Norvir

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
IAIN/0155	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	02/08/2019	n/a		
WS/1588	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.3 and 4.5 of the SmPC in order to	29/05/2019	18/07/2019	SmPC and PL	Lopinavir and ritonavir are inhibitors of the P450 isoform CYP3A in vitro. Co-administration with medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and may increase

[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).

	include information on the contraindication with neratinib and interactions with abemaciclib, neratinib and glecaprevir/pibrentasvir. In addition, the Worksharing applicant (WSA) took the opportunity to update section 4.5 of the SmPC of Kaletra and Aluvia to add information on the interaction of lopinavir/ritonavir with sofosbuvir/velpatasvir/voxilaprevir, as well as to remove information on the interaction with boceprevir and telaprevir since these medicinal products have been withdrawn from the EU market. Furthermore, the quantity of tenofovir disoproxil has been amended as 300 mg tenofovir disoproxil fumarate is equivalent to 245 mg tenofovir disoproxil in sections 4.5 and 5.1 of the Kaletra and Aluvia SmPCs (as requested during procedure WS 1555). The Package Leaflets are updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				the potential for serious and/or life threatening reactions. Therefore, concomitant use of ritonavir and lopinavir/ritonavir with neratinib and abemaciclib, are contraindicated. Furthermore, ritonavir and lopinavir are inhibitors of OATP1B1, P-glycoprotein and BCRP. Therefore, concomitant administration of ritonavir and lopinavir/ritonavir and glecaprevir/pibrentasvir is not recommended due to an increased risk of ALT elevations associated with increased glecaprevir exposure. Moreover, serum concentrations of sofosbuvir, velpatasvir and voxilaprevir may be increased due to P-glycoprotein, BCRP and OATP1B1/3 inhibition by lopinavir/ritonavir. Therefore, it is not recommended to co administer lopinavir/ritonavir and sofosbuvir/velpatasvir/ voxilaprevir due to a potential risk associated with increase in voxilaprevir exposure. Based on these potential drug-drug interactions, sections 4.3 and 4.5 of the SmPC of the product information for ritonavir and lopinavir/ritonavir fixed-dose combination have been updated to provide further guidance for use in combination with these medical products.
IB/0153/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites C.I.7.a - Deletion of - a pharmaceutical form	01/02/2019	29/04/2019	SmPC, Annex II, Labelling and PL	
WS/1486	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	25/10/2018	29/04/2019	SmPC	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
WS/1411/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.5 of the SmPC in order to update the safety information on the interaction with ibrutinib based on the company core data sheets. The Package Leaflet is updated accordingly. Update of section 4.5 of the SmPC in order to update the safety information of ritonavir, lopinavir/ritonavir on the interaction with levothyroxine based on the PRAC signal final assessment report EMA/101535/2018 leading to decreased levothyroxine efficacy and hypothyroidis. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/09/2018	29/04/2019	SmPC and PL	Serum concentrations of ibrutinib co-administration may be increased due to CYP3A inhibition by lopinavir/ritonavir. Co-administration of ibrutinib and ritonavir containing products may increase ibrutinib exposure which may increase the risk of toxicity including risk of tumor lysis syndrome. Co administration of ibrutinib and ritonavir containing products should be avoided. If the benefit is considered to outweigh the risk and ritonavir containing products must be used, reduce the ibrutinib dose to 140 mg and monitor patient closely for toxicity. Post marketing cases have been reported indicating a potential interaction between ritonavir containing products and levothyroxine. Thyroid stimulating hormone (TSH) should be monitored in patients treated with levothyroxine at least the first month after starting and/or ending lopinavir/ritonavir treatment.
T/0149	Transfer of Marketing Authorisation	06/04/2018	24/05/2018	SmPC, Labelling and PL	
IA/0148	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	08/09/2017	n/a		

II/0147	Update of section 4.3 and 4.5 of the SmPC in order to add a contraindication regarding the interaction between ritonavir and venetoclax based on the company's core data sheet. The Package Leaflet is updated accordingly to also include some minor editorial updates. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2017	24/08/2017	SmPC and PL	
II/0146	Update of section 4.6 of the SmPC in order to update the safety information on pregnancy and lactation based on the company's core data sheet information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/07/2017	24/08/2017	SmPC	A large amount 6100 live births) of pregnant women were exposed to ritonavir during pregnancy; of these, 2800 live births were exposed during the first trimester. Norvir can be used during pregnancy if clinically needed. Limited published data reports that ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or the effects of the drug on milk production. Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-postive infants) and (3) serious adverse reactions in a breastfed infant, HIV infected women should not breast feed their infants under any circumstances if they are receiving Norvir.
WS/1077/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.3 and 4.5 of the SmPC in order to	21/04/2017	02/06/2017	SmPC and PL	The concomitant use of lopinavir/ritonavir or ritonavir and ranolazine (antianginal) or lurasidone (antipsychotic/neuroleptic) is contraindicated. This is because due to CYP3A inhibition by lopinavir/ritonavir, concentrations of ranolazine or lurasidone are expected to

