Kivexa

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/0095	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)	18/10/2022	n/a		
IG/1531	C.I.z - Changes (Safety/Efficacy) of Human and	19/08/2022	28/11/2022	SmPC 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).

	Veterinary Medicinal Products - Other variation				
WS/2163	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 5.2 of the SmPC in order to add new information on the elimination half-life of lamivudine, based on final results from studies 204993 and 204994. Study 204993 was a phase I, relative oral bioavailability study of different fixed dose combinations of dolutegravir and lamivudine in healthy subjects. Study 204994 was an open-label, randomized, single dose, crossover, bioequivalence study of fixed-dose combination tablet(s) of dolutegravir and lamivudine versus dolutegravir and lamivudine single entities and food effect assessment in healthy volunteers. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.2 and to introduce minor editorial changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/12/2021	28/11/2022	SmPC, Annex II, Labelling and PL	The CHMP considered results from pharmacokinetic studies 204993 and 204994 with an optimal sampling scheme (until 72 hours post-dose), the bioanalytical methods used, the fasted conditions in these studies and the lack of pharmacokinetic interaction between dolutegravir and lamivudine and between lamivudine and abacavir or zidovudine. Overall, the CHMP concluded that the data reviewed indicated a terminal elimination half-life for lamivudine of 18-19 hours.
WS/2116/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.	11/11/2021	n/a		

	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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
WS/1990	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 4.2, 4.4 and 5.2 of the SmPC of the fixed-dose combination products Combivir, Dovato, Kivexa, Triumeq and Trizivir to include new information about use of the products in patients with renal impairment. Furthermore, minor editorial changes have been implemented throughout the Product Information and the lists of local representatives have been updated for all products. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/07/2021	20/08/2021	SmPC and PL	Patients with a creatinine clearance between 30 and 49 mL/min receiving Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir may experience a 1.6-to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥50 mL/min. There are no safety data from randomized, controlled trials comparing Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir to the individual components in patients with a creatinine clearance between 30 and 49 mL/min who received dose-adjusted lamivudine. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of haematologic toxicities (neutropenia and anaemia), although discontinuations due to neutropenia or anaemia each occurred in <1% of subjects. Other lamivudine-related adverse events (such as gastro-intestinal and hepatic disorders) may occur. The CHMP considered that, with the exception of Epivir, the previous recommendations to adjust the dose in patients with a sustained creatinine clearance between 30 and 49 mL/min can be removed. Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir should be monitored for lamivudine-

					related adverse events, notably haematologic toxicities. If new or worsening neutropenia or anaemia develop, a dose adjustment of lamivudine, per lamivudine prescribing information, is indicated, which cannot be achieved with Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir. Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir should be discontinued and the individual components should be used to construct the treatment regimen. The existing dose recommendations for Epivir have been maintained. The CHMP considered the lack of impact on pill burden when the lamivudine dose is adjusted for a monocomponent product and the fact that dose adjustments may be still used for subjects initially treated with lamivudine-containing fixed dose combinations, but requiring dose-adjusted individual components administration for safety reasons. For more information, please refer to the Summary of Product Characteristics.
IG/1388	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	21/05/2021	n/a		
IG/1362	A.7 - Administrative change - Deletion of manufacturing sites	22/02/2021	n/a		
IG/1332	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 -	18/01/2021	n/a		

