Kaletra

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
II/0193	Submission of the final report from study P19-106 listed as a category 3 study in the RMP. This is a European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) observational study assessing the safety and effectiveness of Kaletra oral solution in children aged 14 days to 2 years with human	27/10/2022	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).

	immunodeficiency virus 1 (HIV-1) infection in Europe. The RMP version 10.0 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0194	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/09/2022		SmPC and PL	
N/0195	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/08/2022		PL	
PSUSA/1905/ 202109	Periodic Safety Update EU Single assessment - lopinavir / ritonavir	10/06/2022	n/a		PRAC Recommendation - maintenance
IB/0190	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	23/04/2021	02/12/2021	PL	
IA/0191	A.7 - Administrative change - Deletion of manufacturing sites	26/03/2021	n/a		
N/0189	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/02/2021	02/12/2021	PL	
IA/0188	A.7 - Administrative change - Deletion of manufacturing sites	26/11/2020	02/12/2021	Annex II and PL	

IB/0187	B.II.a.z - Change in description and composition of the Finished Product - Other variation	05/11/2020	02/12/2021	SmPC and PL	
WS/1845	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4: Update of section 4.5 of the SmPCs in order to add information on drug-drug interactions with fostamatinib. 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	16/07/2020	27/10/2020	SmPC and PL	Co-administration of fostamatinib with strong CYP3A4 inhibitors (e.g. ritonavir) may increase fostamatinib metabolite R406 exposure, resulting in dose-related adverse events such as hepatotoxicity, neutropenia, hypertension or diarrhoea. For more information, including information on dose reduction recommendations if such events occur, please also refer to the Summary of Product Characteristics of Tavlesse (fostamatinib).
WS/1842	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in order to update the safety information for nephrolithiasis as an adverse reaction following an update to the Kaletra and Aluvia (lopinavir/ritonavir) and Norvir (ritonavir) Company Core Data Sheets (CCDS 0220). The Package Leaflet is updated accordingly. In addition, the MAH/SOH takes the opportunity to make additional changes in the PI in order to comply with the current QRD template and provide clarity to instructions contained in the Package Leaflet.	02/07/2020		SmPC, Annex II, Labelling and PL	The proposed variation is based on a safety review conducted by MAH prompted by the publication in July 2019 from Zhao describing a patient who experienced a kidney stone composed entirely of ritonavir. Based on this, the product information of Kaletra and Aluvia (lopinavir/ritonavir) and Norvir (ritonavir) has been reviewed to update the safety information by adding "nephrolithiasis" as an adverse reaction with an unknown frequency. For more information, please refer to the Summary of Product Characteristics.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0184/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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)	26/03/2020	27/10/2020	SmPC	
WS/1711	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	12/03/2020	n/a		
IB/0183	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)	13/02/2020	n/a		
IA/0182	B.II.b.2.a - Change to importer, batch release	20/01/2020	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
WS/1705	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change of section 4.8 of the SmPC to update the safety information of Kaletra and Aluvia following a cumulative safety review of the incidence rate of Stevens-Johnson syndrome, erythema multiforme and jaundice during clinical trials. This variation closes LEG 110. 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	31/10/2019		SmPC and PL	Based on the results of a cumulative safety review from all MAH-sponsored clinical studies identified with LPV/RTV in a total of 2,612 patients, the frequency of 3 adverse reactions has been modified: jaundice changed from "unknown" to "uncommon", since there were 6 reported cases among 2,612 patients; erythema multiforme changed from "unknown" to "rare", since there was one event reported and Stevens-Johnson syndrome (SJS) changed from "unknown" to "rare" since there was one case reported.
WS/1677	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.5 of the SmPC on the potential interaction with apalutamide, a moderate to strong CYP3A4 inducer, as well as with encorafenib, following an evaluation of the potential drug-drug interaction (DDI) between LPV/RTV (Kaletra and Aluvia) with apalutamide (Erleada) and encorafenib (Braftovi) through bibliographic and post-marketing	19/09/2019	27/10/2020	SmPC and PL	A bibliographic and post-marketing data search showed that the concomitant use of lopinavir (LPV)/ritonavir (RTV) (Kaletra and Aluvia) or ritonavir (Norvir) with apalutamide and encorafenib is not recommended. This is due to the fact that LPV/RTV are both inhibitors of CYP3A and the co-administration with apalutamide and encorafenib, both anticancer agents which are primarily metabolised by CYP3A, may result in increased plasma concentrations and lead to increased toxicity and potential risk for serious adverse events. Additionally, apalutamide, an inhibitor of androgen

	data search. The Package Leaflet is also updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				receptors indicated for the treatment of prostate cancer, is a strong inducer of CYP3A4. The co-administration of apalutamide with LPV is expected to decrease LPV exposure and potentially lead to virological failure and resistance emergence. Given the metabolic properties of LPV, RTV and apalutamide, and that these three compounds are metabolised through CYP3A, the net effect of LPV/RTV and apalutamide combination is unpredictable and hence, their co-administration is not recommended. Similarly, encorafenib, a kinase inhibitor indicated for the treatment of metastatic melanoma, is both an inhibitor and inducer of CYP3A4 and may also affect CYP3A4 substrates such as LPV/RTV. Given that its impact on LPV/RTV exposure is also unknown, its coadministration is not recommended.
IB/0178/G	This was an application for a group of variations. B.II.e.1.a.2 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Semi-solid and non-sterile liquid pharmaceutical forms B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form	23/08/2019	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.	29/05/2019	04/07/2019	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,

	Update of sections 4.3 and 4.5 of the SmPC in order to 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. Furthermore, the quantity of tenofovir disoproxil has been amended in sections 4.5 and 5.1 of the Kaletra and Aluvia SmPCs (as requested during procedure WS 1555) as 300 mg tenofovir disoproxil fumarate is equivalent to 245 mg tenofovir disoproxil . 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				which could increase or prolong its therapeutic and may increase 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.
PSUSA/1905/ 201809	Periodic Safety Update EU Single assessment - lopinavir / ritonavir	16/05/2019	n/a		PRAC Recommendation - maintenance
WS/1486	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and	25/10/2018	29/04/2019	SmPC	

	Veterinary Medicinal Products - Other variation				
IAIN/0174	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	19/10/2018	n/a		
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.
IA/0172	A.7 - Administrative change - Deletion of manufacturing sites	11/07/2018	n/a		

IB/0170/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.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	26/06/2018	n/a		
T/0169	Transfer of Marketing Authorisation	06/04/2018	23/05/2018	SmPC, Labelling and PL	
IB/0167	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	05/04/2018	n/a		
IG/0891	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	20/03/2018	n/a		
IB/0165/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any	18/01/2018	23/05/2018	Annex II and Labelling	

	manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing				
WS/1178	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 add new contraindications and interaction information of lopinavir/ritonavir with venetoclax, with elbasvir/grazoprevir and with ombitasvir/paritaprevir/ritonavir with or without dasabuvir based on the company's core data sheet; the package Leaflet is updated accordingly. In addition, the MAH/SOH is taking the opportunity to update section 4.5 of the SmPC to reflect information already contained in section 4.3 for drug-drug interactions with astemizole, terfenadine, pimozide, ergot alkaloids and cisapride. 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/0161/G	This was an application for a group of variations. Extension of Indication to include children aged 14	22/06/2017	26/07/2017	SmPC, Labelling and PL	Please refer to the scientific discussion Kaletra-H-C-368-II-0161G

	days and older in the treatment of HIV-1; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. The studies provided in support of the paediatric indication are part of the agreed PIP (decision P/0144/2012). In addition, the Marketing authorisation holder (MAH) further updated section 4.4 to add a warning regarding the use of Kaletra oral solution with feeding tubes. The updated RMP v.8.2 is provided accordingly. IB-B.II.e.5.a.2-To add a new pack size of 120 ml in (2X 60ml bottles) for Kaletra 80mg/ml/20 mg/ml oral solution (EU/1/01/172/009). IA-B.IV.1.a.1-To add a new 2 ml oral dose syringe for the 120ml presentation. The group of variations leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP). 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 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 C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				

