Telzir

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IA/0097	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	27/02/2019	n/a		
IAIN/0096	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	05/02/2019		Annex II and PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	including batch control/testing				
IAIN/0095	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2018		SmPC	
T/0093	Transfer of Marketing Authorisation	11/09/2018	28/09/2018	SmPC, Labelling and PL	
PSUSA/1470/201710	Periodic Safety Update EU Single assessment - fosamprenavir	14/06/2018	n/a		PRAC Recommendation - maintenance
IA/0092/G	This was an application for a group of variations. B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size 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) 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)	23/05/2018	n/a		
II/0089	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/01/2018	28/09/2018	SmPC, Labelling and PL	

IB/0090	B.II.z - Quality change - Finished product - Other variation	15/12/2017	n/a		
IB/0088	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	27/07/2017	n/a		
N/0087	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/03/2017	28/09/2018	Labelling	
IAIN/0086	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	16/12/2016	n/a		
II/0082	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/02/2016	04/04/2016	SmPC and PL	Co-administration of paritaprevir and fosamprenavir/ritonavir is contraindicated due to the expected increase of paritaprevir exposure and the lack of clinical data assessing the magnitude of this increase. Co-administration with simeprevir and daclatasvir is not recommended (due to an increase of simeprevir and daclatasvir exposure).
IB/0085	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/12/2015	04/04/2016	SmPC and PL	
IAIN/0084	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	09/12/2015	04/04/2016	Annex II and PL	

IB/0083/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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	11/11/2015	n/a		
IB/0081	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	17/08/2015	n/a		
PSUSA/1470/ 201410	Periodic Safety Update EU Single assessment - fosamprenavir	11/06/2015	n/a		PRAC Recommendation - maintenance
WS/0645	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 4.6 of the SmPC to include the WHO guidelines on breastfeeding. The Package Leaflet has been updated accordingly. In addition, the WSA has taken the opportunity to promote consistency across products by updating where relevant (i.e. for Trizivir, Combivir, Lamivudine/Zidovudine ViiV and Triumeq), the pharmacokinetic statements in section 4.6 of the SmPC to reflect the most recently approved wording for the components abacavir and lamivudine (Kivixa	23/04/2015	04/04/2016	SmPC and PL	

	EMEA/H/C/581/R/0051 and Epivir EMEA/H/C/107/II/0084). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0078	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	05/05/2015	SmPC and PL	No dosage adjustment of fosamprenavir or dolutegravir is recommended upon concomitant administration of the two based on observed exposure-response relationships of clinical data. Caution is warranted and clinical monitoring is recommended when these combinations are given in integrase inhibitor-resistant patients.
IG/0438	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	16/05/2014	n/a		
IA/0076	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)	07/05/2014	n/a		
WS/0544	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 4.4 of the SmPC with a revised wording on the risk of transmission as requested by the CHMP. The PL has been updated accordingly. In	25/04/2014	05/05/2015	SmPC and PL	The warnings in product information regarding the risk of transmission have been updated as requested by the CHMP in a class labelling request adopted in December 2013. Minor corrections are made to translations of Combivir SmPC in Danish and PL in Finnish and Slovenian, Celsentri SmPC and PL in Finnish and Hungarian, Telzir PL in Finnish, Tivicay SmPC in Dutch.

	addition, minor corrections are made to translations and an editorial change is implemented in Trizivir PL. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
II/0074	Update of SmPC sections 4.8 and 5.1 with additional information on safety, antiviral response and treatment resistance in HIV-1 infected paediatric subjects, based on results of studies previously submitted as post-authorisation measures. In addition, the Product information is being updated to the latest QRD template version and editorial changes are implemented in SmPC sections 4.4, 4.8 and 5.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	05/05/2015	SmPC and PL	Integrated safety data from Study APV29005 (Week 24 results) and Study APV20003 (Week 168 results), together with Week 48 data from Studies APV29005 and APV20002 demonstrated that RTV-boosted FPV was generally well-tolerated in children 4 weeks to 18 years of age. No new safety concerns have been identified. The CHMP confirmed that safety profile in paediatric patients is considered comparable to that of adults although vomiting occurred more frequently amongst paediatric patients. Using the snapshot analysis, proportions of subjects in study APV29005 achieving <400 copies/mL at Week 48 were 53% and 63% in the 6-<12 year olds and 12-18 year olds respectively, indicating an adequate antiviral response given that the population included PI-naïve and PI/ART-experienced subjects. An immunologic response, as indicated by increases in absolute CD4+ cell counts was demonstrated. As expected, the rate of virological failures was higher in PI-experienced subjects (56%) than PI-naïve subjects (19%). The mutational profile was similar between children and adults.
IB/0073	To include concomitant use of quetiapine as a contra-indication in SmPC Section 4.3 and update table in SmPC section 4.5 with information on interactions with quetiapine, in line with the class labelling request for protease inhibitors. The Package	18/10/2013	20/11/2013	SmPC and PL	

