EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Crixivan

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
IG/0994	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2018		SmPC	
T/0104	Transfer of Marketing Authorisation	17/07/2018	03/08/2018	SmPC, Labelling and PL	
N/0103	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/06/2018	03/08/2018	Labelling and 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).

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PSUSA/1733/201709	Periodic Safety Update EU Single assessment - indinavir	12/04/2018	n/a		PRAC Recommendation - maintenance
IB/0101	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/01/2016	12/12/2016	SmPC and PL	
IA/0100	A.7 - Administrative change - Deletion of manufacturing sites	20/05/2015	n/a		
II/0099	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	11/03/2015	SmPC and PL	
IB/0098	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/03/2014	11/03/2015	SmPC and PL	To implement the changes requested by CHMP to section 4.4 Precautions and Warnings of the SmPC to update the product information with updated wording concerning the risk of sexual transmission of HIV when taking Crixivan. The PL is updated accordingly.
IB/0097	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/12/2013	31/01/2014	SmPC, Annex II and PL	Update of the sections 4.3 and 4.5 of the SmPC and the PL with information on drug drug interaction with quetiapine in line with the class labelling for protease inhibitors. In addition, update the SmPC, Annex II and PL in line with the QRD template v.9 and addition of the local representative for Croatia. Finally, some editorial corrections to the translations have been made.
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 PSMF location	08/11/2013	n/a		

N/0094	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/05/2013	31/01/2014	PL	The Marketing Authorisation Holder updated the Package Leaflet following the results of a User Testing.
IB/0095	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	24/05/2013	31/01/2014	SmPC and PL	To include in SmPC sections 4.4 and 4.8 information regarding autoimmune disorders under Immune Reactivation Syndrome, following a class labelling for all antiretrovirals as requested by the CHMP. The changes have also been reflected in the PL.
N/0093	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/12/2012	31/01/2014	PL	The MAH updated the PL following the results of a User Testing.
IG/0182	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/08/2012	n/a		
IB/0088/G	This was an application for a group of variations. C.I.7.b - Deletion of - a strength C.I.6.b - Change(s) to therapeutic indication(s) - Deletion of a therapeutic indication	11/02/2012	n/a	SmPC, Annex II, Labelling and PL	The 100 mg strength of Crixivan capsule has been deleted further to the MAH decision to discontinue this strength. The paediatric indication in children aged 4 to 18 years has also been deleted based on the fact that treatment could no longer be attained with the remaining dosage forms of 200 mg and 400 mg capsules. Taking into consideration that there are alternatives available for children within the class of protease inhibitors the changes proposed to the product information were considered appropriate. The MAH also took the opportunity to introduce minor linguistic corrections and updates in line with the latest QRD template which were accepted.
II/0089/G	This was an application for a group of variations. Addition of manufacturing site as an alternate manufacturer and to register the same site as a batch	19/01/2012	19/01/2012		

	control/ testing site of CRIXIVAN 200 mg and 400 mg capsules. Changes to the manufacturing process (as a consequence to the manufacturing site transfer) and; Downscaling of the batch size up to 10-fold as a consequence to the manufacturing site transfer. 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 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				
IG/0112	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	11/10/2011	n/a		

R/0087	Renewal of the marketing authorisation.	19/05/2011	18/07/2011	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 Crixivan continues to be favourable. There is no evident new safety signal of concern from the review in the 3rd Renewal application of Crixivan. Although no new safety concerns has been indicated in the pediatric population from the data submitted, the product information has been revised in order to adequately reflect the substantially higher risk of nephrolithiasis in children compared with adults (approximately 30% in children versus 12.4% in adults). Section 4.4 of the SmPC has been revised accordingly. The CHMP is of the opinion that the renewal can be granted with unlimited validity. The product information has also been updated to be in line with the current QRD template and SmPC guideline. The list of local representatives in the package leaflet has been revised to amend contact details for all representatives.
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	

IA/0086/G	This was an application for a group of variations. To change in the name of a manufacturer of the active substance and the finished product from Merck & Co. Inc to Merck Sharp & Dohme Corp. 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 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)	14/06/2010	n/a		
IB/0085	Update of section 4 of the PL to add 2 side effects (inflammation of the liver, liver failure and itching) which are currently in section 4.8 of the SmPC. Minor linguistic changes have been implemented in the FR, BG, DE and ES annexes. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/05/2010	n/a	PL	
IA/0084	B.II.a.3.b.1 - Changes in the composition (excipients) of the finished product - Other excipients - Any minor adjustment of the quantitative composition of the finished product with respect to excipients	08/04/2010	n/a	SmPC and PL	
II/0081	Update sections 4.4 and 4.5 of the SmPC to add interaction information on the concomitant use of indinavir and atazanavir based on mechanistic	19/11/2009	22/12/2009	SmPC and PL	Data from the literature indicate that indinavir causes hyperbilirubinemia via competitive inhibition of bilirubin UDP-glucuronosyltransferase 1A1 (UGT1A1) activity. In

