Mimpara

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/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/06/2024		Labelling	
N/0073	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/11/2022		Labelling	

[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).

PSUSA/756/202202	Periodic Safety Update EU Single assessment - cinacalcet	27/10/2022	n/a		PRAC Recommendation - maintenance
N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/12/2021		PL	
IA/0070	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	22/03/2021	n/a		
IB/0069	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	09/02/2021	n/a		
II/0068	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	14/01/2021	n/a		
IA/0067	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	07/02/2020	n/a		
II/0065	Update of the SmPC, Annex II, labelling and Package Leaflet in line with the latest QRD template version 10.1 and implementation of a minor correction to the List of Excipients in section 6.1 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	23/01/2020	21/01/2021	SmPC, Annex II, Labelling and PL	N/A

	data				
PSUSA/756/201902	Periodic Safety Update EU Single assessment - cinacalcet	03/10/2019	n/a		PRAC Recommendation - maintenance
II/0062/G	This was an application for a group of variations. Update of section 4.2 of the SmPC to provide additional information with reference to switching from etelcalcetide to Mimpara (cinacalcet), upon request by PRAC following the assessment of the etelcalcetide PSUR (dated 14 June 2018). Further, the term 'silica, dental type' has been replaced by 'Amorphous silicon dioxide' in SmPC section 6.1. An updated RMP version 9.0 was provided as part of the application in order to align the RMP with the GVP Module V (template Rev 2) with consequential reclassification of existing safety concerns. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH 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	16/05/2019	01/07/2019	SmPC	The switch from etelcalcetide to Mimpara and the appropriate wash out period has not been studied in patients. In patients who have discontinued etelcalcetide, Mimpara should not be initiated until at least three subsequent haemodialysis sessions have been completed, at which time serum calcium should be measured. Ensure serum calcium levels are within the normal range before Mimpara is initiated.

N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/05/2019	01/07/2019	PL	
IA/0061	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)	27/07/2018	n/a		
IG/0946	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	04/06/2018	12/12/2018	PL	
IA/0058	B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised	28/02/2018	n/a		
IG/0853	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	10/11/2017	12/12/2018	Annex II and PL	
X/0055/G	This was an application for a group of variations. Extension application to introduce a new pharmaceutical form associated with new strengths (1 mg, 2.5 mg and 5 mg hard capsules) grouped with a type II variation (C.1.6.a) to include paediatric use in the approved indication.	22/06/2017	28/08/2017	SmPC, Annex II, Labelling and PL	

	As a consequence, the SmPC has been updated to detail information on paediatric patients and to update the safety information. The Package Leaflet and Labelling are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10. Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0056	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/04/2017	n/a		
PSUSA/756/201602	Periodic Safety Update EU Single assessment - cinacalcet	13/10/2016	08/12/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/756/201602.
N/0053	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/08/2015	08/12/2016	PL	
IA/0052	B.II.b.2.a - Change to importer, batch release	15/04/2015	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
II/0048	Update of section 4.8 of the SmPC to include the ADR 'back pain' and section 5.1 of the SmPC, based on the CSR from Study 20070277 and post-marketing data, to incorporate new information relating to the use of Mimpara for reduction of hypercalcaemia in patients with primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but in whom parathyroidectomy is not appropriate or contraindicated. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet, and to update the contact details for the local representative in Italy in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	08/07/2015	SmPC and PL	The objectives of this type II variation are to update the Product Information with information on the safety and the efficacy supported by a new study (20070277) in primary HPT patients with mild to moderate hypercalcaemia, who were unable to undergo parathyroidectomy. Study 20070277 (N=67) demonstrated a significantly higher frequency of normalisation of serum calcium (≤ 10.3 mg/dl) in the primary HPT population treated with cinacalcet versus placebo (75.8% and 0%, respectively). The study did not include patients with severe hypercalcaemia (total serum calcium > 11.3 mg/dl and ≤ 12.5 mg/dl), unlike the pivotal MA study 20000204 (s-calcium > 12.5 mg/dL). The results for the secondary efficacy endpoint (≥ 1 mg/dl decrease from baseline in serum calcium) in the cinacalcet group were similar to the efficacy seen in the pivotal study (84.8% versus 88%, respectively). In a pooled analysis of PHPT studies, there was an imbalance in hemorrhagic events, 10 (9.3%) in the cinacalcet arm and 2 (2.5%) in the placebo arm, respectively. All these events were non-serious. Furthermore, there were 4 serious cases of hemorrhagic events in an open-label extension phase. There are also 16 cases from post-marketing sources. This issue will be further assessed as part of future PSURs. The benefit-risk balance of Mimpara for the treatment of patients with primary HPT and hypercalcaemia remains