	Leaflet is updated accordingly. In addition, the list of local representatives in the PL is updated, minor linguistic improvements implemented in SmPC and PL, instructions in the PL on disposal of Telzir aligned with QRD template and a correction made in the Finnish translation of SmPC section 4.8. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IG/0295	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	29/04/2013	n/a		
WS/0338	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 4.4 and 4.8 of the SmPC in order to expand existing warning about immune reactivation syndrome with information on autoimmune disorders. The Package Leaflet is updated accordingly. In addition, the list of local representatives was updated in the Package Leaflet. Furthermore, the product information is being brought in line with the latest QRD template version 8.3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/02/2013	26/03/2013	SmPC, Annex II, Labelling and PL	The review performed by the Marketing Authorisation Holder identified 75 cases of different autoimmune disorders occurring in the setting of immune reconstitution. These included Basedow's/Graves' disease, systemic lupus erythematosus, sarcoidosis, rheumatoid arthritis, polymyositis, Guillain-Barré syndrome, Still's syndrome and myasthenia gravis. Cases involving zidovudine, lamivudine, abacavir and fosamprenavir were identified. These disorders all developed when CD4 count was increased or increasing and viral load undetectable. The autoimmune disorders resolved (or improved) spontaneously or with specific therapy and while Anti-Retroviral Therapy was continued. Most of cases had a relatively late onset following Anti-Retroviral Therapy initiation except cases of Guillain-Barré syndrome and adult onset Still's disease. The time to onset ranged from 2 weeks to 37 months. While it was recognised that the number of cases is small, the long and variable time to onset probably causes underreporting of such adverse reactions and therefore little

					is known on the exact pathogenesis and the risk factors. The CHMP agreed that information about autoimmune disorders occurring in the context of immune reconstitution should be reflected in the product information.
II/0066	Update of section 4.5 of the SmPC with regard to the interaction between maraviroc and fosamprenavir, including a recommendation not to use this combination. The PL is being 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	21/02/2013	26/03/2013	SmPC and PL	Data from two interaction studies investigating the effect of maraviroc on fosamprenavir/rtv and vice versa were presented. Both drugs were administered to steady state levels. The results obtained in the two studies were contradictory with regard to the effect of fosamprenavir/rtv on maraviroc: study A4001103 indicated increased maraviroc exposure, whereas the study COL112237 indicated reduced maraviroc exposure. Of note, results from study COL112237 were available only in the form of an abstract, and the assessment was therefore limited. Possible reasons for the different outcomes in the two studies were discussed but no obvious reason for the deviating results was found. In both studies the exposure of amprenavir, the active metabolite of fosamprenavir, decreased when co-administered with maraviroc. Considering that safety of maraviroc has been shown for maraviroc exposure of greater magnitude than in submitted studies, while risk for underexposure is regarded of a more serious concern, the CHMP concluded that the dosage for maraviroc should not be reduced and would have to be maintained at 300 mg BID when given with FPV/RTV. However, the reduction seen in the plasma levels for amprenavir when FPV/RTV is co-administered with MVC 300 mg BID (Cmin reduced by 36%) may be clinically relevant, therefore the CHMP supported not to recommend this combination.

IB/0069/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	29/11/2012	n/a		
II/0068	Update of sections 4.2 and 5.2 of the SmPC regarding dose adjustment in patients with moderate hepatic impairment as requested by CHMP after assessment of a follow-up measure. C.I.3.z - 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 - Other variation	15/11/2012	26/03/2013	SmPC	The MAH has provided results of an observational cohort study to explore the safety and tolerability of fosamprenavir (FPV)/ ritonavir (RTV) therapy in HIV-1 infected patients with mild or moderate hepatic impairment. Due to the apparent impossibility to include patients with moderate impaired hepatic function receiving the recommended reduced dose of FPV 450 mg BID + 100 mg RTV QD, the results of the study were deemed inconclusive. The statements in the SmPC regarding use of fosamprenavir in patients with moderate hepatic impairment have been reinforced.
II/0067	Update of sections 4.4 and 4.5 of the SmPC to include information about drug drug interactions with Hepatitis C virus (HCV) protease inhibitors. The PL is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/09/2012	23/10/2012	SmPC and PL	Based on the review of the available data on pharmacokinetic and safety, the CHMP considered the inclusion of information related to drug-drug interactions with Hepatitis C virus (HCV) protease inhibitors, telaprevir and boceprevir, acceptable. Co-administration of fosamprenavir with ritonavir and the HCV protease inhibitor telaprevir or boceprevir may lead to subtherapeutic levels of both, fosamprenavir and telaprevir or boceprevir, respectively. Thus, co-administration of Telzir with these HCV protease inhibitors is not recommended.
WS/0163	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	21/06/2012	21/06/2012	Annex II	Update of the Detailed Description of the Pharmacovigilance System (DDPS) to ViiV Healthcare Ltd version 4 dated May

	Introduction of a new Detailed Description of the Pharmacovigilance System (DDPS), following the transfer of the marketing authorisation/scientific opinion from GSK to ViiV Healthcare Ltd. This DDPS had previously been assessed for another product of the same MAH/SOH. Annex IIB of Epivir, Kivexa, Lamivudine ViiV and Trizivir have consequently been updated in line with the new QRD template wording for the DDPS. In addition the MAH corrected a minor mistake in the French Annex for Epivir. C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH				2012.
IA/0062	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	22/09/2011	n/a	Annex II and PL	
II/0057	Update of section 4.5 of the SmPC with raltegravir interaction data. The package leaflet has been updated accordingly. In addition, the MAH takes the opportunity to revise the details of the Cyprus local representative. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	23/05/2011	SmPC and PL	The MAH provided data from two pharmacokinetics studies (COL111242 and COL112775 study) conducted to evaluate potential drug interaction between raltegravir and fosamprenavir (with or without ritonavir), under both fasting and fed conditions. Studies COL111242 (fed condition) and COL112775 (fasting conditions) were phase I, randomised, open label, six-arm, three-period, balanced crossover, drug-drug interaction studies conducted in 37 and 41 healthy subjects respectively. Considering the results with fosamprenavir/ritonavir 700 mg/100 mg BID combined with raltegravir 400 mg BID, amprenavir Geometric Mean Ratio (GMR) ratio for Cmin was