	Not including batch control/testing				
WS/1917	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 4.5 of the SmPC (for Ziagen, Kivexa, Trizivir and Triumeq) and 5.2 (for Triumeq only) to add new information about the drug-drug interactions between abacavir and riociguat. The Package Leaflet is updated accordingly. Furthermore, the MAH took the opportunity to introduce an excipient update for Ziagen, Kivexa and Trizivir in line with the SmPC guideline, a syringe instruction update in the Package Leaflet of Ziagen and a revised statetment in section 6.6 of the SmPC for Triumeq in line with the QRD template. Moreover, minor editorial updates have been introduced throughout the Product Information of all four products. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/01/2021	09/03/2021	SmPC and PL	In vitro, abacavir inhibits CYP1A1. Concomitant administration of a single dose (0.5 mg) of riociguat (CYP1A1 substrate) to HIV patients receiving the combination of abacavir/dolutegravir/lamivudine (600mg/50mg/300mg once daily) led to an approximately three-fold higher riociguat AUC(0-∞) when compared to historical riociguat AUC(0-∞) reported in healthy subjects. Therefore, when riociguat is co-administered with abacavir, its dose may need to be reduced. Consult the riociguat prescribing information for dosing recommendations.
WS/1864/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. A.7 - Administrative change - Deletion of	22/10/2020	n/a		

	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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
PSUSA/11/20 1912	Periodic Safety Update EU Single assessment - abacavir / lamivudine	03/09/2020	n/a		PRAC Recommendation - maintenance
IG/1237	A.1 - Administrative change - Change in the name and/or address of the MAH	11/06/2020	09/03/2021	SmPC, Labelling and PL	
WS/1713	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of updated RMPs (Kivexa, Trizivir, Ziagen version 2.0 and Triumeq version 17.0) in order to remove the additional risk minimisation measure of provision of abacavir hypersensitivity education materials for healthcare professionals. Annex II is updated accordingly. In addition, the MAH took the opportunity to introduce an editorial update in the SmPC of Triumeq. 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	12/03/2020	09/03/2021	SmPC and Annex II	

	by new additional data to be submitted by the MAH where significant assessment is required				
IG/1150	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	07/11/2019	n/a		
WS/1521	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	11/04/2019	n/a		
IA/0081	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		
WS/1545	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	14/02/2019	n/a		

	variation				
IAIN/0078	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2018	21/10/2019	SmPC	
IG/0993	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	18/10/2018	n/a		
T/0076	Transfer of Marketing Authorisation	10/09/2018	16/10/2018	SmPC, Labelling and PL	
IG/0923/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 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 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	22/05/2018	n/a		
WS/1334/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.	15/02/2018	n/a		

	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
WS/1156	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 to add information regarding the interaction between lamivudine and sorbitol based on the results of Study 204857. The Package Leaflet has been updated accordingly. Further, a minor amendment has been implemented throughout the SmPC in order to update the clinical terminology of Pneumocystis carinii pneumonia to Pneumocystis jiroveci pneumonia. In addition, the MAH takes the opportunity to make minor editorial changes, to align the annexes with the QRD template version 10 and to update the contact details of the local representatives in the Package Leaflet.	25/01/2018	16/10/2018	SmPC, Labelling and PL	Study 204857 was undertaken to evaluate the effect of sorbitol on the pharmacokinetics of lamivudine. The study concluded that concomitant use of lamivudine with chronic administration of sorbitol containing medicines may reduce the exposure of lamivudine, possibly resulting in reduced virologic suppression or viral resistance. Co-administration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose (Adult HIV daily dose) of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC) and 28%, 52%, and 55% in the Cmax of lamivudine in adults. When possible, avoid chronic co-administration of Zeffix with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/11/201612	Periodic Safety Update EU Single assessment - abacavir / lamivudine	01/09/2017	n/a		PRAC Recommendation - maintenance
IB/0071/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	10/01/2017	n/a		
WS/0956/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.	21/07/2016	06/07/2017	Annex II	