	reasoning on their metabolic pathways. The PL was updated accordingly. The MAH also revised the full section 4.8 as requested by the CHMP to bring it in line with the latest version in force of the Guideline on SmPC. Minor typographical errors were corrected throughout the SmPC. Update of Summary of Product Characteristics and Package Leaflet				addition to UGT1A1 inhibition, indinavir has also been demonstrated to inhibit an organic anion-transporting polypeptide (OATP1B1), a hepatic uptake transporter for bilirubin, which provides an additional potential mechanism for indinavir-induced hyperbilirubinemia. Use of atazanavir is also associated with reversible indirect (unconjugated) hyperbilirubinemia related to inhibition of UGT. Although the combinations of indinavir and atazanavir with or without ritonavir have not been studied the co-administration of these medicinal products is not recommended due to risk of worsening of hyperbilirubinemia. In addition, the full section 4.8 has been revised in line with the recommendations of the Guideline in force on Summary of Product Characteristics including a summary of safety profile, a tabulated summary of adverse reactions reported with indinavir, a description of selected adverse reactions and a description of events reported in paediatric patients.
IA/0083	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	28/07/2009	n/a		
II/0082	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)	25/08/2009	14/07/2009	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.
IA/0080	IA_47_b_Deletion of a strength	16/02/2009	n/a	SmPC, Labelling and PL	
II/0078	Update of section 4.3 and section 4.5 of the SPC to implement the class labelling text agreed by the CHMP	25/09/2008	29/10/2008	SmPC and PL	In 2005 an interaction study on saquinavir boosted with ritonavir together with rifampicin in healthy volunteers had

	in May 2008 on the combination of rifampicin with indinavir given with concomitant low-dose ritonavir. Minor linguistic corrections were made for the Hungarian SPC. Updates were also made to the list of local representatives. Update of Summary of Product Characteristics and Package Leaflet				to be prematurely discontinued due to an increased risk of hepatotoxicity associated with this co-administration. The mechanism for this interaction is not fully elucidated. It has been hypothesised that the predominant effect between the inducer effect of rifampicin and the inhibitor effect of the boosted protease inhibitors might depend on the boosted protease inhibitor involved. Lacking the results of specific interaction studies, the CHMP concluded as a conservative measure to reinforce the contraindication with rifampicin in section 4.4 and improve the guidance provided to physicians regarding the interaction of boosted protease inhibitors with rifampicin in section 4.5.
N/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/09/2008	n/a	Labelling	
II/0075	Update of sections 4.4 and 4.5 of the SPC with new information on the co-administration with HMG-CoA reductase inhibitors. Section 2 of the PL was updated accordingly. The MAH also took the opportunity to update the contact details of some local representatives in the PL. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	20/06/2008	SmPC and PL	In a pharmacokinetic study, co-administration of rosuvastatin (20 mg) and lopinavir/ritonavir (400 mg/ 100 mg) in healthy volunteers resulted in a 2.1 and 4.7-fold increase in rosuvastatin AUC and Cmax respectively. The exact mechanism of interaction behind this significant increase of rosuvastatin exposure is unknown. In view of these results, concomitant use of rosuvastatin with protease inhibitors (PIs) is not recommended. The limited pharmacokinetic data that is available on the interactions between PIs and the HMG-CoA reductase inhibitors (statins) that are not metabolised by cytochrome CYP3A4 do not allow for predictions to be made as to the effects of a given individual PI on an individual statin. Based on literature data, there is evidence that pravastatin and fluvastatin are substrates of transport proteins; thus an interaction between these HMG-CoA reductase inhibitors and indinavir via effect