					positive.
IA/0050/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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure A.7 - Administrative change - Deletion of manufacturing sites B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)	01/07/2014	n/a		
N/0049	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/05/2014	08/07/2015	PL	
IA/0047	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	06/02/2014	n/a		
IAIN/0046	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	26/09/2013	n/a		
II/0042	Updating of the Summary of Product Characteristic	19/09/2013	13/12/2013	SmPC and PL	This Type II variation seeks to update the Summary of

	(Sections 4.2, 4.4, 4.8 and 5.1 of the SmPC) and package leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				Product Characteristic (Sections 4.2, 4.4, 4.8 and 5.1 of the SmPC) to incorporate new or revised information, within the special warnings and precautions for use, undesirable effects and pharmacodymanic properties sections as detailed below. These updates include revisions following the completion of Study 20050182, the long term study of cinacalcet in chronic kidney disease (CKD) patients on dialysis entitled "Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events" (EVOLVE) and a subsequent additional review of data pertaining to hypocalcemia and neoplastic events. EVOLVE (EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events) was a randomized, double-blind clinical study evaluating cinacalcet HCl vs. placebo for the reduction of the risk of all-cause mortality and cardiovascular events in 3,883 patients with secondary HPT and CKD receiving dialysis. Data from the recently completed Study 20050182, taken together with analyses of postmarketing data, add to the existing body of clinical experience in a larger population with longer exposure time. The overall benefit-risk balance for cinacalcet for the treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy is considered to remain favourable. The MAH´s proposed changes to the SmPC are now considered acceptable by the CHMP.
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/09/2013	13/12/2013	PL	
IA/0044/G	This was an application for a group of variations.	18/07/2013	n/a		

	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.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
IB/0043	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	05/07/2013	13/12/2013	SmPC	
IA/0041	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	09/04/2013	n/a		
IAIN/0040	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/03/2013	n/a		
IG/0247	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/12/2012	n/a		
II/0038	Update of sections 4.4 and 4.8 of the SmPC, upon request by the CHMP, in order to add a warning and update the safety information related to the risk of QT prolongation/ventricular arrhythmias for Mimpara. The Package Leaflet is updated	13/12/2012	13/12/2013	SmPC and PL	The PRAC discussed a signal of QT prolongation/ventricular arrhythmias associated with cinacalcet, during its meeting in September 2012, following the retrieval of 15 cases of QT prolongation/ventricular arrhythmias reported in Eudravigilance until 4 July 2012. Upon request by the

	accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				CHMP, the MAH submitted a variation application to update the product information and respond to a number of questions raised by the PRAC. Following the assessment of questions provided, although there is no evidence of a direct effect on repolarisation, there is an obvious risk of QT prolongation/ventricular arrhythmia given the primary pharmacological effect of cinacalcet. Thus, information about this risk has been added to section 4.4 of the SmPC, where other secondary effects to hypocalcemia are listed: "Caution is advised in patients with other risk factors for QT prolongation such as patients with known congenital long QT syndrome or patients receiving medicinal products known to cause QT prolongation". The ADR "QT prolongation and ventricular arrhythmia secondary to hypocalcemia" has been added to section 4.8 of the SmPC and the Package Leaflet has been updated accordingly.
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/11/2012	13/12/2013	PL	
IA/0037	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	09/11/2012	n/a		
IA/0035	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	20/07/2012	n/a		
IAIN/0034/G	This was an application for a group of variations.	16/05/2012	n/a		