	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority 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				
WS/0948	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 4.5 of the SmPC to remove the current information regarding a potential interaction between abacavir and ribavirin. The Package Leaflet has been updated accordingly. In addition, updated RMPs were agreed during the procedure: Ziagen RMP version 13; Kivexa RMP version 5; Triumeq RMP version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/07/2016	06/07/2017	SmPC and PL	PK study COL112055 did not show apparent impact of ABC on the intracellular concentrations of ribavirin triphosphate after 56 days of treatment (RBV alone: 15.93 pmol/106 cells; RBV+ABC: 15.87 pmol/106 cells). Although the variability of these measures is too high (80-100%) to achieve adequate statistical power (a difference between these 2 arms only >40% can be excluded), the data are nonetheless reassuring, the intracellular values being quite similar in between arms. In addition, 3 retrospective studies performed in a large number of HCV/HIV coinfected subjects do not support a potential impact of ABC on the sustained virologic response with Peg-IFN+ribavirin. Moreover, the potential interaction of ABC on RBV is currently not considered in the European guidelines for the treatment of HIV/HCV coinfected subjects.
IB/0068	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	20/04/2016	n/a		

	or addition) for the AS or a starting material/intermediate				
IG/0670/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 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 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	13/04/2016	n/a		
IG/0674	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	13/04/2016	n/a		
WS/0845	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 4.2, 4.3, 4.4 and 5.2 of the SmPC in order to align the Hepatic Impairment wording for the 3 older abacavir-containing products (ZIAGEN™, KIVEXA™ and TRIZIVIR™) with the TRIUMEQ™ SmPC. The Package Leaflet is updated accordingly.	01/04/2016	29/06/2016	SmPC, Annex II and PL	

	In addition, the MAH has taken the opportunity to correct some minor administrative errors in the labelling for the 3 products. The requested worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/0769	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 in order to revise the wording regarding mitochondrial dysfunction following assessment of responses to a relevant LEG and after analysis of the final CSR of the Mitochondrial Toxicity in Children (MITOC) Study (WE027/WWE112888). The Package leaflet is updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	01/04/2016	29/06/2016	SmPC and PL	Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed in utero to nucleos(t)ide analogues, that present with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical

					transmission of HIV.
WS/0888/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. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/01/2016	29/06/2016	SmPC and PL	
IAIN/0063/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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 B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	16/10/2015	29/06/2016	SmPC, Annex II, Labelling and PL	
WS/0755	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 5.1 of the SmPC in order to include information regarding the absence of antagonist	17/09/2015	29/06/2016	SmPC	This procedure update section 5.1 of the SmPC in order to include information regarding the absence of antagonist effects in vitro between the active substances and other retrovirals.

	effects in vitro between the active substances and other retrovirals. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0062/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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	24/08/2015	n/a		
WS/0733	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 4.1, 4.2, 4.3, 4.4 and 4.8 of the SmPC to revise the information on hypersensitivity reactions in line with a recent revision of the Triumeq SmPC. 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	02/07/2015	29/06/2016	SmPC and PL	In this worksharing variation, the information related to hypersensitivity reactions (HSR) to abacavir sulfate (ABC) has been revised to provide a more condensated and less redundant description of the HSR to abacavir. The most detailed description of the HSR have been kept in section 4.8 of the SmPC under the "description of the selected adverse reactions".
II/0057	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	21/05/2015	22/06/2015	SmPC and PL	

	data				
IG/0552	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	08/05/2015	n/a		
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 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	23/04/2015	22/06/2015	SmPC and PL	
IB/0056/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	08/04/2015	n/a		

	authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
WS/0673/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. B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions 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	26/03/2015	n/a		
R/0051	Renewal of the marketing authorisation.	25/09/2014	17/11/2014	SmPC, Annex II, Labelling and PL	
WS/0543	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To add an alternative test method for the active substance. B.I.b.2.e - Change in test procedure for AS or	25/09/2014	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
WS/0542	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change of specification of abacavir sulphate to comply with the Ph.Eur.. 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	25/09/2014	n/a		
PSUV/0053	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
WS/0393/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. This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of intermediate used in the manufacturing process of	22/05/2014	n/a		