					on transport proteins cannot be excluded. Therefore, it is considered no longer adequate to recommend pravastatin and fluvastatin as HMG-CoA reductase inhibitors of choice in the Crixivan SPC.
II/0071	Update of sections 4.2, 4.3, 4.4, 4.5, 5.1 and 5.2 of the SPC with information on the use of Crixivan in a ritonavir boosted regimen and with updated interaction data. The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	20/06/2008	SmPC and PL	The current recommended dosage of Crixivan is 800 mg every 8 hours. However, as several other protease inhibitors, indinavir is mainly used in clinical practice at a lower dose in a ritonavir-boosted regimen, i.e. indinavir (400 mg) / ritonavir (100 mg) twice daily. This alternative regimen, substantiated by data from published studies, has now been reflected in the product information. As a consequence, information on contra-indications and drug interactions relevant to co-administration with ritonavir has also been included. Moreover, in line with the latest CHMP recommendations for HIV medicines, the interaction section has been rearranged in a tabular format with up-to-date information and clear recommendations.
IB/0076	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	19/12/2007	n/a		
IA/0077	IA_11_b_Change in batch size of active substance or intermediate - downscaling	13/12/2007	n/a		
II/0074	Update of sections 4.3 and 4.5 of SPC and section 2 of the PL as regards the interaction with oral and parenteral midazolam, following CHMP request in March 2007. Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	24/07/2007	SmPC and PL	Based on available data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally than when it is injected. Therefore, the coadministration of Crixivan with orally administered midazolam is contraindicated, whereas caution should be used when Crixivan is co-administrated with injection of midazolam. If Crixivan is co-administered with injectable midazolam, it

					should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered. Sections 4.3 and 4.5 of the SPC and section 2 of the PL are updated with this information.
II/0073	Update of section 4.8 of the SPC based on a cumulative safety review of the post-marketing experience to include the term "renal failure". The PL was updated accordingly. Additionally, the MAH took the opportunity to delete duplicate information in section 4 and to replace the term "container" by "bottle" in section 5 of the PL. Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	24/07/2007	SmPC and PL	Based upon the review of cases reported in clinical trials and in the post-authorisation setting, the Undesirable events section was updated with the addition of the term "renal failure". The section 4 "Possible side effects" of the PL was updated accordingly with the inclusion of "loss of renal function". In addition, duplicate information from section 4 of the PL was deleted, the term "container" was replaced by "bottle" in the section 5 of the PL and the Maltese local representative contact was updated.
II/0072	Update of section 4.3 of the SPC to include amiodarone in the list of agents with narrow therapeutic indexes that are also inhibitors of CYP3A4. This update is based on a review of literature data. Consequentially, the PL is updated as well. The MAH took this opportunity to update contact details of the Finnish local representative. Update of Summary of Product Characteristics and Package Leaflet	22/03/2007	03/05/2007	SmPC and PL	The section on contraindications was updated to include amiodarone as a medicine that must not be coadministered with indinavir. The coadministration of amiodarone with indinavir is contraindicated due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias. This is based on the fact that both agents share the CYP3A4 mediated metabolic pathway and therefore co-administration could lead to overexposure of amiodarone and/or indinavir. Additionally as amiodarone is a medicinal product with a narrow therapeutic index, such blood plasma concentration elevations could lead to possibly fatal

					overdosing.
II/0070	Update of section 4.4 and 4.8 of the SPC and section 2 of the PL to implement the class labelling text on osteonecrosis, agreed by the CHMP in September 2006. Section 6 of the PL was updated with the local representatives in Bulgaria, Romania and Norway. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	24/01/2007	SmPC and PL	Cases of osteonecrosis (death of the bone tissue resulting from an insufficient blood supply) have been reported in HIV-infected patients since the end of the 80's. Although the cause of this disease could be due to multiple factors (including the use of corticosteroids, alcohol consumption, severe immunosuppression, higher body mass index) it has occurred specially in patients with HIV advanced disease and/or in patients with long term use of combination antiretroviral therapy (CART). Further to the review of all available data the CHMP agreed that this information should now be included in the SPC and PL of all antiretroviral medicinal products. Patients should be warned to seek medical advice in case they experience joint stiffness, aches and pain especially of the hip, knee and shoulder or if they experienced any difficulty in movement.
II/0069	Update of section 4.8 of the SPC and section 4 of the PL based on a safety review to include the terms renal insufficiency and pyelonephritis. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	24/01/2007	SmPC and PL	Based on the assessment of the safety review of medical literature available in the public domain and of spontaneous adverse events reports collected in the MAH's worldwide adverse events database, cases of "renal insufficiency" and "pyelonephritis" have been identified during the post-marketing experience. Consequentially this information was added to the Product Information.
R/0068	Renewal of the marketing authorisation.	21/09/2006	20/11/2006	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 was 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 Crixivan continues to be favourable. Nevertheless the CHMP acknowledged that due to the