	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV 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				
IB/0033/G	This was an application for a group of variations. B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	10/05/2012	n/a		
II/0029	The MAH submitted a variation type II to update several sections in the SPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/01/2012	21/02/2012	SmPC and PL	To update the SPC and Patient Information Leaflet (PIL) to include additional wording relating to seizures (sections 4.4 and 4.8 of the SmPC), to include the lack of information related to fertility (section 4.6 of the SmPC and section 2 of the PIL), to clarify and correct the interactions sections (Section 4.5 of the SmPC and section 2 of the PIL) and to update the SPC according to QRD 8.0 template, and minor editorial /typographical corrections.
IA/0032	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/01/2012	n/a		

IA/0031	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/01/2012	n/a		
IB/0030/G	This was an application for a group of variations. 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.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	03/11/2011	n/a		
IA/0028	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	12/08/2011	n/a		
IA/0027/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV 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	28/06/2011	n/a	Annex II	

IA/0025/G	This was an application for a group of variations. C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database 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	09/11/2010	n/a	Annex II	
IA/0024/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV 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 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	27/08/2010	n/a	Annex II	
IB/0023	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	20/04/2010	n/a		
IB/0026/G	This was an application for a group of variations.	25/02/2010	n/a		

	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits				
R/0020	Renewal of the marketing authorisation.	25/06/2009	23/09/2009	SmPC, Annex II and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile continues to be favourable. The MAH will continue to submit yearly PSURs, unless otherwise specified by the CHMP. The CHMP was also of the opinion that the renewal can be granted with unlimited validity.
II/0021	Update of section 4.8 of the Summary of Product Characteristics and section 4 of the Package Leaflet to add safety text regarding postmarketing observations of very rare reports of angioedema and urticaria in association with cinacalcet in line with the recently revised Core Data Sheet. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	31/08/2009	SmPC and PL	Based on the review data to present a safety analysis of reports concerning angioedema and other severe anaphylactic reactions received since start of marketing, the MAH was requested to submit a type II variation to update the section 4.8 of the SPC including angioedema and urticaria as a not known frequency under Post-marketing Experience item.
IA/0022	IA_13_a_Change in test proc. for active substance - minor change	31/07/2009	n/a		
II/0016	To implement changes in the manufacturing process (mainly the tabletting step) and the container closure system of the finished product.	29/05/2009	02/07/2009	SmPC and PL	

	Quality changes				
II/0015	Update of section 5.2 of the Summary of Product Characteristics (SPC) with information regarding the pharmacokinetic profile of cinacalcet in paediatric patients (aged 6-17 years) with Chronic Kidney Disease (CKD) receiving dialysis following a single 15 mg dose. Update of Summary of Product Characteristics	19/02/2009	27/03/2009	SmPC	Study 20030227 was designed to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of a single 15-mg dose of cinacalcet in paediatric subjects 6 to 17 years of age with CKD receiving dialysis. The results of the study showed that the mean AUC0-t and Cmax values following administration of a single 15 mg dose of cinacalcet for the combined paediatric cohorts (aged 6-17 years) were within approximately 30% of the mean AUC0-t and Cmax values observed in a single study in healthy adults following administration of a single 30 mg dose of cinacalcet (Study 20060133). Due to the limited data in paediatric subjects, the potential for higher exposures in the lighter/younger relative to heavier/older paediatric subjects for a given dose of cinacalcet cannot be excluded.
IA/0019	IA_09_Deletion of manufacturing site	04/03/2009	n/a		
IA/0018	IA_09_Deletion of manufacturing site	04/03/2009	n/a		
IA/0017	IA_09_Deletion of manufacturing site	04/03/2009	n/a		
II/0014	Update of the Detailed Description of the Pharmacovigilance system (DDPS) version 3.0. Update of DDPS (Pharmacovigilance)	25/09/2008	29/10/2008	Annex II	The MAH updated the Detailed Description of the Pharmacovigilance system (DDPS) with administrative changes to provide further clarity.
IB/0013	IB_12_a_Change in spec. of active subst./agent used	29/07/2008	n/a		

