Invirase

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
IA/0128	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/10/2018		SmPC	
IA/0127	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)	17/08/2018	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).

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N/0126	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/08/2018		PL	
IB/0125	C.I.7.a - Deletion of - a pharmaceutical form	26/07/2018		SmPC, Labelling and PL	
PSUSA/2684/ 201712	Periodic Safety Update EU Single assessment - saquinavir	14/06/2018	n/a		PRAC Recommendation - maintenance
T/0124	Transfer of Marketing Authorisation	20/02/2018	23/03/2018	SmPC, Labelling and PL	
II/0122	Update of sections 4.2, 4.3, and 4.5 of the SmPC following an update to the Company Core Data Sheet in order to include a cross-reference to a new contraindication against switching from rilpivirine to invirase/ritonavir (section 4.2), to include lurasidone in the contraindications section (section 4.3) and to add information on additional interactions regarding lurasidone, rilpivirine, and tyrosine kinase inhibitors (section 4.5). The existing information regarding the interaction with alfuzosin has been updated to include a warning that co-administration may also cause potentially life-threatening cardiac arrhythmia. The existing information regarding interaction with medicines listed in the section 'neuroleptics' has been moved to the section 'antipsychotics' (section 4.5). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct formatting and minor typographical errors in the PI.	15/02/2018	20/03/2018	SmPC and PL	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/2684/ 201612	Periodic Safety Update EU Single assessment - saquinavir	06/07/2017	n/a		PRAC Recommendation - maintenance
II/0120	Update of sections 4.4 and 4.5 of the SmPC in order to add a warning regarding the co-administration of Invirase/ritonavir with cobicistat and other pharmaco-enhancers and to correct an error in the fold increase in exposure of maraviroc in the interaction table. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10, to correct minor typographical errors and to amend Annex A. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/11/2016	23/12/2016	SmPC, Labelling and PL	
PSUSA/2684/ 201512	Periodic Safety Update EU Single assessment - saquinavir	07/07/2016	n/a		PRAC Recommendation - maintenance
IB/0119	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	24/06/2016	n/a		

IG/0667/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)	08/04/2016	n/a		
II/0115	Update of section 4.4 and 4.5 the SmPC in order to update the Drug-Drug interaction information and to revise information regarding use of unboosted Invirase. The Package Leaflet is updated accordingly. RMP v.7.1 is included as consolidated version after PSUR (EMEA/H/C/PSUSA/00002684/201412) assessment requests. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/01/2016	23/12/2016	SmPC and PL	Saquinavir could interact and modify the pharmacokinetics of other drugs that are substrates for CYP3A4 and/or P-gp and should be used with caution. Conversely, other drugs that induce CYP3A4 may also reduce saquinavir plasma concentrations. Monitoring of saquinavir plasma concentration might be indicated. For more information on interactions with drugs known and/or having the potential to interact with saquinavir and specific recommendations please refer to the Product Information.
IB/0116	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/01/2016	23/12/2016	SmPC and PL	
IG/0573	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV	01/07/2015	n/a		

	(including contact details) and/or changes in the PSMF location				
IA/0113	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	12/06/2015	n/a		
PSUSA/2684/ 201412	Periodic Safety Update EU Single assessment - saquinavir	11/06/2015	n/a		PRAC Recommendation - maintenance
IG/0497	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	18/11/2014	n/a		
IB/0110	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	05/08/2014	n/a		
IB/0109	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	05/08/2014	n/a		
PSUV/0108	Periodic Safety Update	10/07/2014	n/a		PRAC Recommendation - maintenance

II/0104	Update of SmPC sections 5.1 and 5.2 with results from phase I clinical study investigating the effect of modified saquinavir/ritonavir dosing regimen (500 mg saquinavir/100 mg ritonavir bid for the first 7 days in treatment naïve patients) on the QTc interval, pharmacokinetics and antiviral activity in HIV-1 infected patients. In line with results of the study, recommendations for on treatment ECG are amended in SmPC section 4.4. This study was conducted as a post authorisation measure required in the RMP and Annex II of the MA. Annex II is updated to delete the requirement to conduct this study. The black symbol and related warnings are removed from the Product Information. In addition, a Direct Healthcare Professional Communication is approved to communicate the updated on treatment ECG recommendations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/03/2014	02/05/2014	SmPC, Annex II and PL	The MAH provided results from a phase I clinical study investigating the effect of modified saquinavir/ritonavir dosing regimen (500 mg saquinavir/100 mg ritonavir BID for first 7 days, then 1000 mg/100 mg BID) on the QTc interval, pharmacokinetics and antiviral activity in HIV-1 infected treatment naïve patients. The mean maximum change from dense predose baseline in QTcF was 3.26, 0.52, 7.13, 11.97, and 7.48 ms on Days 3, 4, 7, 10, and 14, respectively. Across all study days 2 out of 21 (9.5%) patients had a maximum change from baseline in QTcF ≥30 ms, and all changes >30 ms were observed on Day 10. The degree of QTc prolongation observed in the present study decreased considerably compared with the earlier TQT study in healthy volunteers (NP21249), where 51% of subjects receiving dose of 1000 mg/100 mg from day 1 had QTcF change from baseline > 30 ms. Maximum saquinavir exposure was reached on Day 10, when the mean Cmax was 5300 ng/mL and the mean AUC0-12h was 34200 ng * h/mL. The mean HIV-RNA decreased from baseline (4.69 log10 copies/mL) by approximately -1.9 log10 copies/mL on Day 14, comparable to historical data from the GEMINI study (mean decrease in HIV-RNA of -1.88 at Day 14). SQV/r regimen was fairly well tolerated and no new safety concern was identified. The CHMP concluded that the study provides reassurance that the modified dosing for treatment naïve HIV-1 infected patients effectively minimizes the risk of QT prolongation and is unlikely to impair the antiviral efficacy. The CHMP also endorsed the recommendation for on treatment ECG at day 10 (previously day 3 to 4), since in the provided study the highest SQV serum concentrations and the most prominent