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 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	21/04/2017	24/05/2017	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 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.
II/0160	Update of sections 4.2 and 5.1 of the SmPC in order to update information following the analysis of the published 48-week study results "Kaletra ONCE daily randomised Trial of the pharmacokinetics, safety and efficacy of twice-daily versus once-daily lopinavir/ritonavir tablets dosed by weight as part of combination antiretroviral therapy in HIV-1–infected children"(PENTA 18/KONCERT) in fulfilment of a Post Authorisation Measure (Additional PhV activity in the Risk Management Plan). In addition, the MAH takes	15/12/2016	24/05/2017	SmPC	

	the opportunity to remove the Missing Information safety concern of Limited Information of the Kaletra 100 mg/25 mg film-coated tablets in the paediatric population as part of the agreed RMP version 8.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0162	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	27/10/2016	n/a		
II/0159	Update of sections 4.4 and 4.5 of the SmPC in order to include a warning and to add information, respectively, regarding the interaction of Lopinavir/ritonavir and afatinib, riociguat, cetirinib or vorapaxar (as a result of the assessment of the PSUR EMEA/H/C/PSUSA/00001905/201509). The Labelling is updated accordingly. In addition, the 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	15/09/2016	24/05/2017	SmPC, Labelling and PL	
II/0158	Update of sections 4.3 and 4.5 to add information regarding the interaction of Lopinavir/ritonavir and dronedarone. In addition, Sections 4.3, 4.4 and 4.5 have been updated to include information regarding	21/07/2016	18/08/2016	SmPC and PL	Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A like ritonavir. Concomitant administration with colchicine is contraindicated in patients

	the contraindication with colchicine in patients with renal or hepatic impairment and in patients with normal renal or hepatic function if strong CYP3A4-inhibitor (such as ritonavir-boosted PI) is coadministered. The Labelling is updated accordingly. In addition the MAH took the opportunity to update sections 4.4 and 4.8 to change "immune reactivation syndrome" to "immune reconstitution inflammatory syndrome" to reflect current terminology. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				with renal and/or hepatic impairment. Concomitant administration of Kaletra and amiodarone or dronedarone is contraindicated (see section 4.3) as the risk of arrhythmias or other serious adverse reactions may be increased.
PSUSA/1905/ 201509	Periodic Safety Update EU Single assessment - lopinavir / ritonavir	13/05/2016	n/a		PRAC Recommendation - maintenance
IG/0660/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 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	23/02/2016	09/08/2016	Annex II and PL	
II/0154	Update of sections 4.4 and 4.5 of the SmPC in order	18/02/2016	09/08/2016	SmPC, Annex	Co-administration of delamanid with a strong inhibitor of

	to add information regarding the interaction between Lopinavir/ritonavir and delamanid. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives for Spain in the Package Leaflet and to bring the PI in line with the latest QRD template version 9.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			II, Labelling and PL	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.
IB/0155	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/12/2015	09/08/2016	SmPC and PL	
IG/0617	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	10/11/2015	n/a		
II/0151	Update of sections 4.4 and 4.5 of the SmPC to add the interaction of Lopinavir/ritonavir and bedaquiline. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes 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	09/08/2016	SmPC and PL	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 lopinavir/ritonavir should be avoided. However, if the benefit outweighs the risk, co administration of bedaquiline with lopinavir/ritonavir must be done with caution. More frequent electrocardiogram monitoring and monitoring of transaminases is recommended.

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	09/08/2016	SmPC, Labelling and PL	
II/0148	Update of SmPC sections 4.2, 5.1 and 5.2 with information regarding the pharmacokinetic profile, safety and efficacy of twice-daily (BID) versus once-daily (QD) dosing as part of combination antiretroviral therapy in paediatric patients, based on an analysis of the 24-week interim study report for study PENTA 18/KONCERT. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/02/2015	31/03/2015	SmPC	Based on the limited data currently available, Kaletra should not be administered once daily. KONCERT/PENTA 18 is a prospective multicentre, randomised, open-label study that evaluated the pharmacokinetic profile, efficacy and safety of twice-daily versus once-daily dosing of lopinavir/ritonavir 100 mg/25 mg tablets dosed by weight as part of combination antiretroviral therapy (cART) in virologically suppressed HIV-1 infected children (n=173). Children were eligible when they were aged <18 years, ≥15 kg in weight, receiving cART that included lopinavir/ritonavir, HIV-1 ribonucleic acid (RNA) <50 copies/ml for at least 24 weeks and able to swallow tablets. At week 24, the efficacy and safety with twice-daily dosing (n=87) in the paediatric population given lopinavir/ritonavir 100 mg/25 mg tablets was consistent with the efficacy and safety findings in previous adult and paediatric studies using lopinavir/ritonavir twice daily. The percentage of patients achieving HIV-1 RNA <50 copies/ml at Week 24 was lower in the paediatric patients receiving lopinavir/ritonavir tablets once daily (88.2%) than in patients receiving the

					twice-daily dosing (96.6%, p = 0.040), mainly due to lower adherence in the once-daily group. The efficacy data favouring the twice-daily regimen are reinforced by a differential in pharmacokinetic parameters significantly favouring the twice-daily regimen.
II/0147	Update of SmPC section 4.5 to add information regarding the interaction between lopinavir/ritonavir and simeprevir. The Package Leaflet has been updated accordingly. Further, the Package Leaflet has been updated, upon request by the CHMP following the assessment of FUM 110, to provide more specific advice to patients if they forget to take a dose of Kaletra. In addition, the MAH took the opportunity to make editorial changes and update the contact details of the local representatives in Spain, Bulgaria and Poland in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/11/2014	31/03/2015	SmPC and PL	As part of this application pharmacokinetic data for simeprevir were evaluated, a literature review was conducted, and postmarketing safety data sources were searched for reports of adverse events involving co-administration of lopinavir/ritonavir and simeprevir. Co-administration of multiple doses of simeprevir with ritonavir resulted in increases in simeprevir maximum observed concentration (Cmax), area under the time concentration curve (AUC24h), and minimum observed concentraion (Cmin) by 4.7-, 7.2-, and 14.4-fold respectively, compared with simeprevir alone. Administration of simeprevir was generally well tolerated when administered alone or in combination with ritonavir. Based on exploratory exposure-response analysis using safety data from three Phase 3 simeprevir trials, higher simeprevir exposures (AUC24) were shown to be significantly associated with an increased risk of adverse events such as rash, pruritus, anemia, photosensitivity, and increased bilirubin. When darunavir plus ritonavir (800 mg plus 100 mg QD) were administered with simeprevir 50 mg QD, the increases in simeprevir Cmax, AUC24h, and Cmin were 1.8-, 2.6-, and 4.6-fold, respectively, compared with 150 mg QD simeprevir administered alone. Based on the significant effect of ritonavir (with or without darunavir) on simeprevir concentrations, and the reported

					exposure-safety analyses of simeprevir, co-administration of lopinavir/ritonavir and simeprevir is likely to result in substantially increased concentrations of simeprevir and increased potential for simeprevir-related adverse events. Therefore, it is not recommended to co-administer Kaletra and simeprevir. These data mirror the information provided in the SmPC of Olysio. As no specific interaction data are available with lopinavir/ritonavir, and given ritonavir is a strong CYP3A4 inhibitor, it is justified to add this drug interaction also to the Kaletra product information.
IA/0150	A.7 - Administrative change - Deletion of manufacturing sites	14/10/2014	n/a		
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		
II/0142	To add an alternative method of manufacturer for the active substance B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	26/06/2014	n/a		
IA/0146	A.7 - Administrative change - Deletion of manufacturing sites	15/05/2014	n/a		