					0,81, 90% IC [0,58-1,13] (fasting conditions), indicating a significant decreased exposure of amprenavir since the 90% CI was outside the bioequivalence limits of [0,8-1,25]. The decrease of PK parameters for amprenavir in fed conditions was more important than in fast conditions (GMR ratio for Cmin was 0,67, 90% IC [0,50-0,90], in fed conditions). With regards to raltegravir pharmacokinetics, in fast conditions, when combined with fosamprenavir/ritonavir (700 mg/100 mg BID), raltegravir Cmin significantly decreased by 36% with a 90% CI for the GMR [0.43-0,97]. In fed conditions, when combined with fosamprenavir/ritonavir (700 mg/100 mg BID), raltegravir Cmin significantly decreased by 54% with a 90%CI for the GMR [0.26-0,82]. In both conditions, fasted and fed, Cmin values significantly decreased (44 ng/ml and 135 ng/ml, respectively). Moreover, raltegravir AUC decreased by 55% and 54% respectively in fast and fed condition in presence of fosamprenavir/ritonavir (700mg/100mg BID). Therefore, the risk of treatment failure, notably in experienced patients, cannot be ruled out. The CHMP recommends that the combination fosamprenavir/ritonavir with raltegravir should be not-recommended.
II/0058	Update of sections 4.3, 4.4 and 4.5 of the SmPC with information on alfuzocyn and PDE5 inhibitors drug interactions. The Package Leaflet has been updated accordingly. Annex II has been updated in line with the latest QRD recommendations. In addition, the MAH has taken the opportunity to update the list of local representatives. C.I.4 - Variations related to significant modifications of	17/03/2011	18/04/2011	SmPC, Annex II and PL	Following oral administration, fosamprenavir is rapidly and almost completely hydrolysed to amprenavir and inorganic phosphate as it is absorbed through the gut epithelium. Amprenavir is primarily metabolised by the liver with less than 1% excreted unchanged in the urine. Amprenavir and Ritonavir are both inhibitors of CYP3A4. However, amprenavir is a less potent inhibitor of CYP3A4 than ritonavir. Taking into account that CYP3A4 is the principal hepatic

	the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				enzyme isoform involved in the metabolism of alfuzosin, the co-administration of alfuzosin with fosamprenavir and especially ritonavir (which is always co-administered with fosamprenavir as a booster), could increase plasma concentration of alfuzosin and therefore be associated with serious adverse event. Therefore, a contraindication has been included in the product information. Similarly, PDE5 inhibitors metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4. Co-administration of Telzir with these medicinal products is expected to substantially increase their concentrations and may result in adverse events. Therefore, the product information has been updated to include a contraindication with regards to co-administration with PDE5 inhibitors used in the treatment of pulmonary arterial hypertension and a warning regarding co-administration with PDE5 inhibitors used in the treatment of erectile dysfunction.
IA/0060/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	08/04/2011	n/a	Annex II and PL	

IA/0059	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	21/03/2011	n/a	SmPC and Annex II	
IB/0055/G	This was an application for a group of variations. 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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	09/11/2010	n/a		
IB/0056/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	05/11/2010	n/a		

IB/0054	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	18/10/2010	n/a	SmPC and PL	Amendment of section 4.3 of the SmPC and the corresponding section in the PL for Teizir film-coated tablets and oral suspension with lovastatin and simvastatin data to harmonise section 4.3 with the SmPC of these statins and that of Norvir. In addition the following annexes have been revised to make minor editorial and linguistic changes: CS, DA, DE, EL, MT, NL, NO and RO.
II/0053	Update of section 4.8 of the SmPC based on the SmPC Guideline rev 2 in fulfillment of follow up measure. Additionally, Annex II has been revised to reflect that the PSUR is on a yearly cycle. The MAH has also taken this opportunity to correct a minor typographical error in the PL. The information on the local representatives in Spain, Portugal and Cyprus have also been updated in the PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/07/2010	26/08/2010	SmPC, Annex II and PL	The section 4.8 of the SmPC has been fully revised following the SmPC guidelines. However no addition or deletion have been proposed. The MAH also took the opportunity to revise the Annex II to reflect that the PSUR is on a yearly cycle. The MAH has also taken this opportunity to correct a minor typographical error in the PL. The information on the local representatives in Spain, Portugal and Cyprus have also been updated in the PL.
IB/0052	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	24/06/2010	n/a	SmPC	
T/0050	Transfer of Marketing Authorisation	22/03/2010	26/05/2010	SmPC, Labelling and PL	
IB/0051	To amend the Summary of Product Characteristics (SPC) with etravirine interaction data to harmonise	22/04/2010	n/a	SmPC, Annex II, Labelling	

	section 4.5 of the SPC with the Intelence, for consistency purposes. In addition Annex IIB has been updated to refer to version 06 of the RMP which was approved in December 2009. Furthermore some inconsistencies between Annexe IIIB for the oral suspension and the tablets have been corrected: The Dutch Package Leaflet has also been brought in line with the currently approved text. 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			and PL	
II/0048	Update of the Detailed Description of the Pharmacovigilance System (DDPS) including change of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II has been updated with the new version number. The MAH took the opportunity of this variation to correct the version number of the Risk Management Plan. Changes to QPPV Update of DDPS (Pharmacovigilance)	17/12/2009	20/01/2010	Annex II	The DDPS has been updated (version 7.2) to reflect the change of the QPPV as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements.
II/0044	Update of section 4.4 and section 4.8 of the SPC to add a statement on monitoring and management of hyperglycaemia and lipid (cholesterol/triglyceride) elevations based on data from the French Hospital HIV	22/10/2009	23/11/2009	SmPC and PL	Postmarketing data have shown that treatment with fosamprenavir (FPV) resulted in increases in the concentration of triglycerides and cholesterol. Physicians should therefore be recommended to perform triglyceride