	add information regarding the interaction of lopinavir/ritonavir and ritonavir with lurasidone and ranolazine. In addition, sections 4.4 and 4.5 of the SmPC are updated to add information regarding the interaction with triamcinolone. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				increase and this increases the potential for serious and/or life-threatening reactions. Concomitant use of lopinavir/ritonavir or ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4, such as budesonide and triamcinolone, is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.
PSUSA/2651/ 201608	Periodic Safety Update EU Single assessment - ritonavir	06/04/2017	n/a		PRAC Recommendation - maintenance
IAIN/0145/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	20/02/2017	n/a		
II/0142	Update of sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicinal products and other forms of interaction of the SmPC to add information regarding the interactions of ritonavir with afatinib, riociguat, ceritinib and vorapaxar. The Package Leaflet is updated accordingly.	15/09/2016	02/06/2017	SmPC, Labelling and PL	Section 4.5 Interactions with other medicinal products and other forms of interaction of the SmPC has been updated to add information regarding the potential interactions of ritonavir with afatinib, riociguat, ceritinib and vorapaxar. Due to this interaction, plasma concentrations of afatinib, riociguat, ceritinib and vorapaxar may be increased. In addition section 4.4 Special warnings and precautions of the

	In addition, the marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				SmPC was revised to add a warning that the concomitant use of ritonavir with riociguat is not recommended.
IB/0141	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)	06/06/2016	02/06/2017	SmPC	
II/0140	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	02/05/2016	SmPC and PL	
II/0137	Update of sections 4.4 and 4.5 of the SmPC in order to add information regarding the interactions between ritonavir and delamanid. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the Product Information of all the strengths/pharmaceutical forms in line with the QRD comments for the recently approved line extension procedure (EMEA/H/C/000127/X/0127) for Norvir 100 mg powder for oral suspension. The MAH has also introduced some editorial changes. Furthermore the MAH took the opportunity to update the list of local representatives for Spain in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	18/02/2016	02/05/2016	SmPC, Labelling and PL	Co-administration of delamanid with a strong inhibitor of CYP3A (ritonavir) may increase exposure to delamanid metabolite, which has been associated with QTc prolongation. Therefore, if co-administration of delamanid with ritonavir is considered necessary, very frequent ECG monitoring throughout the full delamanid treatment period is recommended.

	data				
IB/0139/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites C.I.7.a - Deletion of - a pharmaceutical form	15/02/2016	02/05/2016	SmPC, Annex II, Labelling and PL	
IB/0136	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/12/2015	02/05/2016	SmPC and PL	
IAIN/0138	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	17/12/2015	02/05/2016	Annex II and PL	
IAIN/0135/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	24/11/2015	n/a		
IA/0134	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	20/11/2015	n/a		
IG/0617	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV	10/11/2015	n/a		

	(including contact details) and/or changes in the PSMF location				
II/0130	Update of sections 4.4 and 4.5 of the SmPC to add the interaction of ritonavir and bedaquiline. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representative in Finland in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/09/2015	02/05/2016	SmPC and PL	Bedaquiline: Strong CYP3A4 inhibitors such as protease inhibitors may increase bedaquiline exposure which could potentially increase the risk of bedaquiline-related adverse reactions. Therefore, combination of bedaquiline with ritonavir should be avoided. However, if the benefit outweighs the risk, co-administration of bedaquiline with ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section 4.5 and refer to the bedaquiline Summary of Product Characteristics).
X/0127	Annex I_2.(d) Change or addition of a new pharmaceutical form	25/06/2015	14/08/2015	SmPC, Annex II, Labelling and PL	
IG/0591/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH 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	24/07/2015	02/05/2016	SmPC, Labelling and PL	
IA/0131/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of	16/07/2015	n/a		

	manufacturing sites				
II/0128	Update of section 4.5 of SmPC to add information regarding the interaction between ritonavir and simeprevir. The PL is updated accordingly. In addition, the MAH proposes to update the information of local representatives of Bulgaria, Spain and Poland in the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/11/2014	05/03/2015	SmPC and PL	Following the review of pharmacokinetic data, literature sources and post-marketing safety database, the MAH proposed to add information on the drug-drug interaction between ritonavir and simeprevir in the Norvir SmPC section 4.5 and more specifically that ritonavir increases plasma concentrations of simeprevir as a result of CYP3A4 inhibition; it is not recommended to co-administer ritonavir with simeprevir. The CHMP agreed with this proposal and noted it was in line with the information already approved in the Olysio SmPC. The addition of information of the DDI between ritonavir and simeprevir in the Norvir SmPC does not affect the benefit/risk balance of Norvir.
IG/0476	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	24/09/2014	n/a		
PSUV/0125	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
IB/0126	To implement the changes requested by CHMP to section 4.4 Precautions and Warnings of the Norvir SmPC to update the product information with updated wording concerning the risk of sexual transmission of HIV when taking Norvir. To take the opportunity to complete QRD9 template changes to the product information where these were missed in the last update. To update the toll free telephone number provided for	25/03/2014	05/03/2015	SmPC, Labelling and PL	