II/0143	Update of sections 4.2, and 5.2 to include dosing recommendation for HIV-1-infected women during pregnancy and postpartum. In addition, section 4.6 was updated with results from the Antiretroviral Pregnancy Registry. The Package leaflet is updated in accordance. Minor corrections to align with QRD 9 were made to Annex IIIA Labelling (heading 6) and Annex IIIB Package Leaflet and to the list of local representatives (Germany). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	31/03/2015	SmPC, Labelling and PL	Lopinavir/ritonavir has no dosing recommendations for HIV-infected women during pregnancy. LPV/r is listed in treatment guidelines as preferred protease inhibitor during pregnancy with the goal of treatment being full plasma HIV RNA suppression, defined as confirmed plasma HIV RNA < 50 copies/mL, by the third trimester of pregnancy and specifically by delivery. The MAH proposed the inclusion of dosing recommendation (the standard adult dose 400/100 mg BID) for HIV-1-infected women during pregnancy and postpartum based on clinical data and literature review. Pharmacokinetic and clinical studies showed comparable efficacy of the standard regimen 400/100 mg BID, based on the suppression of plasma HIV-1 RNA in pregnant women and prevention of MTCT (mother to child transmission). Overall, the standard LPV/r dose 400/100 mg BID in pregnant women provides adequate LPV exposure. However, caution should be warranted for subjects with HIV harbouring PI mutations as described in the literature. Since neither PK nor clinical studies are available to evaluate the risk of virologic failure or safety with once daily dosing of LPV/r during pregnancy, the once daily dosing to treat pregnant women is not recommended. The safety of LPV/r 400/100 mg BID during pregnancy is supported by many available data from clinical studies, APR and post-marketing experience. The birth defects risk is unlikely in humans, but some studies observe an increase of prematurity in women receiving PIs (and notably LPV/r). However, this risk is not clearly identified and varies between studies. In conclusion, the available data support the use of standard LPV/r dose 400/100 mg BID during pregnancy

					and post-partum.
IB/0145	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	02/04/2014	31/03/2015	SmPC, Labelling and PL	
IB/0141/G	This was an application for a group of variations. B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS 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	10/02/2014	n/a		
II/0136	Update of sections 4.2 and 5.2 of the SmPC to add weight based (WB) dosing recommendations for paediatric patients to the Kaletra 100 mg/25 mg film coated tablets and Kaletra (80 mg + 20 mg) oral solution. Further to CHMP request, section 4.5 of the SmPC was revised to include updated information on the concomitant use of non-nucleoside reverse transcriptase analogues and to remove information on nelfinavir. The update of section 4.5 applied to all Kaletra pharmaceutical forms/strengths. In addition, spelling mistakes were corrected and headings in the PL to lower case were changed to comply with the QRD template version 9.	19/12/2013	22/01/2014	SmPC and PL	Dosing regimens based on body weight are the preferred and easy option in paediatric patients. A substudy from study PENTA 18 was performed to support the weight based dosing recommendations. Pharmacokinetics assessments were obtained to test three doses regimen (2, 3 or 4 LPV/rtv 100/25 mg tablets BID) in the following body weight bands: ≥ 15 to ≤ 25 kg; > 25 to ≤ 35 kg; > 35 kg. The pharmacokinetics parameters AUC0-12h, Cmax and Cmin of LPV/rtv were similar between these 3 weight bands. Moreover, AUC0-12h was equivalent to that of previous studies M05-730 (LPV/rtv tablets 400/100 mg BID in adults) and M98-940 (LPV/rtv oral solution at 300/75 mg/m2 in children), where doses were considered safe and effective in the paediatric population. The extrapolation of

	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				PK parameters obtained with lopinavir/ritonavir tablets to the oral solution showed a similar AUC0-12h when LPV/rtv oral solution is used at 10/2.5 mg/kg BID. Overall, although these data are limited they support the inclusion of additional paediatric dosing recommendation based on body weight in the product information of the lopinavir ritonavir tablet and oral solution formations.
IB/0140	B.II.c.1.g - Change in the specification parameters and/or limits of an excipient - Where there is no monograph in the European/National Ph. for the excipient, a change in specification from in-house to a non-official/third country Ph.	06/01/2014	n/a		
II/0137/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.7.a - Deletion of - a pharmaceutical form	21/11/2013	18/12/2013	SmPC, Annex II, Labelling and PL	This group of variations proposed the update to sections 4.3, 4.4 and 4.5 of the Summary of Product Characteristics (SmPC) for Kaletra 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. A similar effect is expected with lopinavir/ritonavir. Based on the study results, the use of avanafil in combination with lopinavir/ritonavir was added as a contra-indication.

					Drug-drug interaction with quetiapine resulting in deep coma 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. In addition, the 133.3 mg/33.3 mg soft capsules formulation was removed from Kaletra Product Information, as this formulation is no longer in use in the EU.
N/0138	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/11/2013	18/12/2013	PL	
IG/0379	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	15/11/2013	n/a		
N/0134	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/06/2013	18/12/2013	Labelling and PL	
IA/0135	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	14/05/2013	18/12/2013	SmPC	
N/0132	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/01/2013	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		
II/0123	Update of section 4.4 Special warnings and precautions for use as well section 4.8 Undesirable effects of the Summary of Product Characteristics	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

	(SmPC) for Kaletra 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, clinical or pharmacovigilance data				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 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	14/12/2012	18/12/2013	Annex II and PL	

	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)				
IA/0131	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)	29/11/2012	n/a		
IA/0129	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size	23/11/2012	n/a		
T/0127	Transfer of Marketing Authorisation	26/09/2012	25/10/2012	SmPC, Labelling and PL	
IB/0124/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the	10/10/2012	18/12/2013	Annex II and PL	

	manufacturing process of an immediate release solid oral dosage form or oral solutions				
II/0122/G	This was an application for a group of variations. Update of sections 4.4 and 4.5 of the SmPC in order to add a warning regarding the interaction of lopinavir/ritonavir and budesonide and update the drug-drug interaction table and clinical recommendations on the interactions of lopinavir/ritonavir with maraviroc, boceprevir, telaprevir, rivaroxaban, lamotrigine and raltegravir. The Package Leaflet is updated accordingly. The requested group of variations 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, clinical or pharmacovigilance data 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	19/07/2012	30/08/2012	SmPC and PL	The medicinal product Kaletra is a co-formulation that contains lopinavir/ritonavir and it is acknowledged that ritonavir as an inducer of glucuronidation may increase the concentrations of drugs the metabolism of which is mainly dependent of this pathway. Pharmacokinetics as well as safety data of the following medicinal products maraviroc, boceprevir, telaprevir, rivaroxaban, lamotrigine, valproate and raltegravir were evaluated when these were co-administered with lopinavir/ritonavir. Consequently information on these drug-dug interactions and clinical recommendations were introduced in the appropriate sections of the Kaletra Product Information.
IA/0126	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	16/07/2012	n/a		