	cohort and to change frequency category of the adverse drug reactions "blood triglycerides increased" and "blood cholesterol increased" based on data from postmarketing studies (ESS100732 and APV109141). Section 4 of the PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				and cholesterol testing prior to initiating therapy with FPV and at periodic intervals during therapy. The precautionary statement regarding the monitoring of hyperglycaemia was brought in line with this wording. Blood glucose testing should be performed prior to initiating therapy with FPV and at periodic intervals during therapy. Based on the results of two 2 postmarketing studies (ESS100732 and APV109141) the frequency category of the adverse drug reaction "blood cholesterol increased" was increased from "uncommon" to "very common". The two large postmarketing studies have demonstrated that Grade 3-4 cholesterol elevations occur at higher incidences than initially observed in the three registration trials APV30001, APV30002 and APV30003. As postmarketing data have shown that the incidence of elevated triglycerides ranges from 0 to 7% i.e. with a frequency category of "common". The frequency category of the ADR "blood triglyceride increased" was downgraded from "very common" to "common".
II/0039	Update of section 4.5 of the SPC to include a dosing recommendation for co-administration of fosamprenavir with atazanavir based on data from interaction study APV 10018. The section 4.5 is also updated in line with the Annex A of the revised Guideline on the clinical development of medicinal products for the treatment of HIV infection (CPMP/EWP/633/02, Rev.2) as requested by the CHMP in January 2008. Update of Summary of Product Characteristics	22/10/2009	23/11/2009	SmPC	In study APV 10018 the co-administration of fosamprenavir/ritonavir (FPV/r) 700/100mg twice daily with atazanavir (ATV) 300 mg once daily showed no effect on steady state plasma amprenavir concentration; the plasma ATV AUC(0-) was decreased by 22% and Cmax by 24%, Cmin remained unchanged, compared to co-administration of ATV/r 300/100 mg once daily. Overall no clinically significant interaction were observed when FPV/r 700/100mg twice daily is coadministered with ATV 300 mg once daily. Therefore no dosage adjustment is considered necessary. The full section 4.5 has been table-formatted with three columns for each product co-administered with FPV/r in accordance with the guideline. The description of the

					interactions data follows a single pattern for all medicinal products co-administered with FPV/r which increases the legibility and facilitates the use of the interaction section for the treating physician as outlined in the guidance. Pharmacokinetics data and recommendations to treating physician are supported by clinical studies already submitted by the MAH and assessed by the CHMP at the time of the original marketing authorisation application or subsequently during the lifecycle of FPV through clinical Follow-Up Measures and type II variation.
II/0045	To change the active substance specifications Quality changes	24/09/2009	01/10/2009		
IA/0047	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	18/09/2009	n/a		
R/0043	Renewal of the marketing authorisation.	19/03/2009	16/04/2009	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 Telzir continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation for Telzir with unlimited validity.
II/0042	Update of Detailed Description of the Pharmacovigilance System (DDPS). Update of or change(s) to the pharmaceutical documentation Update of DDPS (Pharmacovigilance)	19/02/2009	25/03/2009	Annex II	The DDPS has been updated (version 6.2) to reflect the change of the Qualified Person for Pharmacovigilance (QPPV) as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new

					version number of the agreed DDPS.
II/0041	Update of section 4.2, 4.3, 4.4 and 5.2 of the SPC and section 2 and section 3 of the PL with data from clinical study APV10017 to implement dosing recommendation in patients with severe hepatic impairment Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	25/03/2009	SmPC and PL	Please refer to the scientific conclusions: Telzir-H-534-II-41-AR
II/0040	Update of section 4.8 of the SPC to include "paresthesia" as requested by the CHMP in its conclusion on PSUR 7 dated 21 August 2008. Section 4 of the PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	22/01/2009	26/02/2009	SmPC and PL	In the frame of PSUR 7 (covering 21st October 2007 - 20th April 2008) a review of oral paraesthesia with fosamprenavir was conducted since routine signal detection has identified this drug-event pair to be a signal. The review noted the issue is complicated since fosamprenavir is usually coadministered with ritonavir. Oral paraesthesia is a well recognised adverse event with ritonavir therapy and has been reported to occur in over 25% of patients. Nonetheless it was concluded that there appears to be a trend towards oral paraesthesia occurring more frequently during clinical trials with fosamprenavir containing regimens. Overall, as a causal association with fosamprenavir cannot be ruled out "oral paraesthesia" is added to section 4.8 of the SPC with a frequency category of "common" (most conservative approach). The section 4 of the PL is updated accordingly.
II/0038	Update of section 4.2 of the SPC in order to clarify the dosing recommendations in children further to the CHMP conclusion on a clinical follow-up measure (FUM 049). The section 3 of the PL has been updated accordingly.	20/11/2008	22/12/2008	SmPC and PL	As a conclusion of FUM 049, the CHMP considered that the wording proposed in the product information regarding the dosing recommendations in children was confusing. Section 4.2 of the SPC and section 3 of the PL for both the tablets and the oral suspension have been re-worded to be further simplified and in order to gain in clarity. The layout of both