	the German local representative in the Package Leaflet. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
II/0122	Update of sections 4.3, 4.4 and 4.5 of the Summary of Product Characteristics (SmPC) for Norvir to add information regarding the interaction between ritonavir and avanafil as well as the addition of quetapine as a contraindication as requested by the CHMP. The information on the interaction with vardenafil has been revised. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/11/2013	18/12/2013	SmPC, Annex II, Labelling and PL	This variation proposed the update to sections 4.3, 4.4 and 4.5 of the Summary of Product Characteristics (SmPC) for Norvir to add information regarding the interaction between lopinavir/ritonavir and avanafil (indicated for the treatment of erectile dysfunction in adult men) as well as the addition of quetapine (an antipsychotic) as a contraindication as requested by the CHMP. Data on drug-drug interaction between avanafil and ritonavir were presented at American College of Clinical Pharmacology 2012 annual meeting. The study showed a 13-fold increase in avanafil AUCinf when co-administered with ritonavir 600 mg BID demonstrating the major involvement of CYP3A in its metabolism. Based on the study results, the use of avanafil in combination with ritonavir was added as a contra-indication. Revisions on vardenafil were introduced, in line with the lopinavir/ritonavir SmPC. Drug-drug interaction with quetiapine resulting in deep come was identified as a signal and as a consequence the CHMP endorsed the PRAC recommendation to add this information in section 4.5 and include the contra-indication for concomitant use with quetiapine.
IA/0124	A.7 - Administrative change - Deletion of manufacturing sites	11/12/2013	n/a		
IG/0379	C.I.8.a - Introduction of or changes to a summary of	15/11/2013	n/a		

	Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location				
N/0121	The Marketing authorisation holder took this opportunity to update the list of local representatives in the package Leaflet for CZ, HU, NL, PT, SK and UK. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2013	18/12/2013	PL	
IG/0263	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/01/2013	n/a		
N/0119	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/01/2013	18/12/2013	PL	
II/0116	Update of section 4.4 Special warnings and precautions for use as well section 4.8 Undesirable effects of the Summary of Product Characteristics (SmPC) for Norvir to add information regarding autoimmune disorders to the information provided for Immune Reactivation Syndrome. Consequential changes were introduced to the Package Leaflet. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. Changes in the Annex II regarding Pharmacovigilance system, PSUR and RMP were introduced. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical,	17/01/2013	18/12/2013	SmPC, Annex II and PL	Antiretroviral treatment leads to immune reconstitution, which might be responsible of Immune Reconstitution and Inflammatory Syndrome (IRIS) and patients might be at increased risk for autoimmune diseases. A literature review showed a relation between IRIS and autoimmune disease. Although a direct causal relation between IRIS and autoimmune disorders might be possible, there are many other risk factors to take into consideration that may contribute to the pathogenesis of these diseases. There is further evidence available supporting the occurrence of Graves' Disease following HAART therapy in HIV infected patients, because of nucleotide and amino acid homology between a unique region of the human thyrotropin receptor and the HIV-1 nef protein with demonstrated immune cross-reactivity between these two proteins. Although

	clinical or pharmacovigilance data				critical data comparing treated and untreated patients is currently not available, patients with severe immunodeficiency at commencing HAART therapy appear to be at increased risk. There are no data available showing an increased risk with a particular HAART regimen. The incidence of these autoimmune diseases is rare but it warrants the revision of relevant sections of the Product Information.
IG/0240/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS 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.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release 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)	14/12/2012	18/12/2013	Annex II and PL	
T/0117	Transfer of Marketing Authorisation	26/09/2012	24/10/2012	SmPC, Labelling and PL	
II/0115	Update of section 4.5 of the Summary of Product Characteristics (SmPC) to add drug-drug interactions	19/07/2012	10/09/2012	SmPC and PL	Ritonavir has a high affinity for several cytochrome P450 (CYP) isoforms and may inhibit oxidation with the following

	when Norvir is co-administered with other antiretrovirals (raltegravir) and other non-antiretroviral agents (rivaroxabam) resulting from review of pharmacokinetic data. Update of section 4.4 to add the not recommended medicinal product rivaroxabam. The Package Leaflet was proposed to be updated in accordance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				ranked order: CYP3A4 > CYP2D6. Co-administration of Norvir and medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of the other medicinal product, which could increase or prolong its therapeutic and adverse effects. Ritonavir also has a high affinity for P-glycoprotein and may inhibit this transporter. The inhibitory effect of ritonavir (with or without other protease inhibitors) on P-gp activity may decrease over time. Ritonavir may induce glucuronidation and oxidation by CYP1A2, CYP2C8, CYP2C9 and CYP2C19 thereby increasing the biotransformation of some medicinal products metabolised by these pathways, and may result in decreased systemic exposure to such medicinal products, which could decease or shorten their therapeutic effect. Pharmacokinetics data of the following medicinal products raltegravir and rivaroxaban were evaluated when these were co-administered with ritonavir. These data did not affect the risk/benefit of Norvir which still remains positive, but warranted the update of the relevant sections of the Norvir Product Information to introduce information on the drug-drug interactions evaluated.
II/0114	Update of sections 2, 4.2, 4.4 and 4.9 of the Summary of Product Characteristics (SmPC) of Norvir oral solution to add toxicity in neonates based on a safety review of the product. The requested variation procedure proposed amendments to the Update of Summary of Product Characteristics and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical,	19/07/2012	10/09/2012	SmPC and PL	Considering the long half-life of propylene glycol in infants (19.3 hours), neonates may be at increased risk of propylene glycol-associated adverse events due to their diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events and toxicity. Ritonavir oral solution concentrations of alcohol are approximately 43% (v/v) of alcohol (or 369.7 mg alcohol per mL) and 26.0% v/v of propylene glycol (or 265.7 mg propylene glycol per mL). Therefore, the CHMP recommended updating the Norvir oral