	the active substance B.I.a.1.z - Change in the manufacturer of intermediates used in the manufacturing process of the active substance A.4 - Administrative change - Change in the name of a manufacturer of the intermediates used in the manufacture of the active substance A.7 - Administrative change - Deletion of multiple manufacturing sites 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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 intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.3.a - Change in batch size (including batch size ranges) of intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.3.a - Change in batch size (including batch size ranges) of intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.b.1.b - Change in the specification limit of a reagent – Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation B.I.b.1.b - Change in the specification limits of a				

	reagent - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation B.I.b.2.c - Change in test procedure for reagent - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.z - Change in the specification limits of a reagent - Other variation B.I.b.2.c - Change in test procedure for reagent - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation B.I.b.1.z - Change in the specification limit of a reagent - Other variation B.I.b.2.c - Change in test procedure for reagent - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.z - Change in the specification limits of a reagent - Other variation B.I.b.1.z - Change in the specification limit of a reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation B.I.b.1.z - Change in the specification limit of a				

	reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of a 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 a starting material - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.b - Change in the specification parameters and/or limits of a starting material - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of a starting material – Other variation B.I.b.2.e - Change in test procedure for intermediate - Other changes to a test procedure (including replacement or addition) for the intermediate B.I.b.1.z - Change in the specification limit of an intermediate - Other variation B.I.b.1.z - Change in the specification limit of an intermediate - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an intermediate - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of an intermediate - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an intermediate - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an intermediate - Other variation				

	B.I.b.1.z - Change in the specification limit of an intermediate - Other variation B.I.b.1.z - Change in the specification limit of an intermediate - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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 A.7 - Administrative change - Deletion of manufacturing sites 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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 originally approved batch size 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.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.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.z - Change in the specification parameters				

	and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting				

	material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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) B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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.1.z - Change in the specification parameters and/or limits of an AS, starting				

	material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
IG/0438	C.I.8.a - Introduction of or changes to a summary of	16/05/2014	n/a		

	Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location				
IG/0410/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 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 A.7 - Administrative change - Deletion of manufacturing sites B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	28/03/2014	n/a		
N/0046	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/12/2013	17/11/2014	PL	
IB/0043/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-	23/08/2013	n/a		

	release, batch control, primary and secondary packaging, for non-sterile medicinal products 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 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				
IB/0045	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	28/06/2013	n/a		
IA/0044/G	This was an application for a group of variations. 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 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 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 B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits	21/06/2013	n/a		

	applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
WS/0361	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 4.5 of the SmPC in order to reflect a potential drug-drug interaction between lamivudine and cladribine. This labelling update has been assessed via a separate Type II variation procedure (Zeffix; EMEA/H/C/242/II/53) with confirmation that the change should also be implemented for other lamivudine containing ViiV marketed HIV products as listed above. The Package Leaflet was updated accordingly and an error in Trizivir SmPC in one of the sub-headings in the tabular summary of interaction information was also amended. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	25/04/2013	27/05/2013	SmPC and PL	The drug-drug interaction between lamivudine and cladribine (CdA) was assessed in a type II variation of Zeffix (EMEA/H/C/242/II/53) based on a publication by Chtioui et al (Concomitant treatment with lamivudine renders cladribine inactive by inhibition of its phosphorylation. Br.J.Haematology. 2008; 144: 136-137). This article described a patient with chronic lymphoid leukaemia who was treated with CdA and Zeffix. No decrease of the peripheral blood lymphocyte count was observed after the first cycle of CdA. Zeffix was discontinued and the lymphocyte count decreased following the second and third cycles of CdA. The authors suspected a potential interaction based on intracellular phosphorylation when both medicines are administered concomitantly. In addition, an in vitro study was carried out using peripheral blood mononuclear cells isolated from a healthy volunteer. This in vitro study showed that phosphorylated CdA levels were decreased with increasing 3TC concentrations.