					QT changes were observed on Day 10.
IB/0107	To update the information on risk of transmission in Section 4.4 of the SmPC in line with the class labelling request from the CHMP. The PL is updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/03/2014	05/03/2015	SmPC and PL	
IA/0106/G	This was an application for a group of variations. B.II.c.2.b - Change in test procedure for an excipient - Deletion of a test procedure if an alternative test procedure is already authorised B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	13/02/2014	n/a		
IA/0105/G	This was an application for a group of variations. 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 B.II.d.1.i - Change in the specification parameters and/or limits of the finished product - Ph. Eur. 2.9.40 uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 or Ph. Eur. 2.9.6 B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	11/02/2014	n/a		

IB/0103	To include concomitant use of quetiapine as a contra-indication in SmPC Section 4.3 and update table in SmPC section 4.5 with information on interactions with quetiapine, in line with the class labelling request for protease inhibitors. The PL is updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/10/2013	13/11/2013	SmPC and PL	
II/0100	Update of SmPC sections 4.2, 4.4 and 5.2 with warnings that an effective dose recommendation below thresholds of concern for QT and PR interval prolongation could not be established for paediatric patients. In addition, the description of the target population in the PL has been corrected in line with the SmPC. Furthermore, the PI has been brought in line with the latest QRD template version and the list of local representatives in the PL has been updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/07/2013	13/11/2013	SmPC, Annex II and PL	Steady-state exposures in paediatric patients aged 2 to <6 years have previously been found to be substantially higher than historical results in adults. The MAH conducted analysis of the probable in-vivo behaviour of the treatment in children and adolescents 2-16 years, using a modelling and simulation approach (Dickinson modelling and simulation analysis), which showed that the estimated saquinavir exposures in older paediatric patients are also substantially higher than historical steady-state saquinavir exposures in adults. Since saquinavir/ ritonavir combination has been found to have a dose- and exposure-dependent effect on QTc and PR interval prolongation in adults, dose reduction would be warranted in paediatric patients in the light of higher exposure. However, this is expected to lead to decreased efficacy in comparison with what has previously been observed in paediatric clinical trials, therefore it was concluded that for paediatric population it is not possible to establish a dose recommendation that would be both –effective and below thresholds of concern for QT and PR interval prolongation.

IG/0311	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	28/06/2013	n/a		
IB/0101	Update of sections 4.4 and 4.8 of the SmPC to include information regarding autoimmune disorders in relation to Immune Reactivation Syndrome, following a class labelling for all antiretrovirals as requested by the CHMP. The PL has been updated in accordance. 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	25/05/2013	13/11/2013	SmPC and PL	
II/0098	Update of section 4.8 of the SmPC to reflect adverse reactions listed in company core data sheet of the product and to bring it in line with the current SmPC guideline, as requested by the CHMP during assessment of variation II/93. The PL is updated accordingly. Furthermore, the Annex II is being brought in line with the latest QRD template version. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/01/2013	13/11/2013	SmPC, Annex II and PL	Based on review of adverse reactions reported for saquinavir used in combination with ritonavir, the CHMP concluded that there is sufficient evidence to include in the Product Information the following adverse reactions: Stevens Johnson Syndrome, Dermatitis bullous, Appetite decreased, Jaundice, Mucosal ulceration, Pancreatitis and Neutropenia.
IG/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2012	n/a		

II/0097	Following the evaluation of PSUR 19 (covering the period from 01.12.10 to 30.11.11), an update of section 4.5 of the SmPC to reflect data regarding an interaction of saquinavir and fusidic acid as requested by the CHMP was submitted. The Package Leaflet is also updated in accordance. In addition, the MAH took the opportunity of this variation to amend typographical errors C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	20/09/2012	24/10/2012	SmPC and PL	The variation application to update the Invirase Product Information on the interaction between fusidic acid and saquinavir/ritonavir was submitted as per the CHMP request following the assessment of PSUR 19. In the MAH's global safety database 5 cases were retrieved based on a free text search for fusidic acid and a search for fusidic acid as concomitant medication. One well-documented and published case report describes an interaction between saquinavir/ritonavir and fusidic acid, whereby the plasma concentrations of all three medicinal products were increased. There is at least one further case where an interaction between saquinavir and fusidic acid is described, with increased plasma levels; however the information is limited. The CHMP agrees that information of a potential for increased plasma concentrations of both saquinavir and fusidic acid following co-administration is relevant for clinicians and should be reflected in the SmPC for Invirase. However the evidence is too limited to propose any specific recommendation and/or assessment of the potential for hepatotoxicity.
II/0095	Update of section 4.5 of the SmPC of the recommended dose of rifabutin when co-administered with saquinavir/ritonavir. In addition, the PI has been updated in line with QRD template version 8.0. 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, Annex II, Labelling and PL	To prevent possible development of rifabutin resistant disease, the dosing recommendation of rifabutin when co-administered with saquinavir/ritonavir was revised from 150 mg twice weekly to 150 mg every other day or 3 times per week. Furthermore, monitoring of neutropenia and liver enzyme levels is recommended due to an expected increase in exposure to rifabutin.
IG/0176	A.4 - Administrative change - Change in the name	25/06/2012	n/a		