IA/0125	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	16/07/2012	n/a		
IA/0121/G	This was an application for a group of variations. B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition 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	30/03/2012	n/a		
II/0114	Update of sections 2, 4.2, 4.4, 4.9, 5.2 and 6.1 of the SmPC in order to add a warning and update the safety information relative to excipients (ethanol and propylene glycol) in Kaletra Oral solution. The PL was 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	19/01/2012	21/02/2012	SmPC and PL	A cumulative review of the cases involving infants less than 2 years of age receiving oral solution who experienced at least 1 of the following events of interest: renal failure, lactic acidosis, central nervous system (CNS) depression, heart block, and cardiomyopathy. A total of 25 reports were retrieved and in summary, only 10 cases provided reliable data allowing an assessment. The review described events of complete AV block, bradycardia, cardiomyopathy, lactic acidosis, acute renal failure, CNS depression, and respiratory complications leading to death noted in post-marketing reports of neonates coincident with LPV/r oral solution therapy. These adverse events are also described as toxicities of alcohol and/or propylene glycol which are excipients present in the Kaletra oral solution. Information regarding the additive effect of propylene glycol and alcohol in neonates and to

					highlight the total amounts of alcohol from all medicines administered to an infant to avoid toxicity.
II/0110	Update of section 4.3 and Section 4.5 of the SmPC with the available drug interaction data about lopinavir/ritonavir and bosentan, colchicine, tadalafil, alfuzosin fusidic acid and salmeterol. The PL was updated in accordance. In addition, the MAH took the opportunity to update version number of the Risk Management Plan in Annex II. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/01/2012	21/02/2012	SmPC, Annex II and PL	Drug interaction data between lopinavir/ritonavir and alfuzosin, bosentan, colchicine, fusidic acid, salmeterol and tadalafil were evaluated and as a consequence these data are reflected in section 4.5 of the SmPC. In addition, recommendations for the co-administration of alfuzosin, colchicine and fusidic acid were added to section 4.3 of the SmPC.
IA/0119	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	17/02/2012	n/a		
IAIN/0117	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	03/02/2012	n/a		
IA/0120	B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions	27/01/2012	n/a		

IB/0116	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)	11/01/2012	21/02/2012	SmPC	
IA/0115	To make a change in address of a manufacturing site of the active substance (lopinavir and ritonavir) from Abbott S.r.L., Via Pontina, KM52, Camoverde di Aprilia, (Latina) Italy 04010 to Abbott S.r.L., S.R. 148 Pontina, Km 52 snc, 04011 Campoverde di Aprilia (LT) Italy. This site is responsible for manufacture, packaging and analytical testing (release and stability). 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		
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 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	30/09/2011	n/a		

	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				
IB/0109	B.II.e.1.a.2 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Semi-solid and non-sterile liquid pharmaceutical forms	12/08/2011	n/a		
IB/0108	To update the information on the interaction of lopinavirlritonavir and rifabutin provided in Section 4.5 Interaction with other medicinal products and other forms of interaction of Annex I to include the changes recommended by the CHMP in Follow-up Measure 071 (FU2 071.4). The changes described in this variation application are relevant to all pharmaceutical forms and strengths of Kaletra (soft capsules, oral solution and film-coated tablets). The purpose of this variation application is to address and implement, as appropriate, the abovementioned changes as discussed. 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,	28/06/2011	n/a	SmPC	To update the information on the interaction of lopinavirlritonavir and rifabutin provided in Section 4.5 Interaction with other medicinal products and other forms of interaction of Annex I to include the changes recommended by the CHMP in Follow-up Measure 071 (FU2 071.4). The changes described in this variation application are relevant to all pharmaceutical forms and strengths of Kaletra (soft capsules, oral solution and film-coated tablets). The purpose of this variation application is to address and implement, as appropriate, the abovementioned changes as discussed.

	or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				
II/0106	Update of Summary of Product Characteristics Update of section 4.6 of the SmPC to include information from the antiretroviral pregnancy registry concerning the risk of congenital birth defects and the use of Kaletra during pregnancy, following the assessment of PSUR 13. In addition, section 4.6 was updated to comply with the current SmPC guideline (GL), the QRD product information template and the GL of risk assessment of medicinal products on human reproduction and lactation: from data to labelling. The MAH took the opportunity to update section 4.1 of the SmPC in line with the HIV GL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/03/2011	18/04/2011	SmPC	The sample size in the Antiretroviral Pregnancy Registry for lopinavir/ritonavir is sufficient to detect a 2.4-fold increase in the overall risk for congenital birth defects in women exposed to lopinavir/ritonavir during pregnancy. Data from the APR from 2000 through 2007 showed an overall birth defect prevalence of 2.4% among women exposed to lopinavir/ritonavir at any time during pregnancy and a birth defect rate of 1.9% among those exposed during the critical first trimester. The latest update with data cut off as of January 31, 2010 reported the rate of congenital birth defects in infants exposed to lopinavir/ritonavir during the first trimester to be similar to the rate reported previously. As of January 31, 2010, 1,986 infants were exposed to lopinavir/ritonavir during first trimester, and second and/or third trimesters with a rate of congenital birth defects in first trimester (n = 590) exposures of 1.7% (95% CI: 0.8 to 3.1). Based on the above findings, the CHMP agrees to update Section 4.6 of the SmPC to reflect APR findings on congenital birth defects associated to lopinavir/ritonavir exposure during first trimester in pregnancy. The CHMP believes that this additional information will provide more information to help prescribers weigh the benefits and risks for use of lopinavir/ritonavir during pregnancy. The CHMP also acknowledged that the APR is an ongoing study and as additional data becomes available, the language might need future revision, if appropriate.

II/0105	Update of Summary of Product Characteristics, Annex IIB, and Package Leaflet. Update of Section 4.4 of the SPC to provide information about the risk of hepatotoxicity in individuals treated for post exposure prophylaxis and remind the prescriber that this risk also exists in HIV mono infected patients. Annex IIB is updated to reflect the new Risk Management Plan version number 4. The MAH took the opportunity to update section 6 of the Package Leaflet, by introducing the changes of names for the local representatives for Bulgaria and Romania. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/02/2011	18/03/2011	SmPC, Annex II and PL	A data review on hepatotoxicity with LPV/r was performed and due to the systematic associated treatment during post exposure prophylaxis, it was difficult to assess a causal relationship between LPV/r and hepatotoxicity. However, in all these cases the role of LPV/r could not be ruled out. Consequently, the MAH proposed to add a warning in the product information in section 4.4 of the SmPC and provide information about the risk of hepatotoxicity in individuals treated for post-exposure prophylaxis as well as to remind prescribers about this risk in HIV mono infected patients as well. The CHMP therefore agreed that close monitoring is needed in patients treated with LPV/r for a PEP indication. The CHMP also agreed that the results of the data review do not affect the benefit/risk balance of Kaletra. The routine pharmacovigilance risk minimisation activities for monitoring the risk of hepatotoxicity in mono infected and individuals treated for PEP proposed by the MAH were endorsed by the CHMP.
R/0107	Renewal of the marketing authorisation.	16/12/2010	28/02/2011	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Kaletra continues to be favourable. The renewal requires no amendments to the terms of the Community Marketing Authorisation. The CHMP is of the opinion that the renewal can be granted with unlimited validity. Finally, the next PSUR will be a 3-year PSUR covering the period from 1st October 2009 to 30th September 2012.