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/0039	To put in place a Risk Management Plan (RMP) following CHMP request during procedure PSU 042. Annex II has been modified accordingly, to include	21/02/2013	26/03/2013	Annex II	Following assessment of Kivexa PSU 042 (MAH's 24th PSUR) the CHMP requested the MAH to produce a risk management plan (RMP) for Kivexa). The MAH submitted

	details of the additional risk minimisation activities. Furthermore, the MAH proposed this opportunity to bring Annex II in line with the latest QRD template version 8.3. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				the present type II variation to fulfil this request and update Annex IIB to reflect that an RMP is now in place for Kivexa, with all of the requirements that this implies. This RMP version "00" of 31 May 2012 formalises existing pharmacovigilance activities and risk minimisation activities for Kivexa and appropriately reflects its safety profile. Upon CHMP request the educational program and patient Alert Card concerning the abacavir hypersensitivity reactions risk were detailed in the RMP and in the Annex IIC, in accordance with the EMA guideline on good pharmacovigilance practice and the current templates. Also upon request a summary of all the of the risk minimisation activities proposed, routine and additional was included in the RMP.
WS/0163	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	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 2012.

	NCA/EMA for another product of the same MAH				
IA/0036	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	19/12/2011	n/a		
II/0035	Update of sections 4.4 and 4.5 of the SmPC to alert on the possible reduction of SVR in ABC/RBV co-treated patients as requested by the CHMP (Ziagen RMP084). The PL has been amended accordingly. The MAH took the opportunity to reorganize the existing information on Liver Disease in section 4.4 and to correct a typo error in the title "Antihistamines (Histamine H1 receptor antagonists)" in the table in section 4.5. Minor changes have been made in the English and Romanian PL to improve readability. Annex II was amended to reflect the three yearly PSUR cycle, as requested following PSU042. 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	22/09/2011	24/10/2011	SmPC, Annex II and PL	Section 4.4 of the SmPC has been updated with a warning that caution should be exercised when ABC and RBV are co-administered. Conflicting clinical findings are reported in the literature with some data suggesting that HIV/HCV co-infected patients receiving abacavir-containing ART may be at risk of a lower response rate to pegylated interferon/ribavirin therapy. A possible intracellular mechanism has been postulated that ABC and RBV (two guanosine analogues) may be competing for the enzymes of a shared phosphorylation pathway. This could lead to a reduction in intracellular phosphorylated metabolites of ribavirin and, as a potential consequence, a reduced chance of sustained virological response (SVR) for Hepatitis C (HCV) in HCV co-infected patients treated with pegylated interferon plus RBV. SmPC section 4.5 has also been updated accordingly.
II/0032/G	This was an application for a group of variations. Update of sections 4.4, 4.5 and 4.6 of the SmPC in	17/03/2011	06/05/2011	SmPC and PL	

	fulfilment of commitments related to all antiretroviral agents containing lamivudine based on clinical experience gained on the use of lamivudine during pregnancy and on new information available on interactions. The PL was updated accordingly. In addition, further to Kivexa R/23 (FUM 038), section 4.5 has been revised and the format of the pharmacokinetic interaction data updated in line with the latest HIV guideline. The MAH took this opportunity to bring the SmPC in line with the latest QRD template and to update the address list in the PL. 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.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				
II/0034	Update of Summary of Product Characteristics, Labelling and Package Leaflet Update of Section 5.1 of the SmPC in line with the Annex B template of the guideline on the clinical development of medicinal products for the treatment	17/02/2011	18/03/2011	SmPC, Labelling and PL	Section 5.1 has been restructured with data obtained from literature review and reports previously submitted by the MAH, in line with the HIV guideline EMEA/CPMP/EWP/633/02. The revision concerned the data on in vitro antiviral activity against HIV-1, including non-B