	and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS				
II/0093	Update of section 4.5 of the SmPC on interactions with maraviroc, colchicine, alfuzosin and salmeterol and bosentan as per CHMP request following evaluation of PSUR covering the period of 01.12.08 to 30.11.10. Following CHMP request 'vision disturbances' is included in sections 4.7 and 4.8 of the SmPC. The Package Leaflet is updated in accordance. The MAH took the opportunity of this variation to update the PL following user test consultation requested by the CHMP within the Article 20 Referral procedure (EMEA/H/C/113/A-20/0088). In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, annex II is revised to delete the number of the RMP version to bring it in line with the current Agency/QRD template and to reflect the submission by the MAH of the study protocol to determine the effect of the modified SQV/r regimen on the QTc interval, pharmacokinetics and antiviral activity in HIV-1 infected patients. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	19/01/2012	02/03/2012	SmPC, Annex II and PL	Based on the available information mainly from mechanism of interaction, information from the MAH safety database and SmPCs of the concerned active substances, section 4.5 of the Invirase SmPC was updated on interactions with maraviroc, colchicine, alfuzosin, salmeterol and bosentan. Interaction with maraviroc was revised to reflect data in the Celsentri (maraviroc) SmPC. Concomitant use of colchicine, alfuzosin or salmeterol and saquinavir/ritonavir is expected to increase their plasma levels. Alfuzosin is contraindicated in combination with Invirase/ritonavir due to potential increase in alfuzosin concentration which can result in hypotension. Combination with colchicine or salmeterol with saquinavir/ritonavir is not recommended. Concomitant use of bosentan and saquinavir/ritonavir may increase plasma levels of bosentan and may decrease plasma levels of saquinavir/ritonavir. The information on bosetan was revised to be consistent with the information provided in the Tracleer (bosentan) SmPC. Dose adjustment of bosentan may be required. When bosentan is administered concomitantly with saquinavir/ritonavir, the patient's tolerability of bosentan should be monitored. Visual impairment was added to the list of post-marketing experience adverse reactions.

IG/0115/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	16/12/2011	n/a		
II/0094	Update of section 5.3 of the SmPC to reflect new data as requested by the CHMP following evaluation of FU2 50.2 and 51.2 on preclinical data involving cardiac investigations. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	20/10/2011	22/11/2011	SmPC	The preclinical data was revised to reflect results of in vitro studies characterizing effects of saquinavir on cardiac ion channels as well as on cardiac ion channel trafficking and on an in vivo rat study characterizing the distribution of SQV into the myocardium. The clinical relevance of these preclinical results are unknown, however cardiac conduction and repolarisation abnormalities in humans have been observed with saquinavir and ritonavir combination therapy. The section 5.3 of the SmPC was updated to reflect these data.
II/0091	Update of section 4.8, 5.1 and 5.2 of the SmPC with the pharmacokinetic and safety data of the paediatric study NV20911 as requested by the CHMP following evaluation of the study submitted in accordance with Article 46 of Regulation. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC -	19/05/2011	23/06/2011	SmPC	The pharmacokinetics, safety and activity of saquinavir have been evaluated in an open label, multicenter study in 18 children aged 4 months to less than 6 years old in which saquinavir (50 mg/kg twice a day up to the adult dose of 1000 mg twice a day) was administered in combination with ritonavir oral solution (3 mg/kg bid for body weight from 5 to <15 kg, 2.5 mg/kg twice a day for body weight from 15 to 40 kg and 100 mg twice a day for body weight >40 kg plus ?2 background ARVs). The infants and young children were stratified into 2 groups: Group A "Low Age Group" 4 months

	Change(s) with new additional data submitted by the MAH				to less than 2 years old (n=5) and Group B "High Age Group" children 2 years to less than 6 years old (n=13). In the "High Age Group" the number of patients with a viral load <400 copies/mL at week 48 was 11 of 13. The number of patients with viral load <50 copies/mL was 9 out of 13 for the same period. Limited safety data are available from this study. No unexpected adverse events were observed in this study. The size of the study was too small to allow conclusions on risk benefit. Results in the Group A were not reflected in the product information since the number of children was too low to be considered informative.
IB/0092	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	06/05/2011	n/a		
A20/0088	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the CHMP on 24 June 2010 to further assess the QT and PR prolongation and its impact on the risk benefit balance for Invirase, and to give its opinion as to whether measures are necessary to ensure the safe and effective use of Invirase, and specifically whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.	21/10/2010	06/01/2011	SmPC, Annex II and PL	Please refer to the Assessment Report: Invirase-H-113-A20-88-Assessment Report-Article 20
IA/0090/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new or updated Ph. Eur.	09/12/2010	n/a		

	TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer				
IB/0089/G	This was an application for a group of variations. 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 pharmaceutical group as the currently approved manufacturer B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	27/08/2010	n/a		
II/0085	Update of the sections 4.3, 4.4, 4.5 and 5.1 of the SmPC based on a thorough QT/QTc study with ritonavir boosted saquinavir in healthy volunteers. Consequently, the PL was updated. Update of Summary of Product Characteristics and Package Leaflet	24/06/2010	28/07/2010	SmPC and PL	The MAH presented two clinical trials. NP21249, a thorough QT/QTc study, was conducted to investigate the proarrhythmic potential of ritonavir-boosted saquinavir in a therapeutic and a supratherapeutic dosing regimen. In the preceding trial NP21562 a feasible supratherapeutic dose of SQV was determined. Based on the results of these studies the section 4.3, 4.4, 4.5 and 5.1 of the SmPC and the PL have been updated accordingly.
II/0086	Update of SPC sections 4.2, 4.4, 5.2 to include therapeutic guidance and data on pharmacokinetics in hepatically impaired patients based on a clinical study conducted within the additional Follow-up Measure FU2 022.2. Furthermore, revision of SPC section 4.6	18/02/2010	26/03/2010	SmPC and PL	In response to a request by the CHMP for a pharmacokinetic study in patients with hepatic impairment for ritonavir boosted saquinavir, the MAH has conducted a study in patients with moderate liver impairment and submitted this variation in order to include the results in the PI. The study

	and the standard text at the bottom of the PL in accordance with the latest version of the QRD template. Update of Summary of Product Characteristics and Package Leaflet				did not show any major impact of moderate hepatic disease on pharmacokinetics of ritonavir-boosted saquinavir. However, due to the earlier termination of the study and the consequently small sample size the results are unfortunately both variable and inconsistent. Nevertheless, considering the wide exposure boundary and safety profile of saquinavir, the results are regarded as sufficient. Based on the findings, no dosage adjustment for hepatically impaired patients but close monitoring of safety and of virologic response is recommended.
IA/0087	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	17/03/2010	n/a		
II/0078	Update of section 4.5 of the SPC with clinical data and dosing recommendations regarding the interaction of ritonavir-boosted saquinavir with rifabutin following a CHMP request. In addition, the MAH proposed to include information on the interaction with the antidepressant trazodone. Consequently, the PL was updated accordingly. The MAH also used the opportunity to update the contact details of the local representative in Latvia in section 6 of the PL. Update of Summary of Product Characteristics and Package Leaflet	21/01/2010	15/03/2010	SmPC and PL	The MAH submitted a study in healthy volunteers who either started treatment with saquinavir and ritonavir (which is used to boost saquinavir by inhibition of the saquinavir-metabolising enzyme CYP3A4) or rifabutin and added the other compound(s) after 2 weeks. As expected, rifabutin had no clinical significant effect on saquinavir/rifabutin exposure. However, also as expected, due to the potent inhibition of the enzyme CYP3A4 by ritonavir, the exposures of rifabutin and its active metabolite were increased to a great extent. A lowering of the rifabutin standard regimen from daily to twice weekly intake of the same 150 mg dose was identified to deliver exposures in a safe and efficacious range and is therefore recommended for concomitant treatment. However, monitoring for neutropenia and liver enzyme levels is recommended and reducing the dose to once every 4 days may be considered necessary in case these adverse events occur.

IB/0081	IB_38_c_Change in test procedure of finished product - other changes	05/10/2009	n/a		
IB/0080	IB_33_Minor change in the manufacture of the finished product	05/10/2009	n/a		
IB/0079	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	10/09/2009	n/a		
IA/0084	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	09/09/2009	n/a		
IA/0083	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	09/09/2009	n/a		
IA/0082	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	09/09/2009	n/a		
IA/0077	IA_13_a_Change in test proc. for active substance - minor change	16/06/2009	n/a		
N/0076	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/04/2009	n/a	PL	
II/0074	Update of section 5.3 of the SPC to reflect the increased saquinavir exposure achieved in humans under boosted conditions, i.e. with co-administration of low-dose ritonavir as a pharmacokinetic enhancer, compared to the plasma exposure observed in preclinical studies with saquinavir alone.	18/12/2008	27/01/2009	SmPC and Labelling	Preclinical studies for the initial Marketing Authorisation of Invirase had been conducted with saquinavir only, as then the concomitant administration of ritonavir as a pharmacokinetic enhancer was not approved. Therefore, figures of saquinavir exposures achieved in animals in relation to humans were no longer accurate, as the now