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	
IB/0104	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	17/09/2010	n/a		
IB/0103	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	17/09/2010	n/a		
IB/0102	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	17/09/2010	n/a		
IB/0099	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size	09/09/2010	n/a		
II/0090	Update of section 4.8 of the SmPC based on a full analysis of the frequency and the causality of the Adverse Drug Reactions in lopinavir/ritonavir clinical trials database in fulfilment of a follow-up measure. In addition the section is revised in accordance with	22/07/2010	26/08/2010	SmPC and PL	The section 4.8 of the SmPC was fully revised following the SmPC Guideline and a full analysis of the frequency and the causality of Adverse Drug Reactions. Furthermore it has been proposed to add and delete certain Adverse Drugs Reactions following an algorithm provided by the MAH. This

	the Guideline on SmPC rev 2. Consequently the PL is updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				analysis aimed to the addition of cerebrovascular event, cholangitis, rhabdomyolysis, osteonecrosis, convulsion and muscle disorders in the section 4.8 of the SmPC. Moreover, hepatitis, Jaundice, Stevens-Jonhson syndrome and erythema multiform have been added to the tabulated summary with a not known frequency. The PL has been updated accordingly.
II/0089/G	This was an application for a group of variations. This was an application for a group of variations. In section 5.1 of the SmPC, the sub section on resistance is updated in fulfilment of follow-up measure (FUM) 102. In fulfilment of FUM 100, further changes to section 5.1 are made in line with the Annex B of the Guideline on Clinical Development of Medicinal Products for Treatment of HIV Infection. In addition, in fulfilment of FUM 107, references to the lack of clinical experience with lopinavir/ritonavir are being deleted in sections 4.1 for all presentations and 4.4 in the capsule and oral solution formulations. 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 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	22/07/2010	26/08/2010	SmPC	In section 5.1 of the SmPC, the sub section on resistance is updated in fulfilment of FUM 102. The sub-section "Analysis of resistance in ARV-naïve patients" was simplified and the description of study M97-720 and study M98-863 was transferred to a new sub section "Patients without prior antiretroviral therapy". In fulfilment of FUM 100, changes to section 5.1 are made in line with the Annex B of the Guideline on Clinical Development of Medicinal Products for Treatment of HIV Infection. Finally, in fulfilment of FUM 107, references to the lack of clinical experience with lopinavir/ritonavir are being deleted in sections 4.1 for all presentations and 4.4 in the capsule and oral solution formulations.

	NO new additional data are submitted by the MAH				
IA/0101	A.7 - Administrative change - Deletion of manufacturing sites	05/08/2010	n/a		
IA/0100	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	05/08/2010	n/a		
II/0088	Update of section 4.5 of the SmPC in line with the latest version of the Company Core Data Sheet (CCDS) based on a pharmacokinetic analysis of lopinavir/ritonavir and fentanyl, nilotinib and dasatinib. Consequently, the PL was updated. In addition, the MAH took this opportunity to update the name of Pneumocystis jiroveci in the SmPC. Also, the MAH updated the PL with the additional manufacturer registered for batch release. Finally, the MAH took this opportunity to update contact details of 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	24/06/2010	28/07/2010	SmPC and PL	Following some drug interaction studies between lopinavir/ritonavir and two signal transduction inhibitors, dasatinib and nilotinb, which are used in the treatment of chronic myelogenous leukaemia (CML), and fentanyl which is used in pain management the Interaction Table in the section 4.5 of the SmPC has been updated. These drugs are metabolised by CYP3A4 enzymes which are inhibited by Kaletra, therefore there is a potential interaction with increased risk in frequency and intensity of adverse events. The Package Leaflet has been updated accordingly.
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	23/07/2010	n/a	Annex II	

	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				
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		
IA/0096	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	09/07/2010	09/07/2010	SmPC, Labelling and PL	
IA/0095	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	07/07/2010	n/a		
IA/0094	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	07/07/2010	n/a		

IA/0093	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	07/07/2010	n/a		
II/0083	Update of sections 4.2, 4.5, 4.8 and 5.1 of the SmPC of the Kaletra film-coated tablets (200/50 mg and 100/25 mg) based on the Phase III study M06-80 in support of a once-daily dosing regimen in antiretroviral experienced patients. The PL was updated in accordance. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	30/03/2010	SmPC and PL	
IB/0084	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	28/01/2010	n/a		
II/0081	Update of Detailed Description of the Pharmacovigilance System. Update of DDPS (Pharmacovigilance)	19/11/2009	08/01/2010	Annex II	The Marketing Authorisation Holder applied to update the Detailed Description of the Pharmacovigilance System (DDPS). Consequently, Annex II has been updated using standard text including the number of the version agreed for the DDPS (version 3).
IA/0087	IA_13_a_Change in test proc. for active substance - minor change	06/01/2010	n/a		
IA/0086	IA_01_Change in the name and/or address of the marketing authorisation holder	22/12/2009	n/a	SmPC, Labelling and PL	

IA/0085	IA_28_Change in any part of primary packaging material not in contact with finished product	11/12/2009	n/a		
II/0079	Update of section 4.5 of the SmPC based on literature data regarding the interaction of lopinavir/ritonavir and tipranavir. The PL was updated in accordance. Update of Summary of Product Characteristics and Package Leaflet	22/10/2009	23/11/2009	SmPC and PL	In a clinical study of dual boosted protease inhibitor combination therapy in multiple treatment experienced HIV 1 infected adults, tipranavir (500 mg twice daily) with ritonavir (100 mg twice daily), co administered with lopinavir/ritonavir (400/100 mg twice daily), resulted in a 70% reduction in lopinavir Cmin. Due to this reduction in lopinavir exposure, the CHMP concluded that this co-administration should be avoided.
II/0077	Update of sections 4.2 and 4.4 of the SmPC in order to update information on the use of lopinavir/ritonavir in patients with renal impairment. The MAH also took the opportunity to reformat section 4.5 of the SmPC in line with the Annex A to the guideline on Clinical Development of Medicinal Products for Treatment of HIV Infection as requested by the CHMP. As a consequence, sections 4.3 and 4.4 of the SmPC and the PL were updated as well. In addition, a minor mistake in section 5.1 relating to resistance data was corrected. Finally, the MAH took this opportunity to update contact details of local representatives in the PL. Update of Summary of Product Characteristics and Package Leaflet	22/10/2009	23/11/2009	SmPC and PL	The CHMP acknowledged that renal impairment may affect the pharmacokinetics of a medicinal product not only by modifying its clearance but also its distribution or its absorption. Therefore, caution is generally warranted for any medicinal product used in patients with renal impairment. However, this general caution applies to all medicinal products when treating patients with sever renal impairment. In view of the pharmacokinetics of lopinavir/ritonavir (negligible renal clearance), the CHMP concluded that there is no reason to include a specific warning regarding the use of Kaletra in severe renally impaired patients. In addition, based on the review of updated Kaletra interaction data, information on statins and sildenafil was updated.
IB/0082	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	08/09/2009	08/09/2009	SmPC, Labelling and	