					introduction of other HIV-1 protease inhibitors with better safety and efficacy properties, the clinical use of Crixivan has been declining steadily during the last 6 - 7 years. Crixivan is no longer a drug of choice for first line HIV-therapy. Therefore, considering the remaining safety concerns that the MAH has committed to address in connection with future PSURs (i.e cumulative reviews of post-marketing data with regard to renal impairment and the risk for QT-prolongation), and the uncertainty of the place of indinavir in the future management of HIV-1 infected patients, the CHMP recommended that the renewal is limited to five years. Finally, the CHMP recommended that the annual PSURs should be submitted for at least three years.
II/0067	To update section 4.5 of the SPC to include interaction of indinavir with venlaflaxine, as requested by the CHMP further to the assessment of PSUR (13.09.2003-12.09.2004) for Crixivan. Local representatives for Poland and Slovak Republic have been updated in section 6 of the PL. Update of Summary of Product Characteristics and Package Leaflet	23/06/2005	01/08/2005	SmPC and PL	Data are available from a published drug-drug interaction study performed in 9 healthy volunteers. In this study, venlaflaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in AUC and a 36% decrease in Cmax of a singe 800 mg oral dose of indinavir 800 mg single dose. The mechanism for this interaction is unclear and the clinical significance is not known. Section 4.5 of the SPC was amended to reflect this information.
II/0066	To update section 4.4 and 4.8 of the SPC and section 2 of the PL to implement the Class Labelling text regarding the Immune Reactivation Syndrome, as adopted by the CHMP. Update of Summary of Product Characteristics,	18/11/2004	05/01/2005	SmPC, Labelling and PL	In patients treated with any type of combination antiretroviral therapy (CART), an inflammatory response to indolent or residual opportunistic infections may occur, when the immune system responds to treatment. In most cases the inflammatory reaction towards the opportunistic pathogens is not foreseen since the

	Labelling and Package Leaflet				opportunistic infection has not been detected/ diagnosed. If diagnosed prior to the institution of CART, the treatment against the opportunistic infection (OI) is usually given priority. In particular, this is true for the complications most feared in this context; CMV-retinitis, generalised mycobacterial infections and Pneumocystis carinii pneumonia. An additional reason for treating the OI and the HIV-infection sequentially is the great risk of adverse events (toxicity or lack of effect) due to drug interactions. The clinical consequence of the reactivation of the immune system in patients starting CART cannot be prevented and the early recognition and diagnose of these inflammatory reaction is considering to be important for the clinical handling of the patients. Therefore, further to the assessment of the MAH's responses and discussions held at the Pharmacovigilance working party and CHMP, the CHMP adopted a class labelling text regarding the reactivation of the immune system of HIV-infected patients treated with any type of combination antiretroviral therapy (CART) to be implemented in the product information of all anti-retroviral medicinal products.
II/0064	Update of Summary of Product Characteristics and Package Leaflet	29/07/2004	09/09/2004	SmPC and PL	
IA/0065	IA_47_c_Deletion of a pack size(s)	20/08/2004	n/a	SmPC, Labelling and PL	
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/05/2004	09/09/2004	PL	

IA/0062	IA_32_b_Change in batch size of the finished product - downscaling down to 10-fold	25/03/2004	n/a		
II/0060	Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	30/01/2004	SmPC and PL	
I/0061	20_Extension of shelf-life as foreseen at time of authorisation	28/08/2003	03/10/2003	SmPC	
II/0058	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	26/06/2003	SmPC and PL	
I/0059	20a_Extension of shelf-life or retest period of the active substance	26/06/2003	26/06/2003		
II/0057	Update of Summary of Product Characteristics and Package Leaflet	20/02/2003	08/05/2003	SmPC and PL	
II/0052	Update of Summary of Product Characteristics and Package Leaflet	27/06/2002	17/10/2002	SmPC and PL	
I/0056	16_Change in the batch size of finished product	10/09/2002	17/09/2002		
I/0055	15_Minor changes in manufacture of the medicinal product	10/09/2002	17/09/2002		
I/0054	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	10/09/2002	17/09/2002		
I/0053	12_Minor change of manufacturing process of the active substance	12/07/2002	15/07/2002		

II/0051	Change(s) to the test method(s) and/or specifications for the finished product	30/05/2002	07/06/2002		
II/0050	Update of Summary of Product Characteristics and Package Leaflet	13/12/2001	21/03/2002	SmPC and PL	
I/0048	17_Change in specification of the medicinal product	01/06/2001	05/07/2001		
I/0047	04_Replacement of an excipient with a comparable excipient	01/06/2001	05/07/2001		
I/0046	07_Change in coating weight of tablets or change in weight of capsule shells	01/06/2001	05/07/2001		
II/0040	Update of Summary of Product Characteristics and Package Leaflet	01/03/2001	08/06/2001	SmPC, Labelling and PL	
I/0045	26_Changes to comply with supplements to pharmacopoeias	28/03/2001	06/04/2001		
II/0041	Change(s) to the manufacturing process for the active substance Quality changes	01/03/2001	13/03/2001		
I/0042	32_Change of imprints/bossing/marking on tablets/printing on capsules, incl. addition/change of inks	20/12/2000	n/a		
I/0039	15_Minor changes in manufacture of the medicinal product	20/11/2000	18/12/2000		

