Axura

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/0086	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/02/2024		Labelling and PL	
WS/2413/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No	25/05/2023	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).

	1234/2008. B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
N/0085	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/04/2023		PL	
IG/1597/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	03/03/2023	n/a		

	control/testing takes place A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
WS/1980	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/03/2021	04/04/2022	SmPC, Labelling and PL	
WS/1579	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.e.1.a.2 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Semi-solid and non-sterile liquid pharmaceutical forms	29/05/2019	04/05/2020	SmPC and PL	
PSUSA/1967/ 201809	Periodic Safety Update EU Single assessment - memantine	16/05/2019	n/a		PRAC Recommendation - maintenance
IB/0079	C.I.z - Changes (Safety/Efficacy) of Human and	26/06/2018	06/06/2019	SmPC, Annex	

	Veterinary Medicinal Products - Other variation			II, Labelling and PL	
IG/0835/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.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	13/09/2017	n/a		
IG/0768/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 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)	06/03/2017	n/a		
IG/0767	A.7 - Administrative change - Deletion of manufacturing sites	06/03/2017	n/a		

IA/0077	A.7 - Administrative change - Deletion of manufacturing sites	23/02/2017	n/a		
N/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/01/2017	06/06/2019	PL	
PSUSA/1967/ 201509	Periodic Safety Update EU Single assessment - memantine	14/04/2016	n/a		PRAC Recommendation - maintenance
WS/0804	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/02/2016	n/a		
N/0072	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/12/2015	06/06/2019	PL	
N/0070	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/07/2015	06/06/2019	PL	
WS/0668	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Following new data lock point, interim results of the Prostate Cancer study, 4 finalized studies and reformatting in compliance with the new template, submission of a revised and updated RMP version 7.1	23/04/2015	n/a		

	(delete). This RMP update also introduces changes to the required additional Pharmacovigilance activity regarding the identified potential risk of prostate cancer by adjusting the due dates of agreed milestones. The final RMP version is 7.2. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
PSUSA/1967/ 201409	Periodic Safety Update EU Single assessment - memantine	10/04/2015	n/a		PRAC Recommendation - maintenance
IAIN/0069	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	02/02/2015	n/a		
N/0066	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/09/2014	13/04/2015	PL	
WS/0562	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.6 of the SmPC for Axura and Memantine Merz with information currently included in section 5.3 referring to the absence of adverse	25/04/2014	13/04/2015	SmPC, Annex II, Labelling and PL	

	effects noted on non-clinical male and female fertility studies, as per the QRD template. In addition, all the annexes have been brought in line with the QRD template version 9 and linguistic amendments have been introduced in some translations, including a correction of the list of excipients for Iron oxide in the German version. The Croatian local representative has also been included in the package leaflet. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
PSUSA/1967/ 201309	Periodic Safety Update EU Single assessment - memantine	10/04/2014	n/a		PRAC Recommendation - maintenance
II/0062	To introduce a new active substance manufacturer supported by an active substance master file. B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is supported by an ASMF	24/10/2013	n/a		
IG/0260	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/01/2013	n/a		
IB/0061	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	14/09/2012	n/a		

IB/0060/G	This was an application for a group of variations. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	16/05/2012	31/10/2012	SmPC and PL	C.I.3a) Based on the assessment of FUM 34.4 the MAH was requested to submit a type IB variation to include "elevated liver function test" with a frequency "common" and "hepatitis" with a frequency "unknown" in the table of section 4.8 of the memantine SmPC and relevant section of the PL. C.I.3a) Based on the assessment of PSUR 13 the MAH was requested to include "balance disorder" with a frequency "common" in the table of section 4.8 of the SmPC and the relevant section of the PL. As both of the above requests concern table 4.8 of the SmPC and relevant section of the PL, the update has been grouped in one Type IB variation. Further, the local representative for Luxembourg has been updated in all PLs.
II/0059	Addition of a new route of synthesis for the drug substance performed by an already approved drug substance 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	19/04/2012	19/04/2012		
II/0056	Following assessment of PSUR11, the CHMP requested the MAH to update section 4.2 of the SmPC with recommendations to review periodically the need to continue the treatment. C.I.3.b - Implementation of change(s) requested	22/09/2011	27/10/2011	SmPC, Annex II, Labelling and PL	Section 4.2 of the SmPC has been amended to reflect the following: "The tolerance and dosing of memantine should be reassessed on a regular basis, preferably within three months after start of treatment. Thereafter, the clinical benefit of memantine and the patient's tolerance of treatment should be reassessed on a regular basis