				PL	
II/0067	Update of sections 4.2, 4.5, 4.8, 5.1 and 5.2 of the SPC based on data from ongoing pharmacokinetic study M05-730 to add the possibility of a once-daily dosing regimen of the LPV/RTV tablet formulation for antiretroviral treatment naïve patients. In addition, the MAH took this opportunity to update section 4.8 of the SPC to exchange the currently used COSTART terms to MedDRA terminology. Consequently, the PL was updated. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	21/08/2009	SmPC and PL	Study M05-730 was a randomised, open-label, multicentre trial comparing treatment with Kaletra 800/200 mg once daily plus tenofovir DF and emtricitabine versus Kaletra 400/100 mg twice daily plus tenofovir DF and emtricitabine in 664 antiretroviral treatment-naïve patients. The results of the study showed that the once daily regimen of Kaletra tablets was statistically non-inferior to the twice daily regimen, therefore, the CHMP agreed to add this option to the Kaletra SPC for the tablet formulations. However, there were some indicators that in regards to long-term viral suppression the twice-daily regimen might be more optimal. Also, the once daily regimen showed a higher rate of diarrhoea. Cautionary statements highlighting these limitations were therefore added to the new posology option.
IA/0078	IA_09_Deletion of manufacturing site	27/03/2009	n/a		
IB/0075	IB_33_Minor change in the manufacture of the finished product	26/11/2008	n/a		
IB/0074	IB_33_Minor change in the manufacture of the finished product IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	26/11/2008	n/a		
IB/0072	IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance	26/11/2008	n/a		
II/0068	Update of Detailed Description of the	23/10/2008	24/11/2008	Annex II	The Marketing Authorisation Holder applied to update the

	Pharmacovigilance System. Update of DDPS (Pharmacovigilance)				Detailed Description of the Pharmacovigilance System (DDPS). Consequently, Annex II has been updated using standard text including the number of the version agreed for the DDPS (version 2).
IA/0076	IA_32_a_Change in batch size of the finished product - up to 10-fold	06/11/2008	n/a		
IA/0073	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	06/11/2008	n/a		
II/0062	Update of section 5.1 of the SPC, subsection "Resistance" to reflect data from international HIV drug resistance databases. Update of Summary of Product Characteristics	25/09/2008	30/10/2008	SmPC	Based on data available from international HIV drug resistance databases, the current information on the lopinavir/ritonavir mutation score was updated by adding the mutations I47A and L76V in the information for protease inhibitor experienced patients receiving Kaletra therapy. In addition, a sentence was added to the resistance section of the SPC to highlight the necessity to always consult current interpretation systems for analysing resistance test results.
IB/0071	IB_10_Minor change in the manufacturing process of the active substance	10/10/2008	n/a		
IB/0070	IB_10_Minor change in the manufacturing process of the active substance	10/10/2008	n/a		
IB/0069	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	07/10/2008	n/a	SmPC	
II/0063	Update of sections 4.2 and 4.5 of the SPC with recommendations regarding co-administration of	26/06/2008	22/08/2008	SmPC	On the basis of pharmacokinetic data extracted from 4 clinical studies (3 in healthy volunteers and 1 in HIV-

	fosamprenavir and lopinavir/ritonavir (concomitant administration of these medicinal products is not recommended) following assessment of a clinical follow-up measure. Update of Summary of Product Characteristics				infected patients) investigating the recommended dosage regimens for fosamprenavir and lopinavir/ritonavir and other regimens with an increase of fosamprenavir dosage, of lopinavir dosage or of ritonavir dosage, the Product Information of Kaletra was amended. Dosage recommendations and data on co-administration of lopinavir/ritonavir with fosamprenavir have been deleted from sections 4.2 and 4.5 of the SPC and replaced by a non-recommendation of concomitant use of lopinavir/ritonavir with fosamprenavir.
II/0061	Update of section 4.5 of the SPC based on the 11th Periodic Safety Update Report (PSUR) to include the potential interaction between lopinavir/ritonavir and bupropion. Consequently, section 2 of the PL was updated. In addition, the MAH took this opportunity to revise the SPC to incorporate QRD comments made during the assessment of a recent line extension application, to reflect the results of the user testing for the PL, as well as to update the contact details of the Italian local representative in the PL. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	22/08/2008	SmPC and PL	In this study, twelve healthy volunteers received a single 100 mg dose of sustained-release bupropion before and after 2 weeks of treatment with lopinavir/ritonavir 400 mg/100 mg twice daily. Lopinavir/ritonavir administration significantly decreased bupropion and its metabolite's (hydroxybupropion) plasma exposures. This decrease is likely due to the concurrent induction of cytochrome P450 2B6 and UDP-glucuronosyltransferase enzymes. No significant changes in the blood levels of lopinavir or ritonavir were found following administration of a single dose of bupropion. As the maximum recommended dose of bupropion (300 mg / day) should not be increased to compensate for this induction effect, the combination should be avoided. However, if deemed unavoidable, clinical monitoring for lack of bupropion efficacy is necessary.
II/0053	Update of sections 4.2, 4.4 and 4.5 of the SPC to reflect results from an interaction study evaluating the co-administration of lopinavir/ritonavir tablets with efavirenz. The PL was updated in accordance.	26/06/2008	22/08/2008	SmPC and PL	This interaction study, performed in healthy volunteers, had shown that a dose increase to lopinavir/ritonavir 500/125 mg twice daily (two 200/50 mg tablets + one 100/25 mg tablet) co-administered with efavirenz 600 mg

	Update of Summary of Product Characteristics and Package Leaflet				every evening (once daily) allowed to achieve adequate lopinavir plasma exposure compared to the standard lopinavir/ritonavir 400/100 mg twice daily regimen administered alone (Cmax +12%, AUC +6%, Ctrough -5%, Cmin -10%). The SPC was updated to reflect this information together with updated specific dosage recommendations for this co-administration. The PL was updated to highlight to patients that they need to consult with their physician if they are taking either efavirenz or nevirapine together with lopinavir/ritonavir.
IA/0066	IA_09_Deletion of manufacturing site	06/08/2008	n/a	Annex II	
II/0052	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. The MAH also took the opportunity to include the name in Braille on the outer packaging for the oral solution and for the film-coated tablets. In addition, the contact details for the local representatives in Bulgaria, Denmark, Estonia, Latvia and Lithuania have been updated in the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/04/2008	20/06/2008	SmPC, Labelling and PL	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 lopinavir/ritonavir has a potential to induce modest QTc and PR interval prolongation. No subject 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 11.6 ms to 24.4 ms in the 12 hour interval post dose. Maximum PR interval was 286 msec and no second or third degree heart block was observed. The Product Information was updated in accordance.
IA/0065	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/0064	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	
IB/0059	IB_33_Minor change in the manufacture of the finished product	22/04/2008	n/a		
IB/0060	IB_31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits	26/03/2008	n/a		
IB/0058	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	26/03/2008	n/a		
X/0042	The MAH applied for an additional strength of 100/25 mg film-coated tablets. Annex I_2.(c) Change or addition of a new strength/potency	24/01/2008	18/03/2008	SmPC, Labelling and PL	In order to offer more options for the treatment of paediatric patients, the MAH applied for an additional strength 100/25 mg film-coated tablets. These tablets have been developed as an alternative to the oral solution and might bring a significant improvement of the dosing management of infants. Kaletra 100/25 mg film coated tablet contains the same active ingredients and excipients in the same proportional amounts as currently the approved Kaletra 200/50 mg with the exception of coating material. Both strengths of the Kaletra tablets are manufactured at the same manufacturing sites, on the same manufacturing lines, using the same manufacturing processes. Bioequivalence data submitted showed that following a single dose of lopinavir/ritonavir 400/100 mg, the new strength Kaletra 100/25 mg is bioequivalent to the reference formulation Kaletra 200/50 mg. Pharmacokinetic studies were performed on compliance with GLP and GCP.