	clinical or pharmacovigilance data				solution Product Infromation to include this information and to inform the prescribing health care professional about the potential toxicity that may result from the high concentrations of these excipients when used in infants, particularly for neonates. The CHMP considered that the risk/benefit of Norvir oral solution is not adversely affected by the results of this review and the subsequent proposed revisions to the Product Information.
II/0113	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/03/2012	20/04/2012	SmPC	The MAH conducted a review of the changes to the SmPCs of atazanavir, darunavir, fosamprenavir, saquinavir and tipranavir from the period September 2010 – September 2011 and assessed the changes to determine if there was any impact on the ritonavir SmPC. As a result no changes were introduced in the ritonavir SmPC related to co-administration of atazanavir, fosamprenavir and tipranavir with of ritonavir as a pharmacokinetic enhancer; however changes were introduced when ritonavir is co-administered with saquinavir and darunavir.
II/0109	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.5 "Interaction with other medicinal products and other forms of interactions" in line with changes in the Company Core Data Sheet. In addition, a minor revision was introduced in section 4.3. The Package Leaflet was updated accordingly. Section 6 of the PL was updated to include the approved film-coated tablets. The MAH took also the opportunity to update the local representatives. C.I.4 - Variations related to significant modifications of	16/02/2012	19/03/2012	SmPC and PL	The MAH conducted an aggregate review of the clinical trial safety data on adult subjects who participated in RTV Phase 2 – 4 clinical trials to determine the events requiring representation in the ritonavir SmPC as adverse drug reactions. Based on the analysis section 4.8 of the SmPC has been revised. Revisions related to renal impairment were also introduced in section 4.4

	the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0111	Update of section 4.8 of the SmPC in order to update the safety information [addition of toxic epidermal necrolysis (TEN)]. The PL is updated in accordance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/11/2011	22/12/2011	SmPC and PL	Based on the cumulative review of cases of severe skin disorders in patients treated with Norvir, reports of TEN coincident with ritonavir were observed. Although all these reports were confounded by one or more concomitant medications, a causal relationship cannot be excluded. TEN is considered to be a “rare” adverse event. Therefore the product information was updated accordingly.
IA/0112	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	02/12/2011	n/a		
II/0110	Update of section 4.5 in line with changes in the Company Core Data Sheet. In addition, a minor revision was introduced in section 4.3. The PL was updated accordingly. Section 6 of the PL was updated to include the approved film-coated tablets. The MAH took also the opportunity to update the local representatives. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/10/2011	22/11/2011	SmPC and PL	Drug interaction data between ritonavir and dasatinib, nilotinib, fentanyl, bosentan, colchicine, and tadalafil were evaluated and as a consequence these data are reflected in section 4.5 of the SmPC.
IG/0108/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	30/09/2011	n/a		

	back-up procedure of the QPPV C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD 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				
IA/0107	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	29/06/2011	n/a		
IA/0106	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	31/05/2011	n/a		
IA/0105	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	31/03/2011	n/a	SmPC and PL	

IB/0104	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	21/02/2011	n/a		
IB/0101	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	27/01/2011	27/01/2011	SmPC, Annex II, Labelling and PL	
IA/0103	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	24/01/2011	n/a		
IA/0102	A.7 - Administrative change - Deletion of manufacturing sites	15/12/2010	n/a		
IB/0100	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/10/2010	n/a	SmPC	To include "Ritonavir soft capsules contain castor oil polyoxyl which may casue stomach upset and diarrhoea" to the SmPC for soft capsules 100 mg to bring them in line with the PL.
N/0099	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/09/2010	n/a	Labelling	The MAH deleted the term film-coated from the Braille section of the labelling for the 100 mg film-coated tablets
IG/0022/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	22/09/2010	n/a	Annex II	

IG/0014/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.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	23/07/2010	n/a	Annex II	
IA/0098	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	23/07/2010	n/a		
IA/0097	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	23/07/2010	n/a		
IB/0096	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	16/04/2010	16/04/2010	SmPC, Labelling and PL	
II/0093	Update of section 4.2 of the SmPC following the annual review of relevant information on ritonavir-boosted protease inhibitors in line with follow-up measure 033. In addition, QRD comments received during the	18/02/2010	23/03/2010	SmPC and PL	Based on the yearly review to update the Norvir Product Information with information on newly licensed Protease Inhibitors, information on the daily dosing in section 4.2 of the SmPC was added for darunavir and clarified for

	review of the new film-coated tablets line-extension were included in Product Information of the Oral Solution and Capsule formulations. The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				atazanavir and the fixed combination of lopinavir/ritonavir. Wording clarifying the fact that ritonavir is not recommended for children below the age of two was added as well. In addition, it was highlighted that in case of ritonavir use as a pharmacokinetic enhancer, the Product Information of the boosted Protease Inhibitor must be consulted.
X/0090	Annex I_2.(c) Change or addition of a new strength/potency	19/11/2009	25/01/2010	SmPC, Labelling and PL	The MAH applies for a marketing authorisation for the Norvir 100 mg film coated tablet. The proposed film-coated tablet formulation may be stored at room temperature, a significant advantage over the storage requirements for the Norvir capsules.
IA/0094	IA_01_Change in the name and/or address of the marketing authorisation holder	22/12/2009	n/a	SmPC, Labelling and PL	
II/0092	Update of sections 4.3, 4.4 and 4.5 of the SPC to include a contraindication for sildenafil (in patients treated for pulmonary arterial hypertension) and to include a warning for the co-administration of salmeterol based on data available in the public domain. The PL was updated in accordance. In addition, the MAH took this opportunity to correct a typographical error in section 4.2 of the SPC to remove an incorrect reference to lopinavir and update the reference to pneumocystis carinii pneumonia in section 4.4 to pneumocystis jiroveci pneumonia to reflect the new name. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	23/10/2009	SmPC and PL	An interaction study between ritonavir and sildenafil showed that this co-administration leads to marked increases in sildenafil blood levels. Given this pharmacokinetic interaction and resulting increased potential for sildenafil-associated adverse events (which include hypotension and syncope), and the inability to further downward adjust the sildenafil dose below 20 mg in the treatment of pulmonary arterial hypertension patients, this co-administration of sildenafil with ritonavir was contraindicated. In addition, extrapolation of data from an interaction study between salmeterol and ketoconazole to ritonavir allows the conclusion that the co-administration of salmeterol and ritonavir is not recommended, as this could lead to higher than normal blood levels of salmeterol. Such elevation could lead to an increase in beta-agonist-mediated systemic effects, i.e.