	Update of Summary of Product Characteristics and Package Leaflet				sections has been improved. For the oral suspension a dosing recommendation table for fosamprenavir with ritonavir has been inserted. It provides the volume of oral suspension to be administered depending of the body weight. The table eases the readability and clarify the recommendations to the treating physicians.
II/0037	Update of section 4.3 and section 4.5 of the SPC to implement the class labelling text agreed by the CHMP in May 2008 on the combination of rifampicin with fosamprenavir given with concomitant low-dose ritonavir. Update of Summary of Product Characteristics	25/09/2008	21/10/2008	SmPC	In 2005 an interaction study on saquinavir boosted with ritonavir together with rifampicin in healthy volunteers had to be prematurely discontinued due to an increased risk of hepatotoxicity associated with this co-administration. The mechanism for this interaction is not fully elucidated. It has been hypothesised that the predominant effect between the inducer effect of rifampicin and the inhibitor effect of the boosted protease inhibitors might depend on the boosted protease inhibitor involved. Lacking the results of specific interaction studies, the CHMP concluded as a conservative measure to reinforce the contraindication with rifampicin in section 4.4 and improve the guidance provided to physicians regarding the interaction of boosted protease inhibitors with rifampicin in section 4.5.
II/0036	Update of section 4.5 of the SPC with recommendations regarding co-administration of fosamprenavir and lopinavir/ritonavir (concomitant administration of these medicinal products is not recommended) following assessment of a clinical follow-up measure. The PL has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	29/07/2008	SmPC and PL	On the basis of pharmacokinetic data extracted from 4 clinical studies (3 in healthy volunteers and 1 in HIV-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 Telzir was amended. Recommendations and data on co-administration of Telzir with lopinavir and lopinavir/ritonavir have been deleted from section 4.5 of the SPC and replaced by a non-recommendation of concomitant use of lopinavir/ritonavir with fosamprenavir. Section 2 of

					the package Leaflet has been updated accordingly.
II/0035	Update of section 5.3 of the SPC based on data from a 14-day investigational oral toxicity study in male rats as requested by the CHMP. The MAH also took the opportunity to correct a mistake in the PL for the oral suspension. Update of Summary of Product Characteristics and Package Leaflet	30/05/2008	07/07/2008	SmPC and PL	A 14-day oral toxicity study was conducted with fosamprenavir in male rats to investigate the mechanism of thyroid-proliferative effects observed in a previous long-term carcinogenicity study in rats. The effects of fosamprenavir 2250 mg/kg/day on hepatic UDP-glucuronosyl transferase and cytochrome P450 (CYP) activity and serum levels of thyroid hormones, i.e. thyroxine (T4), triiodothyronine (T3), and thyroid stimulating hormone (TSH) were evaluated. A time-related decrease in T4 levels was observed, with subsequent increase in TSH levels. In parallel, there were increases in liver weight, hepatocellular hypertrophy, and increased hepatic gene expression of T4-conjugating enzymes and transport proteins. These results indicate that thyroid follicular cell adenomas observed in rats are related to hepatic enzyme induction and subsequent increase of hepatic clearance of thyroxine. The clinical relevance of these findings is unknown.
II/0034	Update of section 4.5 of the SPC with paroxetin interaction data. The PL was updated accordingly. Additionally, the contact details for Latvia were updated in the PL. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	20/06/2008	SmPC and PL	A drug interaction study between paroxetine 20mg once daily and fosamprenavir (pro-drug of amprenavir)/ritonavir 700/100mg twice daily was done to assess the effect of coadministration of these medicinal products. The exposure of paroxetine was decreased by around 50% when paroxetine was coadministered with fosamprenavir/ritonavir. However, there was no effect of paroxetine on amprenavir or ritonavir. The mechanism for these effects is currently unknown, but the product information was updated to reflect the study results. Subjects taking these medicines together will be closely monitored and, if needed, the doctor will adjust the

					paroxetine dose.
II/0033	Update of section 5.1 of the SPC with in-vivo resistance data based on relevant clinical trials with the ritonavir boosted fosamprenavir regimen. Update of Summary of Product Characteristics	24/04/2008	20/06/2008	SmPC	Based on in-vivo fosamprenavir resistance studies in antiretroviral therapy (ART)-naïve, protease inhibitors (PI)-naïve, PI experienced and ART experienced patients, the product information was updated. No differences were observed between the resistance mutations selected by boosted and unboosted fosamprenavir and the analysis of the virological failure samples defined four main resistance pathways in ART-naïve or PI-naïve patients. Similar resistance patterns were observed in the paediatric patients compared with the adults. The wording on PI experienced patients was also updated; certain mutations were deleted as they were not present or were not treatment emergent (i.e., were already present initially before treatment).
II/0032	Update of sections 4.4 and 4.5 of the SPC based on an interaction study of fosamprenavir/ritonavir with phenytoin. Consequently, the PL was updated as well. Update of Summary of Product Characteristics and Package Leaflet	24/01/2008	28/02/2008	SmPC and PL	A drug-drug interaction study, performed in healthy subjects, has shown that the co-administration of fosamprenavir/ritionavir twice daily 700/100 mg with phenytoin 300 mg once daily: - slightly increased the exposure to amprenavir, which is not expected to be clinically relevant, - slightly decreased the exposure to phenytoin. It is therefore recommended that phenytoin plasma concentrations should be monitored and the phenytoin doses should be adjusted as appropriate. These findings were reflected in the Product Information.
II/0031	Update of section 4.8 of the SPC further to a review of angioedema cases carried out by the MAH to include the adverse reaction angioedema. Consequently, the PL was updated as well. In addition, the MAH has taken the opportunity to update the PL further to user	13/12/2007	18/01/2008	SmPC and PL	Fosamprenavir (FPV) contains a sulphonamide moiety. Published literature acknowledges that sulphonamides have been associated with allergic reactions. Angioedema is often a feature of allergic reactions. As of 20 April 2007, 39 reports of angioedema were identified for FPV from the MAH's