IB/0057	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	13/02/2008	n/a		
IB/0056	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	13/02/2008	n/a		
IA/0055	IA_09_Deletion of manufacturing site	07/02/2008	n/a		
IA/0054	IA_32_a_Change in batch size of the finished product - up to 10-fold	16/01/2008	n/a		
IA/0051	IA_05_Change in the name and/or address of a manufacturer of the finished product	14/12/2007	n/a		
IA/0050	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	14/12/2007	n/a		
II/0043	Update of sections 4.3, 4.4 and 4.5 of the SPC based on a comprehensive review of 3 studies examining the pharmacokinetics of co-administered lopinavir/ritonavir and rifampicin as requested by the CHMP in February 2007. The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/10/2007	20/11/2007	SmPC and PL	Following the review of 3 interaction studies with lopinavir/ritonavir and rifampicin, the CHMP considered that an increased dose of Kaletra might allow compensating for the inducer effect of rifampicin, however such an increased dose appeared to be associated with an increased liver toxicity. Therefore, the CHMP considered to revise the Product Information to downgrade the contra-indication concerning rifampicin to a warning and to point out that: - Rifampicin in combination with Kaletra may cause large decreases in lopinavir concentrations which may in turn significantly decrease the lopinavir therapeutic effect. - Adequate exposure to lopinavir/ritonavir may be achieved when higher dose of Kaletra is used but this is associated with a higher risk of liver and gastrointestinal toxicity.

					- This co-administration should be avoided unless judged strictly necessary.
II/0048	Update of section 1 of the SPC for Kaletra Oral Solution in order to clarify the statement of the actual concentration and to avoid the risk for confusion in the administration of the oral solution in paediatrics. The Labelling and the PL were updated accordingly. Update of Summary of Product Characteristics, Labelling and Package Leaflet	20/09/2007	24/10/2007	SmPC, Labelling and PL	Following a fatal case possibly associated with an accidental overdose in an infant that received Kaletra oral solution in an off-label use, the MAH was asked to improve the product information (PI) of Kaletra oral solution to help preventing dosing mistakes and overdoses. The MAH provided a review of cases of overdose/maladministration with Kaletra oral solution, which found 2 further reports of paediatric cases. These however contained insufficient information to determine the specific cause of the prescribing/medication errors. The CHMP agreed that the changes to the PI help to reduce potential dosing or administration errors. To further substantiate the scientific basis for a contraindication in infants, the MAH committed to provide further paediatric data.
II/0047	Update of sections 4.4 and 4.5 of the SPC following the CHMP's assessment of PSUR 10 for lopinavir/ritonavir in May 2007. Consequently, the Package Leaflet is updated. The MAH also took the opportunity to include a minor correction in section 6 of the PL. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	24/10/2007	SmPC and PL	Based on the information considered in the last Periodic Safety Update Report (PSUR), The MAH was requested to include information regarding the potential for drug interactions between lopinavir/ritonavir, Phenytoin, chemotherapeutic agents such as vincristine/vinblastine and rosuvastatin. A review of cases and literature for these potential interactions of co-administration with lopinavir/ritonavir indicated scientific evidence for : - Increased concentrations of vincristine/vinblastin, - Decreases in both phenytoin and lopinavir/ritonavir exposure, - Increases in rosuvastatin exposure.

					The CHMP agreed to update the Product Information to reflect these findings.
II/0045	Update of section 4.5 of the SPC with information available in the public domain on the interaction of buprenorphine and lopinavir/ritonavir following the CHMP's request on 26 April 2007. Update of Summary of Product Characteristics	20/09/2007	24/10/2007	SmPC	A recent interaction study between buprenorphine and lopinavir/ritonavir, available in the public domain (McCance-Katz et al., 2006), showed that the co-administration of both medicines at normal therapeutic doses did not lead to a significant changes in blood levels of buprenorphine and its metabolites or lopinavir/ritonavir. Based on these data, co-administration of lopinavir/ritonavir and buprenorphine is well tolerated and does not result in clinically significant drug interactions which would require altering of dosing recommendations. The SPC was updated to reflect this finding accordingly.
IA/0049	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	23/08/2007	n/a		
IB/0046	IB_10_Minor change in the manufacturing process of the active substance	13/08/2007	n/a		
II/0041	Update of sections 4.3 and 4.5 of SPC and section 2 of the PL as regards the interaction with oral and parenteral midazolam, following CHMP request in March 2007. 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	25/07/2007	SmPC and PL	A phenotyping cocktail study investigating the co-administration of midazolam with fixed combination lopinavir/ritonavir in 14 healthy volunteers showed an increase of midazolam AUC by about 13 fold when midazolam was given orally and an increase by about 4 fold when midazolam was given parenterally. Therefore, the co-administration of lopinavir/ritonavir with orally administered midazolam is contraindicated, whereas caution should be used when lopinavir/ritonavir is co-administrated with injection of midazolam.

					If lopinavir/ritonavir 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/0044	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	20/06/2007	n/a		
IB/0040	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	16/05/2007	n/a		
IA/0039	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	23/04/2007	n/a		
II/0037	Update of section 4.5 of the SPC based on an interaction study between lopinavir/ritonavir and stomach acid reducing agents (omeprazole or ranitidine). Consequentially, section 2 of the Package Leaflet is updated as well. Update of Summary of Product Characteristics and Package Leaflet	22/02/2007	28/03/2007	SmPC and PL	The study, which was conducted in healthy volunteers, showed that after administration of multiple oral doses of the approved therapeutic regimen in the EU (lopinavir/ritonavir 400/100 mg twice daily) no clinically significant drug-drug interaction with either omeprazole or ranitidine was observed. The results were in accordance with the pH-solubility profiles of lopinavir and ritonavir and with the physico-chemical mechanism involved in the drug-drug interaction between protease inhibitors and acid-reducing agents related to a decreased solubility of the molecule with increasing pH. As this co-administration is frequent in clinical practice and therefore of practical relevance to the prescribers, the results from this

					interaction study were included in the SPC and PL.
II/0036	Update of sections 4.8 and 5.1 of the SPC to reflect the long-term (7 year) safety and efficacy data now available from a phase I/II study in antiretroviral naïve patients. Consequentially, the PL is updated as well. Update of Summary of Product Characteristics and Package Leaflet	22/02/2007	28/03/2007	SmPC and PL	The submitted data demonstrate long term sustainability of lopinavir/ritonavir in the treatment of antiretroviral naïve HIV-1 infected patients. The study was originally designed as a dose selection study and consequently, the study population was small. This limited the evaluation of the provided data. Nevertheless, Week 360 results of the study showed that lopinavir/ritonavir is safe while maintaining antiretroviral efficacy, with 61% and 59% of antiretroviral naïve patients initially enrolled demonstrating plasma HIV-1 RNA levels < 400 copies/ml and < 50 copies/ml, respectively. The safety profile of lopinavir/ritonavir remains essentially unchanged, as the reported adverse events did not show new or major issues. However, based on the analysis of the updated information about adverse events reported within this study, the frequency categories for pain, acne and paresthesia were changed from uncommon to common.
II/0038	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. Section 6 of the PL was updated to include the local representatives in Bulgaria and Romania and to mend the local representatives in Belgium, Cyprus, Estonia, Finland, Iceland, Latvia, Lithuania, Luxembourg, The Netherlands, Portugal, Slovenia and United Kingdom. Update of Summary of Product Characteristics and	14/12/2006	16/01/2007	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