					cardiovascular side effects, which should be avoided.
II/0091	Update of section 5.1 of the Norvir SPC to include a brief summary of the study results in paediatric patients using therapeutic ritonavir doses in line with the February 2009 CHMP request following the assessment of Paediatric study W97-225, submitted in October 2008 in accordance with Article 45 of Regulation (EC) No1901/2006, as amended. Update of Summary of Product Characteristics	23/07/2009	02/09/2009	SmPC	In the provided study in HIV-infected children from 6 months to 12 years of age, the tested ritonavir therapeutic dosing regimens of 350 mg/m2 or 400 mg/m2 in combination with lamivudine and stavudine demonstrated similar antiviral and immunological results at Week 24 and Week 48. The results were consistent with published data in the literature. No new safety concerns were raised. The data underline the validity of the currently approved indication and posology for children 2 years of age and above and were therefore added to section 5.1 of the SPC.
II/0089	Update of section 4.4 of the SPC based on the review of relevant information on boosted protease inhibitors in fulfilment of FUM 033 as requested on the CHMP in July 2006. The MAH took the opportunity to update sections 4.3 and 4.5 of the SPC and replace the term meperidine with pethidine and replace the term normeperidine with norpethidine. Consequently, the PL has been updated. In addition, the MAH took this opportunity to correct a typographical error in section 4.2 of the SPC and as well as to update the address of the local representative in Denmark in section 6 of the PL. Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	01/07/2009	SmPC and PL	In line with a recent update for the Reyataz SPC, section 4.4 of the Norvir SPC was updated in order to modify the statement for the co-administration of low-dose ritonavir with atazanavir. As a rule, ritonavir doses above 100mg have not been clinically evaluated and should therefore be avoided. However, based on data from an interaction study of atazanavir/ritonavir with the non-nucleoside reverse-transcriptase inhibitor efavirenz, this statement was modified to allow a ritonavir dosage increase to 200mg in this co-administration, under close clinical monitoring. Furthermore, the CHMP agreed to the other proposed minor updates.
IB/0087	IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance	18/11/2008	n/a		

IA/0088	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	04/11/2008	n/a		
II/0079	Update of sections 4.4 and 5.1 of the SPC with information on the potential for QTc and PR interval prolongation based on the results from a clinical study in healthy volunteers. Update of Summary of Product Characteristics	24/04/2008	18/06/2008	SmPC	Based on the results of a study in healthy volunteers which evaluated the potential for ritonavir and lopinavir/ritonavir to induce QTc interval and PR interval prolongation at doses (administered over 3 days) chosen to provide maximal concentrations of both lopinavir and ritonavir, the CHMP concluded that ritonavir has a potential to induce modest QTc and PR interval prolongation. No study participant experienced an increase in QTcF of > 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec. The mean changes from baseline in PR interval ranged from 11.0 to 24.0 msec in the 12 hour interval post dose. Maximum PR interval was 252 msec and no second or third degree heart block was observed. The Product Information was updated in accordance.
II/0076	Update of sections 4.2 and 4.5 of the SPC based on the annual review of relevant information on boosted protease inhibitors. In addition, clarification of terminology in section 4.8 was given. Consequently, the PL is revised. Update of Annex II to reflect the reversion to the 3-yearly PSUR cycle. The MAH also took this opportunity to update contact details of local representatives in the PL. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	18/06/2008	SmPC, Annex II and PL	Ritonavir is a substrate and potent inhibitor of cytochrome P450 (CYP), in particular, the CYP3A isoform subfamily. Co-administration of ritonavir with drugs primarily metabolised by CYP3A has been shown to result in increased plasma concentrations of the other drug. The activity of certain CYP isoforms (CYP1A2, CYP2C8, CYP2C9 and CYP2C19) and uridine diphosphate glucuronyltransferase (UDPGT) enzymes is induced by ritonavir. This may result in decreased exposure to some drugs that are metabolised by these CYP and UDPGT enzymes. Based on the annual review, information on drug interactions between ritonavir and acid reducing agents, darunavir, everolimus, fusidic acid, maraviroc, vincristine and vinblastine was updated.