	in manuf. of active subst. - tightening				
II/0010	Addition of a new indication for reduction of hypercalcaemia in patients with primary hyperparathyroidism (HPT), for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated. The Package Leaflet has been updated further to the results of the readability testing. The list of local representatives has been updated. In addition, the MAH has submitted the Pharmacovigilance System (version 2.1) and an updated Risk Management Plan (version 1.0). Annex II has been updated to reflect this update. Extension of Indication	24/04/2008	19/06/2008	SmPC, Annex II and PL	For further information please refer to the conclusion: Mimpara H-C-570-II-10-AR-Variation.
II/0011	Update section 4.4 of the SPC to reflect data from the Study 20020158 regarding testosterone levels, as requested by the CHMP. Update of Summary of Product Characteristics	21/02/2008	17/03/2008	SmPC	Update to section 4.4 of the Summary of Product Characteristics (SPC) with the results of the Study 20020158, showing no further reductions in free and total testosterone concentrations over a period of 3 years in cinacalcet-treated patients.
IA/0012	IA_13_a_Change in test proc. for active substance - minor change	13/02/2008	n/a		

II/0009	Update of the section 4.5 of the Summary of Product Characteristics to reflect the data from the study 20050226 using midazolam, demonstrating that the co-administration of cinacalcet would not alter the pharmacokinetics of classes of drugs metabolised by CYP3A4 and CYP3A5 enzymes. Update of Summary of Product Characteristics	15/11/2007	21/12/2007	SmPC	The study 20050226 was a randomized, single center, open-label, 2-period, 2 treatment, 2-sequence, crossover study in healthy volunteers. The results show no effect of cinacalcet on midazolam plasma concentrations indicating low inhibitory potential of cinacalcet on CYP3A4/5. These data suggest that cinacalcet would not affect the pharmacokinetics of those classes of drugs that are metabolized by CYP3A4 and CYP3A5, such as certain immunosuppressants, including cyclosporine and tacrolimus.
II/0007	Update of the Summary of Product Characteristics (SPC), sections 4.4 and 5.1, to reflect Safety data from the final analysis of Study 20000178, assessing the safety and efficacy of cinacalcet in patients with chronic Kedney Disease (CKD) with secondary hygerparathyroidism, not on dialysis (CKD stage 3 and 4 population). Update of Summary of Product Characteristics	19/07/2007	31/08/2007	SmPC	The MAH submitted the Study 20000178 in patients with secondary HPT and CKD not receiving dialysis. The efficacy results of this study were presented and they were in principle consistent with those previously submitted. Even if the current study was modified to reduce the incidence of hypocalcaemia, the incidence of low serum calcium concentrations remained in principle similar with that observed in previous studies. The events of hypocalcemia were predominantly asymptomatic laboratory findings without discernible clinical sequelae. Consequently section 4.4 of the SPC was updated to include the warning for hypocalcaemia in patients not on dialysis compared with cinacalcet-treated CKD patients on dialysis. Section 5.1 of the SPC has been updated as well to include the information derived from the study 20000178 in patients with CKD and secondary HPT not undergoing dialysis.
II/0008	Update of safety information following observations from post-marketing surveillance to include hypotension and/or worsening of heart failure, in sections 4.4 and 4.8 of the SPC, as weel as diarrheoa in sections 4.8 and in line with the recently revised	19/07/2007	30/08/2007	SmPC, Labelling and PL	The MAH has submitted this variation application to update the SPC and the PL with post-marketing information and post-hoc analysis of clinical trials regarding cases of hypotension and/or worsening of heart failure in patients. In addition diarrhea has been added to section 4.8 of the

	Core Data Sheet. The section 4 of the Package Leaflet has been updated to reflect these changes, as well as minor editorial corrections. The contact details of the local representatives of Bulgaria and Romania have also been inserted. The Latvian local representative contact details have been amended. Minor editorial corrections are inserted in Labelling. Update of Summary of Product Characteristics, Labelling and Package Leaflet				SPC and in the relative section of the PL. The contact details of the local representatives of Bulgaria and Romania have also been inserted. Minor editorial corrections are inserted in Labelling.
II/0006	Update of Summary of Product Characteristics	01/06/2006	13/07/2006	SmPC	
IB/0005	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	19/04/2006	n/a	SmPC	
II/0004	Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/02/2006	29/03/2006	SmPC, Annex II, Labelling and PL	
II/0003	Update of Summary of Product Characteristics and Package Leaflet	26/01/2006	28/02/2006	SmPC and PL	
IB/0001	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	02/02/2005	n/a	SmPC	
IA/0002	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	27/01/2005	n/a		