	of HIV infection, as requested by the CHMP. The MAH took the opportunity to introduce minor changes to the SmPC, labelling and patient leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				subtypes, and HIV-2 for the individual drug components abacavir and lamivudine and/or in combination; data on the impact of selection for additional resistance mutations upon the susceptibility to abacavir or lamivudine in-vitro and in vivo and for therapy-naive versus experienced patients. Furthermore the clinical experience data was organised under separate headings for treatment naïve patients and treatment-experienced patients. In addition the results of treatment-naïve studies CNA30021, EPZ104057 (HEAT), CNA109586 (ASSERT) are now presented in the proposed tabulated format. The tables for CNA30021, EPZ104057 (HEAT) and CNA109586 (ASSERT) have been updated with additional sub-group analyses for baseline ribonucleic acid (RNA) for each of the studies and also for baseline CD4 categories for the CNA30021 study. Data from studies CAL30001 and ESS30008 has been revised to expand on the statistical test results of the analyses. Two tables were introduced from CAL30001 and CNA30021 studies on the Proportion of Patients with <50 cps/mL at Week 48 by Genotypic Sensitivity Score in OBT and Number of Baseline Mutations.
IA/0033	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	07/10/2010	n/a	Annex II and PL	
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/07/2010	n/a	PL	
II/0025	Update of section 5.1 of the SmPC based on data from long-term studies evaluating the relative efficacy of different combination regimens in	24/06/2010	28/07/2010	SmPC and PL	Major changes affected section 5.1 of the SmPC due to the introduction of new data from three comparative clinical trials (HEAT, ACTG5052 and ASSERT). These data are

	fulfilment of follow-up measures (FUMs) 029.3, 029.4 and 029.5. Update of Summary of Product Characteristics and Package Leaflet				partially conflicting; however they clearly show the emergence of a signal towards a higher risk of virological failure for Kivexa versus other backbones. A warning statement has therefore been introduced in section 4.4 which also redirects the reader to section 5.1. A cross-reference was added for the same reason in section 4.1. In the PL the contact details for the Spanish local representative were amended.
T/0030	Transfer of Marketing Authorisation	29/03/2010	26/05/2010	SmPC, Labelling and PL	
IB/0027	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	28/01/2010	n/a		
IB/0026	To introduce a minor change in the manufacturing process of a starting material IB_10_Minor change in the manufacturing process of the active substance	25/01/2010	n/a		
IA/0028	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	12/01/2010	n/a		
R/0023	Renewal of the marketing authorisation.	24/09/2009	11/12/2009	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 Kivexa (3TC-ABC fixed dose combination) remains positive. However specific safety issues related to pharmacovigilance remain, which

					warrant a close monitoring. The main safety issue of Kivexa is hypersensitivity reaction (HSR) associated with ABC, which can be severe and life threatening and is a matter of concern. Studies showed an association between patients carrying HLA B5701 allele and occurrence of HSR. Based on this information the screening for carriage of the HLA-B*5701 allele should be performed before initiating treatment with Kivexa and Kivexa should not be used in patients known to carry HLA B5701 allele. Two further issues are of potential concern involving the use of Kivexa. First, results from a clinical trial show that Kivexa has been associated with a statistically significantly shorter time to virologic failure versus the group receiving emtricitabine-tenofovir. Further clinical trial results have supported this signal and the MAH has submitted a variation to reflect this information on the product information. Secondly, a signal has been raised towards an association between ABC and risk of myocardial infarction. A causal relationship between myocardial infarction and ABC could neither be confirmed nor refuted, however as a precautionary measure, a warning was included in the SPC to reflect this information. Based on these issues, the CHMP is of the opinion that one additional five-year renewal on the basis of pharmacovigilance grounds is required. The MAH should continue to submit yearly PSURs and other safety information, until otherwise specified by the CHMP.