	testing. Update of Summary of Product Characteristics and Package Leaflet				worldwide safety database. Nine reports were classified as key cases of which 4 were assessed as providing the best evidence of a causal relationship (e.g. events resolved when FPV was discontinued + compatible time to onset + occurred with rash). Based on evidence from clinical trials, the frequency category for this adverse reaction was calculated as "uncommon".
II/0028	Update of the resistance data in section 5.1 of the SPC based on a cumulative summary of all emergent mutations observed during clinical trials with unboosted and boosted fosamprenavir in previously Protease Inhibitor-naïve as well as experienced patients. Update of Summary of Product Characteristics	18/10/2007	21/11/2007	SmPC	Further to the annual review on resistance and cross-resistance carried out by the Marketing Authorisation Holder, the information in the SPC has been updated with mutations observed during clinical trials in adult and paediatric patients with unboosted and boosted fosamprenavir in previously PI-naïve as well as experienced patients.
II/0027	Update of sections 4.4 and 4.5 of the SPC based on a methadone drug-drug interaction study with fosamprenavir/ritonavir. The PL is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	23/10/2007	SmPC and PL	An interaction study in healthy volunteers who were on a stable methadone substitution therapy and who were given fosamprenavir/ritonavir showed that neither R-methadone (which is the active moiety in methadone substitution therapy) nor amprenavir (which is the active moiety in fosamprenavir/ritonavir therapy) blood levels were affected to a clinically relevant extent by the interaction of the tested compounds. This information was reflected in an update of both the interaction section in the SPC and the PL.
IA/0030	IA_05_Change in the name and/or address of a manufacturer of the finished product	14/09/2007	n/a	Annex II and PL	
II/0018	Extension of the therapeutic indication of Telzir in combination with ritonavir for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected	19/07/2007	13/09/2007	SmPC, Annex II and PL	For further information please refer to the Scientific Discussion:

	adults in combination with other antiretroviral medicinal products to include adolescents and children of 6 years and above. Extension of Indication				EMEA-H-534-II-18-AR
IB/0029	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	08/08/2007	n/a		
II/0021	Update of sections 4.3, 4.4 and 4.5 of SPC and section 2 of the PL as regards the interaction of Telzir with oral and parenteral midazolam, following a CHMP request in March 2007. Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	24/07/2007	SmPC and PL	Based on available data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally than when it is injected. Therefore, the co-administration of Telzir/ritonavir with orally administered midazolam is contraindicated, whereas caution is recommended when Telzir/rtv is co-administrated with injection of midazolam. If Telzir/rtv 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, 4.4 and 4.5 of the SPC and section 2 of the PL are updated with this information.
IB/0022	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	06/07/2007	n/a		
II/0020	Update of sections 4.2, 4.4 and 5.2 of the SPC based on a study in mildly and moderately hepatically impaired patients. Consequently, the PL is updated as	24/05/2007	02/07/2007	SmPC and PL	This study was performed to establish dosage recommendations in patients with mild or moderate hepatic impairment. The results showed that in these patients, the

	well. Update of Summary of Product Characteristics and Package Leaflet				recommended daily dosage needs to be reduced in order to avoid high plasma concentrations of amprenavir, the active compound of Telzir in blood. While some dose recommendations can be given based on the findings of the study, it was also demonstrated that in patients with mild or moderate hepatic impairment high patient-to-patient variability of plasma concentration may be found. Therefore, an additional warning to monitor these patients when starting this treatment schedule was added to the new dosage recommendations.
IA/0026	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	12/06/2007	n/a		
IA/0025	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/06/2007	n/a		
IA/0024	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	12/06/2007	n/a		
IA/0023	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	12/06/2007	n/a		
II/0009	Update of section 5.1 of the SPC to provide recommendations with regards to the mutation predictive of virological response to fosamprenavir/ritonavir and to review available in vitro resistance data and assess the possibility of cross-resistance to other licensed protease inhibitors such as lopinavir, atazanavir and tipranavir. Update of Summary of Product Characteristics	24/01/2007	28/02/2007	SmPC	During the study APV30001 in PI-naïve subjects treated with unboosted fosamprenavir, PI-mutations were identified in patients failing fosamprenavir therapy. During studies in PI-naïve patients treated with boosted fosamprenavir (studies APV30005 (APV30002 extension after Week 48) and ESS100732) PI-mutations were identified in failing patients after 96 to 204 weeks therapy (study APV30005) and by Week 48 in study ESS100732; in study APV30002 PI resistance-associated mutations did not