	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				according to current clinical guidelines. Maintenance treatment can be continued for as long as a therapeutic benefit is favourable and the patient tolerates treatment with memantine. Discontinuation of memantine should be considered when evidence of a therapeutic effect is no longer present or if the patient does not tolerate treatment."
IA/0058	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	25/07/2011	n/a		
IA/0057	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	13/07/2011	n/a		
IB/0055	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	10/12/2010	n/a		
II/0054	Following reports of overdose cases due to administration errors with the use of the new pump device approved for memantine oral drops, solution, the expression of the strength in the name of the product for the oral drop solution presentation has been changed to reflect the actual dose that is delivered by one pump actuation. "Axura 10mg/g, oral drop solution" was replaced by "Axura 5mg/pump, oral solution".	23/09/2010	25/10/2010	SmPC, Labelling and PL	Following reports of overdose cases due to administration errors with the use of the new pump device approved for memantine oral drops, solution, the expression of the strength in the name of the product for the oral drop solution presentation has been changed to reflect the actual dose that is delivered by one pump actuation. "Axura 10mg/g, oral drop solution" was replaced by "Axura 5mg/pump, oral solution". The term "drop" was removed from the product information

	The term "drop" was removed from the product information and the term "stroke" was replaced by "pump" throughout the Product Information. In addition, the phone number of the Austrian local representative in the PL has been updated for all presentations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				and the term "stroke" was replaced by "pump" throughout the Product Information. In addition, the phone number of the Austrian local representative in the PL has been updated for all presentations.
IA/0053	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	06/09/2010	06/09/2010	SmPC, Labelling and PL	
N/0052	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/07/2010	n/a	Labelling	
IB/0051	Update of the section 4.8 of the SmPC and corresponding section of the PL to include drug hypersensitivity as an ADR of Memantine. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	04/06/2010	n/a	SmPC and PL	
II/0050	Change in the composition of the 10 mg film-coated tablet	18/02/2010	23/03/2010	SmPC, Labelling and PL	

	Change in formulation				
II/0049	To add an alternative synthesis process for the active substance memantine hydrochloride. Quality changes	17/12/2009	20/01/2010		
II/0048	to change the administration device from a dropper to a dosing pump. Only the Axura oral drops solution presentations with a content of 50 g or 100 g are affected, AND to delete a presentation; the Aura oral drops solution with a content of 20 g. Quality changes	25/06/2009	31/07/2009	SmPC, Labelling and PL	
II/0047	To update section 4.8 of the Summary Product Information (SPC) to include Dyspnoea and a subsequent update of section 4 of the Package Leaflet (PL). In addition, the MAH included a linguistic correction in the Italian SPC section 4.8 and the name of the local representative in Spain was updated. Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	24/06/2009	SmPC and PL	Following the assessment of PSUR No. 10 of memantine (Axura) on 19 February 2009 the CHMP requested the Marketing Authorisation Holder (MAH) to submit within 2 months a Type II variation to include dyspnoea as an adverse drug reaction in section 4.8 of the SPC. The basis for the CHMP request was the result of a review of clinical trials that was performed to elucidate the incidence rates of dyspnoea. The events were analysed by dose, seriousness and indication. Overall, the incidence rates of dyspnoea were higher in patients treated with memantine compared to those receiving placebo. No notable differences between treatments were found when considered all studies with Alzheimer's dementia indication.
II/0046	to register an new starting material supplier Quality changes	29/05/2009	17/06/2009		

IB/0045	IB_38_c_Change in test procedure of finished product - other changes	03/02/2009	n/a		
IA/0044	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	14/01/2009	n/a		
II/0041	Update of section 4.8 (Undesirable Effects) of the Summary of Product Characteristics and section 4 of the Package Leaflet, to include "cardiac failure" (heart failure). Update of Summary of Product Characteristics and Package Leaflet	23/10/2008	02/12/2008	SmPC and PL	Following the assessment of PSUR 9, the CHMP requested data on heart failure observed during Axura use. Based on an analysis of the clinical data provided, 'cardiac failure' has been introduced to section 4.8 of the Summary of Product Characteristics and section 4 of the Package Leaflet (as 'heart failure').
IA/0043	IA_05_Change in the name and/or address of a manufacturer of the finished product	26/11/2008	n/a		
IB/0042	IB_38_c_Change in test procedure of finished product - other changes	12/11/2008	n/a		
IB/0038	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	20/06/2008	n/a		
IA/0039	IA_37_a_Change in the specification of the finished product - tightening of specification limits	22/05/2008	n/a		
X/0030	Annex I_2.(c) Change or addition of a new strength/potency	21/02/2008	08/05/2008	SmPC, Labelling and PL	The MAH applied for a new treatment initiation pack (5 mg, 10mg 15 mg and 20 mg of film-coated tablets) to facilitate the initial up-titration recommended for patients starting the therapy and a new 20 mg film-coated tablets to be

