reports and ranged from 30 minutes to 6 days. Documentation of mental status level on discontinuation of ertapenem sodium was provided in 7/13 reports. Full recovery to baseline mental status occurred in 5 patients, 1 patient experienced partial recovery and 1 did not return to baseline. The 6 remaining reports did not provide information regarding the patient's mental status after discontinuation of ertapenem sodium. One/13 case reported both a positive de-challenge and a positive re-challenge with reoccurrence of MSC within days of restarting ertapenem sodium, although the remaining 13 cases have less detail and causality is less clear. However, on the basis of the likely causal association of the main case, and possible association of remaining cases, altered mental status has been included in the product information. The balance of risks and benefits remains positive and no additional action is warranted at this stage.
IA/0027	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	29/09/2008	n/a		
IA/0025	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	11/03/2008	n/a		
II/0023	Quality changes	18/10/2007	24/10/2007		
II/0022	Update of section 5.1 of the SmPC with EUCAST breakpoints as requested by the CHMP in July 2003 and reconfirmed in January 2007 further to publication of EUCAST breakpoints for ertapenem in	19/07/2007	27/08/2007	SmPC and PL	Following the type II variation II/05, the MAH committed to update section 5.1 of the SmPC to add MIC breakpoints as defined for the European Union. In 2006 the MIC breakpoints were defined and published by EUCAST

	2006. The MAH took the opportunity to update contact details of Maltese local representative in the PL. Update of Summary of Product Characteristics and Package Leaflet				(European Committee for Antimicrobial Susceptibility Testing). Following the first renewal for Invanz R/19, the MAH reconfirmed its commitment and submitted the type II variation II/22 in April 2007 to update section 5.1 of the SmPC according to the EUCAST MIC breakpoints.
IB/0021	IB_33_Minor change in the manufacture of the finished product	17/04/2007	n/a		
R/0019	Renewal of the marketing authorisation.	24/01/2007	21/03/2007	SmPC, Labelling and PL	
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/01/2007	n/a	PL	
II/0016	Update of Sections 4.4 and 4.8 of the SPC following the assessment of PSURs and bridging report covering the period from 30.03.2004 to 29.03.2005 to include a warning relating to the occurrence of seizures. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	24/10/2006	SmPC and PL	Further to the assessment of PSURs and bridging report covering the period from 30.03.2004 to 29.03.2005, the MAH provided a cumulative review of convulsions up to 30 September 2005. Until that time 86 cases of convulsions were reported post-marketing mostly in elderly and for patients with central nervous system abnormalities. The section 4.4 of the SmPC has been updated as "Seizures have been reported during clinical investigation in adult patients treated with ertapenem sodium (1g once a day) during therapy or in the 14 day follow-up period. Seizures occurred most commonly in elderly patients and those with pre-existing CNS disorders (e.g. brain lesions or history of seizures) and/or compromised renal function. Similar observations have been made in the post-marketing

					environment." The section 4.8 has been updated to separate adverse drug reactions which occurred during clinical trials and post-marketing.
II/0015	Extension of the current therapeutic indication to add prophylaxis of surgical site infection elective colorectal surgery on the basis of a prospective, multicentre, double-blind, randomised clinical study versus cefotetan. Consequently, the SPC have been amended in Sections 4.1, 4.2, 4.4 and 4.8. The PL has been updated accordingly in its sections 1, 3 and 4. The MAH took the opportunity to amend the sections 2 and 4.4 to add information on the quantity of sodium Invanz contains. In addition, the MAH took the opportunity to revise the Product Information according to the new EMEA/QRD template. Extension of Indication	27/07/2006	01/09/2006	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion: Invanz-H-389-II-15
II/0017	Quality changes	27/07/2006	18/08/2006		
II/0013	To extend the current indication to diabetic foot infections of the skin and soft tissue and consequent amendments of Sections 4.1, 4.4 and 4.8 of the SmPC. The PL has been updated accordingly. In addition, the MAH took the opportunity to rearrange section 4.8 of the SmPC to allow for a better overview of data belonging to different age	14/12/2005	25/01/2006	SmPC and PL	Please refer to the sientific discission: Invanz -H-389-II-13

	groups, as well as to make corrections in Section 5.1 of the SmPC and update this section according to the Note for Guidance on Evaluation of Medicinal Products indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95, adopted in April 2004). Extension of Indication				
II/0011	Extension of the current indication to include children 3 months to 17 years of age and consequent amendments of the Product Information. Extension of Indication	26/05/2005	07/07/2005	SmPC and PL	Please refer to the Scientific Discussion Invanz H-389-II-11
IB/0014	IB_10_Minor change in the manufacturing process of the active substance	18/03/2005	n/a		
IB/0012	IB_38_c_Change in test procedure of finished product - other changes	22/02/2005	n/a		
II/0010	Quality changes	15/12/2004	20/12/2004		
N/0009	To update the Package Leaflet to include the list of local representatives of the ten new member states. The Marketing Authorisation Holder also took the opportunity to update Annex II according to the latest QRD template. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/07/2004	n/a	Annex II and PL	

II/0007	Update of Section 4.8 of the SmPC further to post-marketing experience. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) Update of Summary of Product Characteristics and Package Leaflet	17/12/2003	10/03/2004	SmPC and PL	The SmPC was updated in its section 4.8 by adding: - "anaphylaxis including anaphylactoid reactions" as very rare reaction, - "hallucinations" as very rare reaction. Section 5 of the PL was updated accordingly. The section 4.8 of the SmPC was also reformatted according to MedDRA and to the revised QRD template.
II/0005	Update of Section 5.1 of the SmPC further to microbiological susceptibility breakpoints updated standards. Update of Summary of Product Characteristics and Package Leaflet	24/07/2003	01/12/2003	SmPC and PL	The SmPC has been updated in its section 5.1 by including microbiological susceptibility breakpoints updated according to the National Committee for Clinical Laboratory Standards (NCCLS).
I/0008	IB_42_b_Change in storage conditions of the finished/diluted/reconstituted product IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	26/11/2003	n/a	SmPC, Labelling and PL	
I/0006	20a_Extension of shelf-life or retest period of the active substance	29/09/2003	06/10/2003		
II/0003	Quality changes Change(s) to the manufacturing process for the finished product	24/07/2003	28/07/2003		
I/0004	30_Change in pack size for a medicinal product	24/03/2003	22/04/2003	SmPC, Labelling and	

				PL	
I/0001	20_Extension of shelf-life as foreseen at time of authorisation	15/10/2002	12/11/2002	SmPC	