IA/0086	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	13/06/2008	n/a		
IA/0085	IA_05_Change in the name and/or address of a manufacturer of the finished product	13/05/2008	n/a	Annex II and PL	
II/0078	Update of sections 4.3, 4.4 and 4.5 of the SPC based on data derived from PSUR 15 on the interaction of bupropion and rosuvastatin. Consequently, section 2 of the PL is updated. Update of Summary of Product Characteristics and Package Leaflet	21/02/2008	27/03/2008	SmPC and PL	Two studies evaluating the effects of repeated doses of ritonavir (100 mg BID and 600 mg BID) on the pharmacokinetics of a single 150 mg dose of bupropion in healthy volunteers showed that bupropion exposure was decreased after administration of repeated doses of ritonavir. A study evaluating the steady state pharmacokinetics of rosuvastatin alone (20 mg QD), LPV/r alone (400/100 mg BID) and rosuvastatin co-administered with LPV/r in 15 healthy volunteers showed that co-administration of rosuvastatin and LPV/r resulted in 2.1- and 4.7-fold increase in rosuvastatin AUC and Cmax, respectively. No changes in LPV/r pharmacokinetics were observed with co-administration of rosuvastatin. Although the exact mechanism of this interaction is unknown, it may be mediated by a transporter inhibition mechanism by ritonavir. Therefore, a drug interaction with rosuvastatin and ritonavir cannot be ruled out.
IB/0084	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	18/02/2008	n/a		
IB/0081	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	07/02/2008	n/a		
IA/0083	IA_05_Change in the name and/or address of a	25/01/2008	n/a		

	manufacturer of the finished product				
IA/0082	IA_05_Change in the name and/or address of a manufacturer of the finished product	25/01/2008	n/a		
IA/0080	IA_09_Deletion of manufacturing site	15/01/2008	n/a		
II/0074	Update of section 4.5 of the SPC with information available in the public domain on the interaction of buprenorphine and ritonavir in line with a CHMP request in April 2007 following a CHMP review of data on interactions with buprenorphine. Update of Summary of Product Characteristics	18/10/2007	20/11/2007	SmPC	A review of available literature describing the interaction of ritonavir with buprenorphine in vitro and in vivo showed that the administration of ritonavir increased the AUC of buprenorphine by 57% due to an approximately 40% decrease in oral clearance. The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine may therefore not be necessary when the two are dosed together. In addition, the ritonavir plasma levels are not expected to change during this co-administration. When ritonavir is used in combination with another protease inhibitor (as a "booster") and buprenorphine, the SPC of the co-administered protease inhibitor should be taken into consideration for specific dosing information.
II/0072	Update of section 4.5 of the SPC based on a comprehensive review of 2 studies examining the pharmacokinetics of co-administered ritonavir and rifampicin as requested by the CHMP in February 2007. Update of Summary of Product Characteristics	18/10/2007	20/11/2007	SmPC	In an interaction study between ritonavir and rifampicin reduced levels of ritonavir were observed. However, due to the auto-induction effect of ritonavir it could not be concluded that this effect was due to induction by rifampicin. The SPC was revised to reflect that although rifampicin may induce metabolism of ritonavir, limited data indicate that when high doses of ritonavir (600 mg twice daily) is co-administered with rifampicin, the additional inducing

					effect of rifampicin (next to that of ritonavir itself) is small and may have no clinical relevant effect on ritonavir levels in high-dose ritonavir therapy. The information that the effect of ritonavir on rifampicin is not known was also included in the SPC.
II/0070	Update of sections 4.3 and 4.5 of the SPC and section 2 of the PL as regards the interaction with oral and parenteral midazolam, following CHMP request in March 2007. Contact details of the local representative in Poland and Slovak Republic were updated in section 6 of the PL. Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	10/08/2007	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 Norvir with orally administered midazolam is contraindicated, whereas caution should be used when Norvir is co-administrated with injection of midazolam. If Norvir 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.
IA/0073	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	21/06/2007	n/a		
IA/0071	IA_39_Change/addition of imprints, bossing or other markings	21/05/2007	n/a		
IB/0069	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	04/05/2007	n/a		

II/0061	Update of sections 4.2 and 5.2 of the SPC concerning ritonavir pharmacokinetics in elderly patients as requested by the CHMP in July 2006. This follows the CHMP assessment of the renewal dossier of Norvir. Update of Summary of Product Characteristics	22/03/2007	02/05/2007	SmPC	At present, data in elderly patients using ritonavir are very limited. Pharmacokinetic data in elderly patients from clinical studies were compared to those of younger adults receiving the same dose regimens. Additional data analysis confirmed that there was no accumulation of ritonavir in the elderly aged between 50-70 years in these studies. The data are limited, but this may be expected for a HIV-infected population. Age effects are mainly observed for renally cleared medicinal products, which is not applicable in the case of ritonavir. Therefore, a statement that no dose adjustment in the elderly is necessary was introduced and the results of this pharmacokinetic analysis were added to the SPC.
IA/0068	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	23/04/2007	n/a		
II/0058	To update safety information in section 4.6 of the SPC based on pregnancy registry data. The package leaflet has been revised accordingly. In addition, contact details of the local representatives in Iceland and The Netherlands were updated in the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/01/2007	27/02/2007	SmPC, Labelling and PL	The Antiretroviral Pregnancy Registry was created to monitor pregnant women exposed to antiretroviral therapy, including to ritonavir. A limited number of pregnant women were exposed to ritonavir during pregnancy, of which only a very limited number were exposed during the first trimester. These limited data indicate no increase in the rate of birth defects compared to rates expected in the general population. The use of Norvir may be considered in pregnancy only if the benefits outweigh the risk to the foetus.
II/0060	To update 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. In addition, section 6 of the PL was updated with the	14/12/2006	12/01/2007	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