X/0036	X-3-iii_Addition of new strength	29/06/2000	16/11/2000	SmPC, Annex II, Labelling and PL	
II/0038	Update of Summary of Product Characteristics and Package Leaflet	16/03/2000	05/07/2000	SmPC and PL	
II/0033	Update of Summary of Product Characteristics and Package Leaflet	14/01/2000	11/05/2000	SmPC and PL	
I/0035	30_Change in pack size for a medicinal product	10/02/2000	11/05/2000	SmPC, Labelling and PL	
I/0034	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	10/02/2000	11/05/2000	Annex II and PL	
I/0032	20_Extension of shelf-life as foreseen at time of authorisation	27/10/1999	21/02/2000	SmPC	
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/02/2000	11/05/2000	Labelling	
I/0030	30_Change in pack size for a medicinal product	27/10/1999	08/02/2000	SmPC, Labelling and PL	
II/0027	Update of Summary of Product Characteristics and Package Leaflet	30/07/1999	08/12/1999	SmPC and PL	
II/0025	Update of Summary of Product Characteristics and Package Leaflet	30/07/1999	08/12/1999	SmPC, Labelling and PL	

I/0028	20_Extension of shelf-life as foreseen at time of authorisation	25/08/1999	08/12/1999	SmPC	
I/0031	08_Change in the qualitative composition of immediate packaging material	27/10/1999	n/a		
II/0026	Change(s) to the test method(s) and/or specifications for the finished product	30/07/1999	10/09/1999		
I/0029	12_Minor change of manufacturing process of the active substance 15_Minor changes in manufacture of the medicinal product	07/09/1999	n/a		
II/0022	Update of Summary of Product Characteristics and Package Leaflet	17/12/1998	19/04/1999	SmPC and PL	
X/0021	X-3-iii_Addition of new strength	17/12/1998	13/04/1999	SmPC, Annex II, Labelling and PL	
II/0023	Update of Summary of Product Characteristics and Package Leaflet	19/11/1998	12/03/1999	SmPC and PL	
I/0024	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	17/02/1999	26/02/1999		
II/0020	New presentation(s)	23/07/1998	06/11/1998	SmPC, Labelling and PL	
II/0019	Update of Summary of Product Characteristics and Package Leaflet	24/06/1998	29/10/1998	SmPC and PL	

II/0016	Update of Summary of Product Characteristics	25/02/1998	24/06/1998	SmPC	
I/0014	20_Extension of shelf-life as foreseen at time of authorisation	09/02/1998	13/05/1998	SmPC	
I/0013	07_Change in coating weight of tablets or change in weight of capsule shells 17_Change in specification of the medicinal product	09/02/1998	13/05/1998	SmPC	
II/0007	Update of Summary of Product Characteristics and Package Leaflet	17/12/1997	29/04/1998	SmPC and PL	
S/0006	Annual re-assessment.	17/12/1997	08/04/1998	SmPC, Annex II and PL	
I/0018	24_Change in test procedure of active substance	24/03/1998	n/a		
I/0017	25_Change in test procedures of the medicinal product	12/03/1998	n/a		
I/0015	25_Change in test procedures of the medicinal product	09/02/1998	n/a		
I/0012	15_Minor changes in manufacture of the medicinal product	09/02/1998	n/a		
I/0011	24_Change in test procedure of active substance	09/02/1998	n/a		
I/0010	24_Change in test procedure of active substance	09/02/1998	n/a		
I/0009	14_Change in specifications of active substance	09/02/1998	n/a		

I/0008	12_Minor change of manufacturing process of the active substance	09/02/1998	n/a		
II/0005	Update of Summary of Product Characteristics and Package Leaflet	24/09/1997	22/01/1998	SmPC and PL	
II/0003	Update of Summary of Product Characteristics and Package Leaflet	15/05/1997	27/08/1997	SmPC and PL	
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/07/1997	01/10/1997	Labelling	
I/0001	20_Extension of shelf-life as foreseen at time of authorisation	10/04/1997	13/06/1997	SmPC	
I/0002	13_Batch size of active substance	10/04/1997	n/a		