					emerge by Week 48. In studies in PI-experienced patients (APV30003 and its extension and APV30005), mutations emerged in patients with virological failure. HIV-1 isolates with a decreased susceptibility to amprenavir have been selected during in vitro serial passage experiments. Reduced susceptibility to amprenavir was associated with virus that had developed I50V or I84V or V32I+I47Vor I54M mutations. Each of these four genetic patterns associated with reduced susceptibility to amprenavir produces some cross-resistance to ritonavir but susceptibility to indinavir, nelfinavir and saquinavir is generally retained. There are currently insufficient data on cross-resistance between amprenavir and other protease inhibitors. Based on data from thirteen antiretroviral naïve patients failing a fosamprenavir containing regimen and on limited in vitro data (site directed mutagenesis) the resistance pathways associated with amprenavir produce limited cross-resistance to lopinavir (clinical data available from thirteen isolates) while susceptibility to atazanavir (from four isolates) and tipranavir (from two isolates) is generally retained. Conversely, amprenavir retains activity against some isolates with resistance to other PIs and this retained activity would depend on the number and type of protease resistance mutations present in the isolates.
II/0017	Update of sections 4.4 and 4.8 of the SPC and section 2 of the PL to implement the class labelling text on osteonecrosis, agreed by the CHMP in September 2006. Update of Summary of Product Characteristics and	14/12/2006	18/01/2007	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

	Package Leaflet				occurred specially in patients with HIV advanced disease and/or in patients with long term use of combination antiretroviral therapy (CART). Further to the review of all available data the CHMP agreed that this information should now be included in the SPC and PL of all antiretroviral medicinal products. Patients should be warned to seek medical advice in case they experience joint stiffness, aches and pain especially of the hip, knee and shoulder or if they experienced any difficulty in movement.
II/0008	To update section 5.3 of the SPC with data from two carcinogenicity studies in mice and rats, as requested by the CHMP further to the assessment of the Initial Marketing Authorisation Application dossier on 3 June 2004. Update of Summary of Product Characteristics	14/12/2006	18/01/2007	SmPC	Information from long-term carcinogenicity studies with fosamprenavir in mice and rats have been included and replace the previous wording in the preclinical safety section that was based on amprenavir data only. The studies performed with fosamprenavir showed increases in hepatocellular adenomas and hepatocellular carcinomas in mice and increases in hepatocellular adenomas and thyroid follicular cell adenomas in rats. In rats, an increase in interstitial cell hyperplasia in males and an increase in uterine endometrial adenocarcinoma in females was observed. At his point In time the clinical relevance of this finding is unknown.
IA/0019	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	05/01/2007	n/a		
II/0012	Update of section 5.1 of the SPC with data from a clinical a study of Telzir/ritonavir twice daily vs. lopinavir/ritonavir twice daily in treatment naïve population. The abbreviation FOS for fosamprenavir has also been amended to FVP in the SPC.	16/11/2006	03/01/2007	SmPC and PL	The KLEAN study showed the non-inferiority of fosamprenavir/ritonavir to lopinavir/ritonavir in a head to head comparison of both protease inhibitors in this multicentre, randomised, open label study, both in association with the abacavir/lamivudine (ABC/3TC 600/300mg) fixed-dose combination tablet once daily, in

	In addition section 6 of the PL was updated with the local representatives in Bulgaria and Romania. Update of Summary of Product Characteristics and Package Leaflet				antiretroviral naïve patients. This study therefore reinforced the dosing recommendation in naïve patients, which followed the twice daily regimen in agreement with the dosing recommendations for antiretroviral experienced patients. Both efficacy and safety results were comparable for both tested medicinal products in the studied population and for the duration of this study (48 weeks analysis).
IB/0016	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	10/11/2006	n/a		
IB/0015	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	10/11/2006	n/a		
II/0011	Update of section 4.5 of the SPC in regard of the interaction with ketoconazole, as requested by the CHMP on 7 June 2006, following the assessment of an interaction study comparing ketoconazole 200mg once daily and fosamprenavir/ritonavir 700/100mg twice daily in healthy volunteers. Update of Summary of Product Characteristics	21/09/2006	31/10/2006	SmPC	This was a phase I, randomised, open-label, three period, single sequence, drug-drug interaction study comparing plasma ketoconazole and amprenavir pharmacokinetics following administration of ketoconazole 200 mg once daily, fosamprenavir 700mg + ritonavir 100mg (twice daily) and ketoconazole 200 mg once daily + fosamprenavir 700 mg twice daily + ritonavir 100 mg twice daily in healthy adult volunteers. Results of this study showed that ketoconazole pharmacokinetic parameters (essentially AUC) are significantly increased when ketoconazole 200 mg once daily is co-administered with fosamprenavir 700 mg twice daily boosted with ritonavir 100 mg twice daily (exposure increased about 2.69 fold). Thus these results confirm that fosamprenavir boosted leads to an increase on ketoconazole AUC, which is much higher (2.69 fold) than what was observed with amprenavir unboosted (44%). No significant