	In addition, the MAH took this opportunity to correct a minor inconsistency between the tablets and the capsules in the Labelling. Update of Summary of Product Characteristics and Labelling				approved ritonavir "boosted" saquinavir regimen achieves consistently higher saquinavir exposures in humans. Therefore, the CHMP agreed to the MAH's proposal to update the non-clinical section of the Invirase SPC to reflect this relative change in comparative plasma exposures between animals and humans.
IA/0075	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	06/11/2008	n/a		
II/0073	Update of sections 4.2 and 4.5 of the SPC based on a drug-drug interaction study of ritonavir boosted saquinavir with nelfinavir as well as on data on the CYP3A4 inhibition of nelfinavir, indinavir and delavirdine in human liver microsomes. Update of Summary of Product Characteristics	25/09/2008	31/10/2008	SmPC	Based on literature data, the CHMP concluded that there was no significant interaction when saquinavir/ritonavir was co-administered with nelfinavir, indinavir and delavirdine. Therefore, specific recommendations for this co-administration from section 4.2 of the SPC were deleted. In addition, section 4.5 was complemented with available information on the co-administration of saquinavir/ritonavir with nelfinavir, as it was shown that the concomitant use of nelfinavir 1250 mg twice daily and saquinavir/ritonavir 1000/100 mg twice daily had no relevant impact on the blood levels of either medicine.
II/0071	Update of the section 4.5 "Interaction with other medicinal products and other forms of interaction" of the Summary of Product Characteristics (SPC) based on an interaction study of ketoconazole with saquinavir/ritonavir. In addition, wording regarding omeprazole and other proton pump inhibitors was updated, in line with the CHMP request of 3 October 2007; the section 2 of the PL is updated accordingly. The MAH also re-ordered the section 4.5 of the SPC	30/05/2008	07/07/2008	SmPC and PL	Administration of saquinavir/ritonavir 1000/100 mg twice daily and ketoconazole once daily at steady state resulted in a 2.68-fold increase in ketoconazole exposure. The higher exposure to ketoconazole when given in combination with saquinavir/ritonavir was not associated with decreased safety or tolerability. Since the ketoconazole exposure at 200 mg once daily in the presence of saquinavir/ritonavir (1000/100 mg twice daily) is close to the exposure achieved at 400 mg once daily when given alone, and less than the exposure achieved by

	into tabular format according to Annex A of the draft "Guideline on clinical development of medicinal products for the treatment of HIV infection" to improve the clarity of the SPC. Furthermore, the MAH took the opportunity to update the PL with the results of the user testing. Finally, an inconsistency in the paragraph on renal and hepatic impairment of the section 4.2 of the SPC was corrected in line with section 4.3. Update of Summary of Product Characteristics and Package Leaflet				ketoconazole (200 mg once daily.) in the presence of ritonavir (500 mg twice daily), the recommendation not to use doses of ketoconazole > 200 mg/day when combined with saquinavir/ritonavir (1000/100 mg twice daily) is appropriate to reduce the risk of ketoconazole overdosing. In addition and following the CHMP's request, the warning regarding the co-administration of saquinavir/ritonavir and omeprazole regarding saquinavir over-exposure was extended to all Proton Pump Inhibitors, as the underlying mechanism observed in the interaction study with omeprazole (gastric pH increase) was judged applicable to the entire class of medicinal products.
II/0062	Update of section 5.1 of the SPC based on a literature review with resistance data as regards ritonavir boosted saquinavir and with IC50 and IC90 values for saquinavir in cell cultures. This follows the CHMP's request in September 2006. Furthermore, section 5.1 was updated in order to reflect only information in relation to ritonavir boosted saquinavir therapy, as unboosted saquinavir is no longer used in clinical practice. In addition, the MAH took the opportunity to update the PL with new contact details of the local representatives in Estonia and Finland. Update of Summary of Product Characteristics and Package Leaflet	30/05/2008	07/07/2008	SmPC and PL	For a detailed description of Invirase antiviral activity in vitro, please refer to the Scientific Discussion: Invirase H-113-II-62
IA/0072	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	03/07/2008	n/a	Annex II and PL	

IB/0070	IB_12_b_01_Change in spec. of active subst./agent in manuf. of active subst. - test parameter AS	29/01/2008	n/a		
IA/0069	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	23/11/2007	n/a		
IA/0068	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	29/10/2007	n/a		
II/0066	Update of section 4.5 of the SPC based on a methadone drug-drug interaction study with saquinavir/ritonavir. Consequently, the PL is updated as well. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	19/10/2007	SmPC and PL	The submitted interaction study showed that saquinavir/ritonavir at the currently approved posology led to slight decreases in methadone plasma concentrations. However, this decrease had no clinical significance and no methadone-withdrawal symptoms were observed. The SPC and PL were updated in line with this information.
II/0065	Update of section 4.9 of the SPC following a revision of the Company Core Data Sheet and a cumulative evaluation based on a review of available clinical data, reported cases of overdose and literature data available in the public domain. Update of Summary of Product Characteristics	20/09/2007	19/10/2007	SmPC	Based on the review of the result of the MAH's database search, no clear description of adverse events resulting from saquinavir overdose could be provided. Firstly, many of the overdose cases reported concern unboosted saquinavir, and plasma levels resulting from the overdose were probably lower than those achieved with the currently approved ritonavir boosted saquinavir regimen 1000/100 mg bid. Secondly, several of the cases concern mixed overdoses. Thirdly, the cases where saquinavir/ritonavir was taken prior to the saquinavir overdose, either had a medical history that could explain the events or there was insufficient information available from the patient. Therefore, old information on overdoses with unboosted saquinavir was deleted from section 4.9 and the results of the cumulative review, together with information on possible