	local representatives in Bulgaria and Romania. The MAH also took the opportunity to update the contact details for Belgium, Estonia, Finland, Iceland, Latvia, Lithuania, Luxembourg, The Netherlands, Portugal and United Kingdom in the PL. Update of Summary of Product Characteristics and Package Leaflet				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.
IA/0067	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	06/12/2006	06/12/2006	SmPC, Labelling and PL	
IA/0065	IA_09_Deletion of manufacturing site	01/12/2006	n/a		
IA/0064	IA_09_Deletion of manufacturing site	01/12/2006	n/a		
IA/0063	IA_09_Deletion of manufacturing site	01/12/2006	n/a		
IA/0062	IA_09_Deletion of manufacturing site	01/12/2006	n/a		
R/0055	Renewal of the marketing authorisation.	27/07/2006	20/11/2006	SmPC, Annex II, Labelling and PL	Over the years the use of Norvir has shifted from its usage as a single Protease Inhibitor (PI) to that of pharmacokinetic enhancer for other PI's. This is due to its strong inhibitory effect on the enzyme that is mainly responsible for the metabolism of most of the currently used PIs. During the renewal procedure this issue has been extensively discussed and the product information has been thoroughly amended to better reflect the current clinical practice in Europe. Although over the years the use of Norvir has changed, the benefit risk balance remains positive.

II/0056	To update sections 4.3, 4.4 and 4.5 of the Norvir SPC to include information on the interaction between saquinavir boosted with ritonavir and rifampicin as well as between ritonavir and alfuzosin following the CHMP assessment of PSUR 13 covering the period 1 Sep 04 to 31 Aug 05. Consequential changes to section 2 of the Package Leaflet were introduced. The MAH took the opportunity to update information about local representatives in the PL. Update of Summary of Product Characteristics and Package Leaflet	28/06/2006	28/07/2006	SmPC and PL	Both rifampicin and Protease Inhibitors like saquinavir and ritonavir are reported to cause Liver Function Test (LFT) elevations in healthy subjects and patients. Based on available data, it is not clear whether the interaction between saquinavir boosted with ritonavir given concomitantly with rifampicin is pharmacokinetic or pharmacodynamic. However, it was agreed that a warning should be included in the SPC that the risk of hepatotoxicity may be higher in patients using saquinavir boosted with ritonavir when co-administered with rifampicin. Sections 4.4 and 4.5 of the SPC were updated accordingly. Alfuzosin is indicated for treatment of functional symptoms of benign prostatic hypertrophia, by reducing urethral tone and bladder outlet resistance, and facilitating bladder emptying. At high doses, central effects like hypotension and orthostatic hypotension can occur. Because ritonavir is a potent inhibitor of the CYP3A4 hepatic enzyme responsible for alfuzosin metabolism, co-administration of ritonavir and alfuzosin may cause significant increases in alfuzosin exposure and the risk for serious adverse reactions, such as hypotension. The combination was therefore contra-indicated. Sections 4.3 and 4.5 of the SPC as well as section 2 of the PL were amended in accordance.
IA/0054	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	07/12/2005	n/a		
IA/0053	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	14/11/2005	n/a		
II/0052	To update the SPC sections 4.4 and 4.5 with safety	27/07/2005	31/08/2005	SmPC,	Based on PSUR 12, the following variations SPC text were

	information based on the assessment of the 12th PSUR (Periodic Safety Update Report covering the period of 1 September 2003 to 31 August 2004) and with a class-labelling on the interaction between fluticasone propionate and ritonavir. Consequential amendments are introduced in section 2 of the PL. Additionally, the MAH proposes to correct values with regard to protein binding in SPC section 5.2. Minor corrections are made to sections 8 and 13 of the labelling and section 6 of the PL. Linguistic corrections are made to the Dutch, German, Latvian, Lithuanian and Norwegian texts. On the basis of the information provided by the Marketing Authorisation Holder and as set out in the appended variation assessment report, the CHMP considers this variation to be a Type II variation. Update of Summary of Product Characteristics, Labelling and Package Leaflet			Labelling and PL	requested by CHMP (report EMEA/H/C/127/PSU 006): SPC section 4.4: add wording regarding the drug interaction between ritonavir and tadalafil and vardenafil. SPC section 4.5: add wording regarding the drug interaction between ritonavir and digoxin, trazodone, tadalafil, vardenafil and voriconazole. SPC section 4.5: revise wording regarding oral contraceptives to include patch contraceptives SPC section 4.8: add menorrhagia Consequential amendments are introduced in section 2 "Before you take Norvir" of the PL. The MAH also implements the class-labelling agreed on the fluticasone propionate-ritonavir interaction. To support this interaction, the MAH previously provided the results of one multiple-dose crossover design clinical study in healthy subjects conducted by GSK in July-October 2002 (study FNM10004). 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/0051	To include statements in relation to an interaction between ritonavir (norvir) and fluticasone in sections 4.4 and 4.5 of the SPC. Additionally, the CHMP requested class labelling with regard to Immune Reactivation Syndrome is added in sections 4.4 and 4.8 of the SPC and in point 2 of the PL. In addition Annex II has been updated to comply with the current QRD/EMEA template.	18/11/2004	20/01/2005	SmPC, Annex II and PL	Fluticasone propionate interaction Study FNM10004 (GSK): Fluticasone propionate aqueous nasal spray, 200µg once daily was administered alone for 7 days (n=18) as well as co-administered for 7 days with ritonavir 100 mg twice daily (n=11); there was at least a 14 day washout between treatment arms. Plasma fluticasone concentrations were below the limit of quantification of the fluticasone assay in most subjects (61%) when fluticasone