					used during the maintenance treatment. The new strengths are aimed to improve compliance with the dosing regimen of Axura and avoid confusion for the patients and caretakers by eliminating the need to divide tablets during the up-titration phase The formulation of the additional strengths (5 mg, 15 mg and 20 mg) is similar to the approved Axura 10 mg. All three strengths (5 mg, 15 mg, and 20 mg) of the newly formulated tablets were tested to determine their in vitro dissolution profile, which were considered similar.
II/0024	Update of section 4.2 of the Summary of Product Characteristics and section 3 of the Package Leaflet Update of Summary of Product Characteristics, Labelling and Package Leaflet	21/02/2008	08/05/2008	SmPC, Annex II, Labelling and PL	The scope of this variation application is to replace the currently recommended 10 mg twice-daily posology of memantine with a 20 mg once-daily dosing regimen for memantine. The CHMP agreed that the Pharmacokinetic data obtained in healthy volunteers showed minimal differences in the plasma concentration-time profile between twice-daily and once-daily dosing regimen. Five clinical studies in patients with AD supported the efficacy and safety assessment of the once-daily dosing regimen with memantine. In relation to efficacy results, no relevant differences were observed when AD patients were treated with memantine 20 mg once-daily with respect to patients treated with 10 mg twice-daily. In relation to the safety and tolerability both regimens showed similar safety profile.
IB/0037	IB_37_b_Change in the specification of the finished product - add. of new test parameter	07/05/2008	n/a		

IB/0033	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	19/09/2007	19/09/2007	SmPC, Labelling and PL	
IA/0036	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	19/09/2007	19/09/2007	SmPC, Labelling and PL	
IA/0035	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	19/09/2007	19/09/2007	SmPC, Labelling and PL	
IA/0034	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	19/09/2007	19/09/2007	SmPC, Labelling and PL	
II/0023	Update of section 4.5 of the Summary of Product Characteristics regarding data from three drug interaction studies looking at the effect of memantine and glyburide/metformin, donepezil and galantamine. Update of Summary of Product Characteristics	21/06/2007	30/07/2007	SmPC	The MAH submitted 3 drug interaction studies investigating the pharmacokinetic effect of memantine and glyburide/metformin, the pharmacokinetic effect of memantine and donepezil and the pharmacokinetic effect of memantine on galantamine. Section 4.5 of the SPC was updated to reflect the results of the studies as follows: In single-dose PK studies in young healthy subjects no relevant drug-drug interaction of memantine with glyburide/metformin or donepezil was observed and in a clinical study in young healthy subjects no relevant effect of memantine on the pharmacokinetics of galantamine was observed.
II/0022	Update of Summary of Product Characteristics regarding data from a study in patients with moderate hepatic impairment.	21/06/2007	30/07/2007	SmPC	The MAH performed a study to investigate the influence of the hepatic impairment on the pharmacokinetic profile of memantine.

	Update of Summary of Product Characteristics				The results of the pharmacokinetic study suggest that moderate hepatic impairment does not alter the pharmacokinetics of memantine. In patients with moderate hepatic impaired function (Child-Pugh A and Child-Pugh B) no dosage adjustment is needed. No data on the use of memantine in patients with severe hepatic impairment are available. The product information was updated to reflect these results.
II/0021	Update of Summary of Product Characteristics and Package Leaflet to give dose recommendations for patients with moderate and severe renal impairment. Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	30/07/2007	SmPC and PL	The MAH performed a pharmacokinetic study to investigate the influence of the renal impairment on the pharmacokinetic profile of memantine. The study showed that: The exposure of patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) is comparable to the exposure in healthy subjects. No dosage adjustment is required in these patients. The extent of exposure in patients with moderate renal impairment (creatinine clearance 30 49 ml/min) is about 60% higher than the extent of exposure of healthy subjects. In these patients the daily dose should be reduced to 10 mg per day. If tolerated well after at least 7 days of treatment, the dose could be increased up to 20 mg/day according to standard titration scheme. The exposure in patients with severe renal impairment (creatinine clearance 5 - 29 ml/min) is about 100% higher than in healthy subjects. In these patients the daily dose should be 10 mg per day.
IA/0032	IA_04_Change in name and/or address of a manuf.	27/07/2007	n/a		

	of the active substance (no Ph. Eur. cert. avail.)				
R/0015	Renewal of the marketing authorisation.	22/03/2007	20/06/2007	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 Axura continues to be favourable. The CHMP was also of the opinion that the renewal can be granted with unlimited validity; however, the MAH is required to continue to submit Periodic Safety Update Reports (PSURs) once a year at least until the final study reports of the two ongoing long-term (two years of exposure) trials are provided. The MAH has taken the opportunity to update the information on symptoms and treatment required in case of overdose. 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 Axura continues to be favourable.