					effects of saquinavir over-exposure added.
IB/0063	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	30/05/2007	n/a	SmPC	
IA/0064	IA_09_Deletion of manufacturing site	11/05/2007	n/a		
II/0060	Update of sections 4.4 and 4.5 of the SPC based on the results of the clinical study "Effect of multiple dose ritonavir boosted saquinavir on the single dose pharmacokinetics of digoxin in healthy volunteers". Consequential update of the PL. Additionally, the MAH took this opportunity to update contact details of the German local representative. Update of Summary of Product Characteristics and Package Leaflet	22/03/2007	02/05/2007	SmPC and PL	The results of study BP18426 "Effect of multiple dose ritonavir boosted saquinavir on the single dose pharmacokinetics of digoxin in healthy volunteers" evaluated the inhibition potential of saquinavir/ritonavir on a model substrate for P-gp, digoxin. Administration of saquinavir/ritonavir 1000/100 mg twice daily at steady state resulted in the inhibition of P-gp mediated efflux transport. This was demonstrated by the increased digoxin Cmax and plasma exposure. Consequentially, the Product Information was revised to reflect the new information obtained from this study.
II/0058	Update of sections 4.3 and 4.5 of the SPC with data from a clinical study on the effect of multiple dose ritonavir boosted saquinavir on the single dose pharmacokinetics of orally administered midazolam in healthy volunteers. Based on data available in the public domain, a precaution for use in section 4.4 for parenteral midazolam was introduced. Section 2 of the Package Leaflet was updated consequentially. Update of Summary of Product Characteristics and Package Leaflet	22/02/2007	29/03/2007	SmPC and PL	Sections 4.3 and 4.5 of the SPC are amended based on the results of a study on the effect of multiple dose ritonavir boosted saquinavir on the single dose pharmacokinetics of oral midazolam in healthy volunteers. This study evaluated the inhibition potential of saquinavir/ritonavir on a model substrate for CYP3A4, midazolam. Saquinavir/ritonavir was administered twice a day at 1000/100 mg. At steady state concentration potent inhibition of CYP3A4 activity occurred as demonstrated by the significant increase of midazolam concentration. The existing contraindication for saquinavir and oral midazolam was therefore also confirmed for ritonavir boosted saquinavir. Literature data on the interaction of parenteral midazolam

					and potent CYP 3A4 inhibitors show that the increase in midazolam plasma levels is much lower, as compared to when midazolam is orally administered. Therefore, a precaution for use is now specified in section 4.4 for the intravenous route of administration. This specification takes into account the possible need of HIV patients on a saquinavir/ritonavir regimen for parenteral midazolam in anaesthesia. Additionally, in this context close clinical monitoring of patients, as recommended by the amended wording, can be adequately performed.
IA/0061	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/02/2007	n/a	SmPC, Annex II and PL	
II/0059	Update of sections 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. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	11/01/2007	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 multi 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/0057	Update of section 5.2 of the SPC to add the results of a clinical study on the effect of food on the pharmacokinetics of saquinavir in HIV-infected	16/11/2006	03/01/2007	SmPC and PL	The results of this study showed that there is a great influence of food on the exposure of saquinavir, which is not balanced by the co-administration of ritonavir as a

	patients treated with saquinavir/ritonavir 1000/100 mg twice daily. Consequentially, section 4.2 and the PL are updated as well. In addition, the section 6 of the PL was updated with the local representatives in Bulgaria and Romania. Update of Summary of Product Characteristics and Package Leaflet				pharmacokinetic enhancer. Therefore, already existing recommendations for the method of administration - with or after food - were reconfirmed. Additionally, in order to focus on relevant information only, data based on the withdrawn soft gel capsule formulation and on the unboosted regimen were deleted from the section on food effects.
II/0055	To update section 4.5 of the SPC and section 2 of the PL of Invirase on the basis of recent findings from a drug interaction study investigating the pharmacokinetic and tolerability profile of saquinavir/ritonavir co-administered with omeprazole in healthy adult volunteers and further supportive published references and available safety data. This follows the CHMP's request dated February 2006 further to the assessment of preliminary information on this interaction. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	27/10/2006	SmPC and PL	An interaction study with saquinavir/ritonavir and omeprazole (a Proton Pump Inhibitor commonly used to treat over-acidity in the stomach) in healthy adult volunteers at the usual therapeutic dosages showed markedly increased plasma values for saquinavir when given in this combination. The blood levels for ritonavir remained almost unchanged. There were no adverse events reported during the study showing a deteriorating safety profile due to the high exposure to saquinavir. These findings were further substantiated by a review of clinical safety data of two studies with very high saquinavir exposure. A cumulative review of reported adverse reactions in the MAH's safety database further backed the conclusion that the findings of this interaction study do not change the safety profile for the ritonavir boosted saquinavir regimen.
R/0053	Renewal of the marketing authorisation.	21/09/2006	20/10/2006	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk balance of Invirase continues to be favourable.