	On the basis of the information provided by the Marketing Authorisation Holder and as set out in the appended variation assessment report, the CHMP considers this variation to be a Type II variation. Update of Summary of Product Characteristics and Package Leaflet				was administered for 7 days alone; additionally, plasma cortisol concentrations over 24 h were not significantly affected from baseline. When fluticasone concentrations were detectable (n=7), geometric mean Cmax was 11.9 pg/ml (range 11.0 to 13.0) and geometric mean AUC24 was equal to 8.43 pg.h/ml (range from 3.15 to 22.6 pg·h/ml). After 7 days of ritonavir co-administration (n=11), fluticasone mean Cmax was 318 pg/ml (range 224 to 451 pg/ml) and AUC24 was 3103 pg·h/ml (range 2252 to 4275 pg·h/ml). These significant increases in fluticasone exposure resulted in a corresponding decrease in cortisol plasma exposure [86% decrease [90% CI of 82 to 89%] in cortisol AUC24]. Immune reactivation syndrome 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 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 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 interactio
IA/0050	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	21/09/2004	n/a	Annex II and PL	
II/0049	Update of Summary of Product Characteristics and Package Leaflet	23/06/2004	02/08/2004	SmPC, Labelling and PL	
II/0048	Update of Summary of Product Characteristics and Package Leaflet	21/01/2004	25/03/2004	SmPC and PL	
II/0045	Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	27/01/2004	SmPC and PL	
I/0047	01_Change in the name of a manufacturer of the medicinal product	07/10/2003	09/10/2003		
I/0046	24_Change in test procedure of active substance	05/08/2003	18/08/2003		
II/0044	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	09/07/2003	SmPC and PL	
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/10/2002	07/11/2002	PL	
I/0041	25_Change in test procedures of the medicinal product	03/10/2002	10/10/2002		
I/0040	25_Change in test procedures of the medicinal product	03/10/2002	10/10/2002		
I/0039	25_Change in test procedures of the medicinal product	03/10/2002	10/10/2002		

I/0038	25_Change in test procedures of the medicinal product	03/10/2002	10/10/2002		
I/0037	25_Change in test procedures of the medicinal product	03/10/2002	10/10/2002		
II/0036	Update of Summary of Product Characteristics and Package Leaflet	30/05/2002	10/09/2002	SmPC and PL	
I/0035	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	27/02/2002	04/03/2002		
I/0034	20_Extension of shelf-life as foreseen at time of authorisation	26/10/2001	17/12/2001	SmPC	
II/0027	Update of or change(s) to the pharmaceutical documentation	15/11/2001	28/11/2001		
R/0029	Renewal of the marketing authorisation.	27/06/2001	12/11/2001	SmPC, Annex II, Labelling and PL	
II/0033	Change(s) to the test method(s) and/or specifications for the finished product	27/06/2001	03/07/2001		
II/0022	Update of Summary of Product Characteristics and Package Leaflet	01/03/2001	14/06/2001	SmPC and PL	
II/0021	Update of Summary of Product Characteristics	01/03/2001	14/06/2001	SmPC	
I/0024	15_Minor changes in manufacture of the medicinal product	12/01/2001	22/01/2001		

I/0026	01_Change following modification(s) of the manufacturing authorisation(s)	05/01/2001	05/01/2001		
II/0020	Update of Summary of Product Characteristics and Package Leaflet	29/06/2000	24/10/2000	SmPC and PL	
S/0019	Annual re-assessment.	18/11/1999	09/03/2000	Annex II	
X/0017	X-3-iv_Change or addition of a new pharmaceutical form	30/07/1999	29/11/1999	SmPC, Annex II, Labelling and PL	
II/0018	Update of Summary of Product Characteristics and Package Leaflet	30/07/1999	29/11/1999	SmPC and PL	
II/0016	Update of Summary of Product Characteristics and Package Leaflet	19/11/1998	26/02/1999	SmPC and PL	
II/0014	Update of Summary of Product Characteristics and Package Leaflet	19/11/1998	26/02/1999	SmPC and PL	
II/0010	Extension of Indication	19/11/1998	26/02/1999	SmPC and PL	
S/0015	Annual re-assessment.	19/11/1998	23/02/1999	Annex II	
II/0012	Update of Summary of Product Characteristics and Package Leaflet	16/09/1998	11/01/1999	SmPC, Labelling and PL	
I/0013	15_Minor changes in manufacture of the medicinal product	27/11/1998	n/a		

I/0011	12_Minor change of manufacturing process of the active substance	13/08/1998	15/09/1998		
S/0008	Annual re-assessment.	19/11/1997	20/03/1998	SmPC, Annex II and PL	
II/0005	Update of Summary of Product Characteristics and Package Leaflet	19/11/1997	17/03/1998	SmPC and PL	
II/0004	Update of Summary of Product Characteristics and Package Leaflet	19/11/1997	17/03/1998	SmPC and PL	
I/0007	23_Change in storage conditions	06/11/1997	15/01/1998	SmPC, Labelling and PL	
I/0006	11_Change in or addition of manufacturer(s) of active substance	06/11/1997	15/01/1998	Annex II	
II/0002	Update of Summary of Product Characteristics and Package Leaflet	19/03/1997	22/07/1997	SmPC and PL	
I/0001	01_Change following modification(s) of the manufacturing authorisation(s)	29/08/1996	n/a	Annex II	