					The CHMP was also of the opinion that the renewal can be granted with unlimited validity; however, the MAH is required to continue to submit Periodic Safety Update Reports (PSURs) once a year at least until the final study reports of the two ongoing long-term (two years of exposure) trials are provided. The MAH has taken the opportunity to update the information on symptoms and treatment required in case of overdose.
IB/0019	IB_37_b_Change in the specification of the finished product - add. of new test parameter	16/05/2007	n/a		
II/0017	Change(s) to the manufacturing process for the active substance	22/03/2007	30/03/2007		
II/0016	Change(s) to the manufacturing process for the active substance	22/03/2007	30/03/2007		
IB/0020	IB_37_b_Change in the specification of the finished product - add. of new test parameter	26/03/2007	n/a		
II/0014	Update of section 4.8 of the Summary of Product Characteristics and section 4 of the Package Leaflet with information on hypertension, venous thrombosis/thromboembolism and fungal infections as ADRs of memantine. Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	28/11/2006	SmPC and PL	Following the evaluation of Periodic Safety Update Report (PSUR 7), and the review provided by the MAH on specific adverse reactions the MAH was requested to submit a type II variation to update product information with information on hypertension, venous thrombosis/thromboembolism and fungal infections as Adverse Drug Reactions (ADRs) of memantine. This update was based on a review of the pooled

					comparative incidences of these ADRs from clinical trials. The incidence rates of hypertension were classified as common (4.1% in memantine treated patients vs 2.8% in placebo). Venous thrombosis/thromboembolism were classified as uncommon ADRs.
II/0013	This application concerns an update of the product information following the evaluation of the 6th PSUR. Section 4.5 of the SPC has been updated in relation to interactions with warfarin and section 4.8 of the SPC regarding pancreatitis, depression, suicidal ideation, suicide and psychotic reactions. Relevant sections of the PL was amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	23/03/2006	27/04/2006	SmPC and PL	Following the assessment of the 6th PSUR, the SPC and PL have been updated in relation to interactions with warfarin. Close monitoring of prothrombin time or INR in patients treated concomitantly with oral anticoagulants was advised which is also reflected in the SPC. Following PSUR 6, the MAH performed also a re-analysis of each individual case report with pancreatitis reported either through the spontaneous reporting system or in clinical trials. It was concluded that isolated cases of pancreatitis had been observed in post-marketing experience. Alzheimer's disease, has been associated with psychotic reactions, depression, suicidal ideation and suicide. Although confounding factors cannot be excluded, these events have been reported in patients treated with Memantine.
II/0011	Extension of Indication	13/10/2005	15/11/2005	SmPC and PL	Please refer to Scientific Discussion: Axura-H-378-II-11-SD
N/0012	The Marketing Authorisation Holder applied for some changes in the list of local representatives in the Package Leaflet. The MAH also tranlated the country "Germany" in the correspondent national language when reference is made to the German local representative.	29/04/2005	n/a	PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
II/0010	Update of sections 4.4, 4.5 and 4.8 of the Summary of Product Characteristics and relevant sections of Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	24/03/2004	13/07/2004	SmPC and PL	This variation relates to an update of sections 4.4 and 4.8 of the SPC following the assessment of the second PSUR to include information on the risk of convulsion in patients with previous history of convulsions. An existing warning on interaction with HCT has also been modified in section 4.5 of the SPC. In addition, minor linguistic modifications have been made to improve the quality of the translations and the local representative section of the PL has been updated.
I/0009	15_Minor changes in manufacture of the medicinal product	29/08/2003	18/09/2003		
I/0007	11a_Change in the name of a manufacturer of the active substance	14/07/2003	30/07/2003		
I/0006	30_Change in pack size for a medicinal product	13/08/2002	02/10/2002	SmPC, Labelling and PL	
I/0005	30_Change in pack size for a medicinal product	13/08/2002	02/10/2002	SmPC, Labelling and PL	
I/0004	30_Change in pack size for a medicinal product	13/08/2002	02/10/2002	SmPC, Labelling and PL	
I/0003	30_Change in pack size for a medicinal product	13/08/2002	02/10/2002	SmPC, Labelling and	

				PL	
I/0002	30_Change in pack size for a medicinal product	13/08/2002	02/10/2002	SmPC, Labelling and PL	
I/0001	02_Change in the name of the medicinal product (either invented name of common name)	21/06/2002	19/07/2002	SmPC, Labelling and PL	