					impact of ketoconazole on amprenavir and ritonavir exposures is observed.
II/0010	Update of sections 4.4 and 4.5 of the SPC with data, as requested by the CHMP, on the interaction of oral contraceptives with fosamprenavir based on a clinical study. Consequentially, the PL has also been updated to reflect these new data. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	31/10/2006	SmPC and PL	This was an interaction study between ritonavir-boosted fosamprenavir (fosamprenavir/ritonavir 700/100 mg twice daily) and a combination product of ethinyl estradiol /norethisterone 0.035/0.5 mg once daily (an oral contraceptive) at steady state in healthy female volunteers. The findings showed that the concentrations of the oral contraceptive were markedly decreased. This decrease, however, does not necessarily seem to lead to contraceptive failure, as indicated by the measured relevant female hormones. However, laboratory findings of increased liver transaminase levels together with clinical manifestations warranted a special warning that this combination may lead to risk of hepatic transaminase elevations.
IA/0014	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	27/10/2006	n/a		
IA/0013	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	27/10/2006	n/a		
II/0007	Update of section 4.5 of the SPC with new data on the interaction of rifabutin and fosamprenavir based on the wording proposed by the CHMP on 14 December 2005 further to the assessment of an interaction study. Update of Summary of Product Characteristics	23/03/2006	18/04/2006	SmPC	This was a phase I, randomised, open label, two period, two-sequence, cross-over, drug-drug interaction study conducted in healthy adult volunteers at one study centre in the United States. It was conducted to further substantiate the recommendation of co-administration of fosamprenavir/ritonavir with rifabutin. Based on the new data, the recommendation for dosage reduction of at least 75% for rifabutin when co-administered with fosamprenavir/ritonavir was maintained.

					Additionally, as the resulting blood levels for the rifabutin metabolite 25-O-desacetylrifabutin were much higher than for rifabutin, a warning was included. This addressed the potential of an increase of rifabutin related adverse reactions, notably uveitis, that are associated with its metabolite.
II/0005	Update of section 4.5 of the SPC with data on the nevirapine interaction with fosamprenavir further to the CHMP assessment of the clinical interaction study. Update of the Product Information according to the current EMEA/QRD template. Additionally, section 4 of the Package Leaflet "Possible Side Effects" has been amended to improve patient readability. Update of Summary of Product Characteristics, Labelling and Package Leaflet	26/01/2006	28/02/2006	SmPC, Annex II, Labelling and PL	The co-administration of fosamprenavir 700mg twice daily + ritonavir 100mg twice daily with nevirapine 200mg twice daily increased plasma nevirapine AUC(0-t) by 14%, Cmax by 13% and Ct by 22%. Therefore, the CHMP considered that there was no significant impact of fosamprenavir/ritonavir on the nevirapine PK parameters that would justify a nevirapine dose adjustment.
IB/0006	IB_12_b_01_Change in spec. of active subst./agent in manuf. of active subst. - test parameter AS	16/12/2005	n/a		
II/0003	To update section 5.1 of the SPC following a CHMP request dated 17 March 2005 with information on protein adjusted ratios of Cmin/IC50 and Cmin/IC95, presented as median ratios and ranges further to the assessment of the Follow-up measure 017. In addition, point 6 of the PL is subject to a minor revision to reflect the change of the MAH's name in Poland. Update of Summary of Product Characteristics and Package Leaflet	15/09/2005	25/10/2005	SmPC and PL	The MAH submittied the ratio APV Ct,ss/IC95 derived from study APV 30003 in treatment-experienced patients. The ratio plasma Ct,ss APV / baseline IC95 adjusted for protein binding obtained with the regimen fosamprenavir 700mg BID + RTV 100mg BID was equal to 3.21, and 2.55 with the regimen FAPV 1400mg QD + RTV 200mg QD. The median IC95 values were 0.054µg/ml [0.013-0.669], i.e around 6-fold the IC 50 values. Interestingly, the geometric mean plasma Cmin of 1.74µg/ml reported in study APV30003 was above the median IC95 values. Even though

					these data have to be interpreted with caution due to the experimental variability of determining this value (IC95), they allow to appreciate the true level of resistance in treatment-experienced subjects.
II/0002	To update section 4.4 and 4.5 of the SPC with the clas labelling text on "fluticasone" following the CHMP Assessment Report on the "Interaction with ritonavir boosted protease inhibitors and fluticasone" dated 26 May 2005. Point 2 of the PL is amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	24/08/2005	SmPC and PL	The MAH implements the class labelling on the fluticasone propionate- ritonavir interaction. This interaction is supported by the results of one multiple-dose crossover design clinical study in healthy subjects, conducted by GSK in July- October 2002 (Study FNM 10004). This study aimed at evaluating the effects of several CYP3A4 inhibitors, including ritonavir, ketoconazole and erythromycin on systemic concentrations of fluticasone after nasal inhalation.
IB/0004	IB_10_Minor change in the manufacturing process of the active substance	10/08/2005	n/a		
II/0001	To update section 4.4 and 4.8 of the SPC and section 2 of the PL, to implement the class labelling text regarding the Immune Reactivation Syndrome, as adopted by the CHMP in July 2004. Update of Summary of Product Characteristics and Package Leaflet	18/11/2004	17/12/2004	SmPC and PL	In patients treated with any type of combination antiretroviral therapy (CART), an inflammatory response to indolent or residual opportunistic infections may occur, when the immune system responds to treatment. In most cases, the inflammatory reactions towards the opportunistic pathogens in question cannot be foreseen since the opportunistic infection has not yet been detected/ diagnosed. If diagnosed prior to institution of CART, the treatment against the opportunistic infection (OI) is usually given priority. In particular, this is true for the complications most feared in this context; CMV-retinitis, generalised mycobacterial infections and Pneumocystic 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. In conclusion, in most cases, the clinical consequences of the awakening immune system in patients starting ART cannot be prevented. therefore, early recognition and diagnosis of these inflammatory reactions are important in the clinical handling of the patient. The description and the guidelines for treatment of the numerous clinical conditions potentially arising in association with the reactivation of the immune system in HIV-infected patients are given in the textbooks of infectious diseases. However, as the clinical conditions associated with the reactivation of the immune system may constitute a threat to the patient, a reminder of the phenomenon is deemed of value and has been included in the SPC and PL of all antiretroviral medicinal products.