					The CHMP is also of the opinion that the renewal can be granted with unlimited validity.
II/0056	To update section 4.4 of the Invirase SPC with a warning about the possible liver toxicity associated with the co-administration of boosted saquinavir and efavirenz. This follows the CHMP's assessment of the premature stop of an interaction study in healthy volunteers, concluding in the CHMP's request to update the Product Information with this warning, dated 1 June 2006. Consequentially, the CHMP also requested the update of section 2 of the Package Leaflet, to include efavirenz in the list of medicines that can interact with saquinavir/ritonavir. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	11/10/2006	SmPC and PL	The SPC and PL of Invirase are amended based on information on the safety and interaction of ritonavir-boosted saquinavir with efavirenz. This follows the premature stop of a study investigating this interaction where the first two healthy volunteers experienced adverse events implying a possible hepatotoxicity of this combination. However, significant alterations in saquinavir or efavirenz plasma levels were not observed after administration of saquinavir/ritonavir combined with efavirenz 600 mg once daily. There are limited reports of hepatotoxicity associated with the combined use of saquinavir/ritonavir and efavirenz and the mechanism of hepatotoxicity is not clearly understood. However, based on the reports of hepatotoxicity observed with the administration of another CYP3A inducer, rifampicin, combined with ritonavir-boosted saquinavir, patients should be monitored for potential hepatotoxicity when taking the combination of saquinavir/ritonavir and efavirenz. The revision of the SPC/PL reflects the possible risk, and restricts the use of saquinavir.
IA/0054	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	23/05/2006	n/a		
II/0052	Quality changes	23/03/2006	29/03/2006		
II/0050	Update of sections 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 and complete restructuring of sections 4.8, 5.1 and 5.2 of the SPC to include the information on the boosted dosing regimen (co-administration of ritonavir as a	17/11/2005	23/12/2005	SmPC, Annex II, Labelling and PL	The recommended dose of Invirase is 1000 mg two twice with ritonavir 100 mg twice daily as a pharmacokinetic enhancer in combination with other antiretroviral agents, as saquinavir, when given alone, has a very low systemic

	pharmacokinetic enhancer). Additionally, update of section 4.5 of the SPC to add new drug-drug interactions of boosted saquinavir with tenofovir, atazanavir, fosamprenavir and lopinavir. Update of Summary of Product Characteristics, Labelling and Package Leaflet				bioavailability. This regimen is now an established part of therapy for HIV infection. Therefore, Invirase hard capsules and/or film-coated tablets should be taken at the same time as ritonavir within 2 hours following a meal. The SPC has been reworded to reflect the current state of scientific knowledege for the boosted regimen to better focus on the relevant information. The following changes were introduced: · Sections 4.2, 4.4, 4.8, 4.9, 5.1 and 5.2 have been revised according to the boosted dosing regimen (concomitant administration of ritonavir). · In this context SPC sections 4.8, 5.1 and 5.2 have been completely restructured, and the information on un-boosted saquinavir has been deleted as appropriate. · New pharmacokinetic findings on drug-drug interactions of boosted saquinavir with tenofovir, atazanavir, fosamprenavir and lopinavir have been added to section 4.5 of the SPC. The subsections of section 4.5 regarding interactions with rifampicin and midazolam were shortened in order to clarify their absolute contraindication. Further on, the wordings regarding interactions with erythromycin, fluticasone propionate and ethinyl estradiol in section 4.5 were harmonised between Fortovase and Invirase SPCs. The wordings for efavirenz, ritonavir and rifabutin in section 4.5 were abridged in order to be more succinct. · Consequently, section 2 of the Package Leaflet was also changed. Moreover, all annexes have been formally revised according to the "Guideline on Summary of Product Characteristics", the latest QRD template and comments received during the linguistic review process for Invirase 500 mg film-coated tablets. Further to a request from CHMP for harmonisation

					between certain parts of the SPCs, some small linguistic changes were performed in order to harmonise all three SPCs.
IA/0051	IA_01_Change in the name and/or address of the marketing authorisation holder	11/10/2005	n/a	SmPC, Labelling and PL	
II/0049	To update sections 4.4 and 4.5 of SPC with the class labelling text on "fluticasone" following the CHMP Assessment Report on the "Interaction with ritonavir boosted protease inhibitors and fluticasone" dated 26 May 2005. Point 2 of the PL is amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	31/08/2005	SmPC and PL	The MAH implements the class labelling on the fluticasone propionate- ritonavir interaction. This interaction is supported by the results of one multiple-dose crossover design clinical study in healthy subjects, conducted by GSK in July- October 2002 (Study FNM 10004). This study aimed at evaluating the effects of several CYP3A4 inhibitors, including ritonavir, ketoconazole and erythromycin on systemic concentrations of fluticasone after nasal inhalation.
II/0045	To update sections 4.3 and 4.5 of the SPC and point 2 of the PL with the advice to contraindicate the use of rifampicine for patients receiving saquinavir/ritonavir. In addition, the SPC of 200mg hard capsules has been revised with respect to gender effect, and in analogy with Invirase 500mg film coated tablets, section 5.2 has been updated to indicate that the studies were performed with food only. Typing errors have been corrected in the SPC. Update of Summary of Product Characteristics and Package Leaflet	26/05/2005	28/06/2005	SmPC and PL	Study BP18180 is a phase I single-centre, open-label, randomised two-arm study designed to investigate the effect of multiple dose rifampicin on the steady-state pharmacokinetics of film-coated saquinavir tablets combined with low dose ritonavir and vice versa. Subjects were randomized to receive study medication in one of the following two sequences as follows: Arm 1: Saquinavir 1000 mg/ritonavir 100 mg bid (ritonavir boosted saquinavir, SQV/r) for 14 days followed by ritonavir boosted saquinavir with rifampicin 600 mg qd for 14 days; Arm 2: Rifampicin alone for 14 days followed by rifampicin with ritonavir boosted saquinavir for 14 days A total of 28 subjects were enrolled into the study and received at least one dose of the study drugs. Of the