	Package Leaflet				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/0033	Update of section 5.1 of the SPC to include recommendations on the therapeutic options in case of virological failure, as requested by the CHMP following the renewal of the Marketing Authorisation in January 2006. To this purpose, the information in the cross-resistance section is updated with new information. Update of Summary of Product Characteristics	18/10/2006	04/12/2006	SmPC	Based on the in vitro data presented on cross-resistance of lopinavir with other protease inhibitors, tipranavir could be a suitable option for salvage therapy to Kaletra, provided that the viral strains do not harbour the pejorative mutations for clinical response to tipranavir (three or more mutations at positions 33, 82, 84 or 90). The cross-resistance subsection was therefore reworded to reflect these findings. Furthermore, the resistance section was re-structured and updated with information on in vitro data in antiretroviral naïve and experienced patients.
II/0032	To update sections 4.3, 4.4, 4.5 and 4.8 of the SPC with new safety information, following the CHMP assessment reports for PSUR 6 and 7. Changes include the addition of wordings regarding the drug interaction with digoxin, fosamprenavir, tadalafil, vardenafil, trazodone, tenofovir and voriconazole. In addition, the wording regarding oral contraceptives was revised to include patch contraceptives. Furthermore, Stevens-Johnson syndrome and erythema multiforme was added to the post-marketing experience sub-section of section 4.8. Consequentially, sections 2 and 4 of the PL are updated accordingly. Also, following the CHMP's request endorsed during the Renewal procedure, section 4 of the PL is updated to include a comprehensive list of all other common and	18/10/2006	04/12/2006	SmPC and PL	Further to the assessment of PSUR 6 and 7 (covering the period from 1.10.03 to 30.9.04) the safety information of Kaletra was updated in regards to potential interactions with digoxin, fosamprenavir, tadalafil, vardenafil, trazodone, tenofovir and voriconazole as well as in regards to serious skin reactions. To this purpose, a cumulative review was submitted per CHMP request and assessed in this type II variation. Information on interaction with other medicinal products has been refined during the CHMP's assessment process to focus more closely on the low dose of ritonavir given concomitantly with lopinavir in the Kaletra co-formulation. In line with the Guideline on Summary of Product Characteristics information on interactions that are not non-recommended had been moved from section 4.4 to section 4.5 only.

	uncommon side effects. Update of Summary of Product Characteristics and Package Leaflet				
IB/0035	IB_10_Minor change in the manufacturing process of the active substance	18/08/2006	n/a		
IA/0034	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	31/07/2006	n/a		
X/0027	Addition of a new pharmaceutical form Addition of new strength Addition of film-coated tablets containing 200 mg lopinavir / 50 mg ritonavir X-3-iv_Change or addition of a new pharmaceutical form X-3-iii_Addition of new strength	27/04/2006	27/06/2006	SmPC, Labelling and PL	Please refer to the Scientific Discussion: Kaletra H-368-X-27
R/0031	Renewal of the marketing authorisation.	23/02/2006	06/04/2006	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit risk balance of remains positive but that its safety profile should be closely monitored for the following reasons: The salient aspects of the safety profile of Kaletra remain lipid disorders, hepatotoxicity and, probably more pronounced than in some other Protease Inhibitors, pancreatitis.

					The following adverse reactions should continue to be closely monitored: pancreatitis, hepatic events, hypersensitivity and allergic reactions, lipid disorders and clinical events potentially attributable to hyperlipidaemia, bone disorders, acute renal failure and renal insufficiency particularly in case of concomitant tenofovir use or dehydration, lipodystrophy, pregnancy and congenital disorders. In addition, thrombocytopenia, hallucination and eye disorders should be put under monitoring. Also, there is the constant need to carefully control the emergence of new resistance patterns for Kaletra and an associated virological failure as well as the possible cross-resistance to other Protease Inhibitors. Therefore, based on the safety profile of Kaletra, the CHMP concluded that the MAH should submit one additional renewal application for Kaletra in 5 years time.
IA/0030	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	18/10/2005	n/a		
IA/0029	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	16/09/2005	n/a		
II/0028	To update sections 4.4 and 4.5 of the 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. Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	24/08/2005	SmPC and PL	The MAH implements the class labelling 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 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/0025	To include statements in relation to an interaction between ritonavir and fluticasone in section 4.4 and 4.5 of SPC. Additionally, to update sections 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	12/01/2005	SmPC 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 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 interactions.
II/0026	To include a statement in section 4.2 of the SPC for Kaletra oral solution and Kaletra soft capsules in relation to paediatric dosing recommendations and specifically concerning the use of Kaletra soft gel capsules. Additionally, some minor linguistic changes to the Latvian SPC, labelling and PL text are made. Update of Summary of Product Characteristics, Labelling and Package Leaflet	18/11/2004	17/12/2004	SmPC, Labelling and PL	Based on a request from the ad-hoc Paediatric Expert Group to define at what body weight/surface area children should change from 1 capsule to 2 or 3 capsules twice daily. Estimates of the potential over- and under-exposures using soft capsule doses for children (and based on BSA ranges) were provided assuming that a proportional increase in lopinavir concentrations is observed with change in dose when maintaining a 4:1 ratio of lopinavir/ritonavir. Underdosing of Kaletra likely carries more risk than in case of producing higher exposures. It is however unclear what the lower bound of acceptable lopinavir exposures are in children. Therapeutic drug monitoring may be useful to ensure adequate lopinavir exposures in an individual patient.
IB/0024	IB_33_Minor change in the manufacture of the finished product	26/09/2004	n/a		
II/0022	Update of Summary of Product Characteristics	29/07/2004	09/09/2004	SmPC	
II/0021	Update of Summary of Product Characteristics,	29/07/2004	09/09/2004	SmPC,	

	Labelling and Package Leaflet			Labelling and PL	
II/0019	Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	30/01/2004	SmPC and PL	
II/0016	Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	30/01/2004	SmPC and PL	
II/0020	Quality changes	17/12/2003	23/12/2003		
I/0018	01_Change in the name of a manufacturer of the medicinal product	07/10/2003	13/10/2003		
I/0017	24_Change in test procedure of active substance	05/08/2003	18/08/2003		
II/0014	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	09/07/2003	SmPC and PL	
I/0015	14_Change in specifications of active substance	11/06/2003	26/06/2003		
S/0005	Annual re-assessment.	27/06/2002	12/11/2002	Annex II	
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/10/2002	13/11/2002	PL	
I/0008	20_Extension of shelf-life as foreseen at time of authorisation	22/08/2002	07/10/2002	SmPC	
I/0012	25_Change in test procedures of the medicinal product	13/09/2002	25/09/2002		

I/0011	25_Change in test procedures of the medicinal product	13/09/2002	25/09/2002		
I/0010	25_Change in test procedures of the medicinal product	13/09/2002	25/09/2002		
I/0009	25_Change in test procedures of the medicinal product	13/09/2002	25/09/2002		
I/0007	12_Minor change of manufacturing process of the active substance	16/08/2002	18/09/2002		
II/0006	Update of Summary of Product Characteristics and Package Leaflet	27/06/2002	13/09/2002	SmPC and PL	
II/0002	Update of Summary of Product Characteristics	18/10/2001	26/03/2002	SmPC	
II/0001	Update of Summary of Product Characteristics and Package Leaflet	18/10/2001	26/03/2002	SmPC, Labelling and PL	
I/0004	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	27/02/2002	06/03/2002		
I/0003	25_Change in test procedures of the medicinal product	17/01/2002	13/02/2002		