					seventeen subjects that started triple drug treatment, 11 (65%) developed biochemical evidence of hepatic dysfunction. Nine of these subjects were in Arm 2 and had taken 14 days treatment with rifampicin 600 mg qd prior to starting treatment with SQV/r.
IA/0048	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	01/06/2005	n/a		
X/0043	Annex I_2.(c) Change or addition of a new strength/potency	17/02/2005	25/05/2005	SmPC, Labelling and PL	
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/05/2005	n/a	Labelling	
IA/0046	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	13/04/2005	n/a		
II/0044	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 in July 2004. Update of Summary of Product Characteristics and Package Leaflet	18/11/2004	17/12/2004	SmPC 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 reactions towards the opportunistic pathogens in question cannot be foreseen since the opportunistic infection has not yet been detected/ diagnosed. If diagnosed prior to institution of CART, the treatment against the opportunistic infection (OI) is usually given priority. In particular, this is true for the complications most feared inthis context; CNX-retinitis, generalised mycobacterial infections and Pneumocystis carinii pnumonia. 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. In conclusion, in most cases, the clinical consequences of the awakening immune system in patients starting ART cannot be prevented. Therefore, early recognition and diagnosis of these inflammatory reactionsare important in the clinical handling of the patient. The description and the guidelines for treatment of the numerous clinical conditions potentially arising in association with the reactivation of the immune system in HIV-infected patients are given inthe textbooks of infectious diseases. However, as the clinical conditions associated with the reactivation of the immune system may constitute a threat to the patient, a reminder of the phenomenon is deemed of value and has been included in the SPC and PL of all antiretroviral medicinal products.
II/0041	Update of Summary of Product Characteristics and Package Leaflet	29/07/2004	10/09/2004	SmPC, Annex II and PL	
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/06/2004	n/a	PL	
II/0040	Quality changes	22/04/2004	27/04/2004		
II/0034	Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	27/01/2004	SmPC and PL	
I/0035	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	06/10/2003	15/10/2003		

II/0033	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	09/07/2003	SmPC and PL	
II/0032	Update of Summary of Product Characteristics and Package Leaflet	30/05/2002	10/09/2002	SmPC and PL	
R/0031	Renewal of the marketing authorisation.	26/07/2001	12/11/2001	SmPC, Annex II, Labelling and PL	
I/0030	11_Change in or addition of manufacturer(s) of active substance	04/05/2001	10/05/2001		
II/0029	Update of or change(s) to the pharmaceutical documentation	25/04/2001	04/05/2001		
II/0027	Update of Summary of Product Characteristics and Package Leaflet	21/09/2000	27/12/2000	SmPC and PL	
II/0026	Update of Summary of Product Characteristics and Package Leaflet	29/06/2000	20/10/2000	SmPC and PL	
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/06/2000	27/07/2000	Labelling	
I/0025	16_Change in the batch size of finished product	05/04/2000	11/04/2000		
I/0024	15_Minor changes in manufacture of the medicinal product	05/04/2000	11/04/2000		
I/0023	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	05/04/2000	11/04/2000		

I/0022	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	16/03/2000	29/03/2000		
I/0021	15a_Change in IPCs applied during the manufacture of the product	16/03/2000	29/03/2000		
I/0020	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	16/03/2000	29/03/2000		
I/0019	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	16/03/2000	29/03/2000		
I/0018	12_Minor change of manufacturing process of the active substance 12a_Change in specification of starting material/intermediate used in manuf. of the active substance	16/03/2000	29/03/2000		
I/0017	12_Minor change of manufacturing process of the active substance	16/03/2000	29/03/2000		
II/0016	Update of Summary of Product Characteristics and Package Leaflet	30/07/1999	29/11/1999	SmPC and PL	
I/0015	12_Minor change of manufacturing process of the active substance	03/06/1999	n/a		
S/0013	Annual re-assessment.	16/12/1998	08/04/1999	SmPC, Annex II, Labelling and PL	

II/0011	Update of Summary of Product Characteristics and Package Leaflet	16/12/1998	08/04/1999	SmPC and PL	
II/0014	Update of Summary of Product Characteristics and Package Leaflet	19/11/1998	25/02/1999	SmPC and PL	
I/0010	20_Extension of shelf-life as foreseen at time of authorisation	20/08/1998	24/11/1998	SmPC	
II/0006	Change(s) to the test method(s) and/or specifications for the active substance	16/09/1998	25/09/1998		
I/0009	11_Change in or addition of manufacturer(s) of active substance	20/08/1998	16/09/1998		
I/0008	24_Change in test procedure of active substance	20/08/1998	16/09/1998		
I/0007	24_Change in test procedure of active substance	20/08/1998	16/09/1998		
S/0004	Annual re-assessment.	28/01/1998	13/05/1998	SmPC, Annex II, Labelling and PL	
II/0005	Update of Summary of Product Characteristics and Package Leaflet	28/01/1998	12/05/1998	SmPC and PL	
II/0003	Change(s) to the manufacturing process for the active substance	16/04/1997	n/a		
I/0002	11_Change in or addition of manufacturer(s) of active substance	20/03/1997	n/a		

I/0001	12_Minor change of manufacturing process of the active substance	20/03/1997	n/a		