II/0024	Update of section 4.1 "Therapeutic indications", section 4.4 "Special warnings and precaution for use" and section 4.8 "Undesirable Effects" of the SPC to improve clarity for prescribers on HLA-B*5701 screening and the clinical management of abacavir (ABC) hypersensitivity reaction (HSR), as requested in the CHMP's assessment of the abacavir PSUR covering the period 01 January 2008 to 31 December 2008. The information on the HSR incidence was revised. Section 2 "Before you take Kivexa" of the PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	22/10/2009	25/11/2009	SmPC and PL	There has been one report of a case of hypersensitivity reaction (HSR) against the active substance abacavir at re-initiation of treatment in a patient who previously had well tolerated this medicinal product. However afterwards, this patient was tested positive for the gene HLA-B*5701, which is associated with a higher HSR risk. There have also been case reports of HSR in patients who already had shown HSR symptoms before, but were tested HLA-B*5701 negative. Based on these facts, it was regarded as necessary to amend the recommendation for HLA-B*5701 testing before re-initiation of abacavir treatment and to highlight that HSR can also occur in HLA-B*5701 negative patients in the Product Information. Regarding the latter issue, also the information on HSR incidence was updated and is now reflecting the still significant HSR incidence obtained for HLA-B*5701 negative patients in recent studies which differentiated between HLA-B*5701 negative and positive patients.
II/0021	Update of Summary of Product Characteristics, Labelling and Package Leaflet To update section 4.4 of the SPC and section 2 of the Package Leaflet for Kivexa Tablets to include information regarding abacavir use and the potential increased risk of myocardial infarction. Annex IIIA was updated with information in Braille. Furthermore, the contact details for Denmark, Latvia and Slovakia were updated in the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/04/2009	08/06/2009	SmPC, Labelling and PL	In April 2008 EMEA issued a press release on an association between the use of abacavir and the risk of myocardial infarction shown in an observational study (DAD study). Since then additional data derived from observational studies and clinical trials have become available on this issue including FHDH study. Observational studies have shown an association between myocardial infarction and the use of abacavir. The patients studied have generally received antiretroviral treatment prior inclusion in the study (experienced patients). There were limited numbers of myocardial infarction in data from clinical trials and a small increase in risk could not be excluded.

					The data available so far present some inconsistencies and can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there is no established biological mechanism to explain a potential increase in risk. The CHMP concluded that on the basis of the data available no recommendation could be made for changing the therapeutic management of patients. When prescribing Kivexa action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).
IA/0022	IA_06_a_Change in ATC code: Medicinal products for human use	14/08/2008	n/a	SmPC	
II/0018	Update of Summary of Product Characteristics and Package Leaflet To update sections 4.1 and 4.4 of the SPC to inform prescribers that before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed. Abacavir should not be used in patients known to carry the HLA-B*5701 allele. This update on genetic risk factors associated to abacavir hypersensitivity was supported by two recently completed clinical studies. Section 2 of the PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/01/2008	29/02/2008	SmPC and PL	Hypersensitivity reaction (HSR) is a potential life-threatening adverse reaction which occurs in approximately 5% of patients taking abacavir (ABC). Retrospective studies reported a highly significant association between HLA-B*5701 allele carriage and ABC HSR. The MAH has conducted two new phase IV studies to assess the association of HLA-B*5701 and the occurrence of ABC HSR as well as the clinical utility of a pharmacogenetic pre-screening strategy prior to initiating therapy with ABC. Results from a prospective study demonstrate that patients with the HLA-B*5701 allele are at a significantly higher risk of developing an HSR than patients without the HLA-B*5701 allele (i.e. 48 to 61% of patients with the HLA-B*5701 allele will develop and HSR versus 0 to 4% in patients without the HLA-B*5701 allele). Therefore, HLA-

					B*5701 testing should be performed before any initiation of abacavir treatment. Moreover, CHMP recommended that patients carrying the HLA-B*5701 allele should not be considered for the treatment with abacavir. Furthermore, results show that skin patch testing fails to detect ABC HSR in a subset of patients and therefore should not be used in clinical practice for the purpose of HSR diagnosis.
II/0020	Change(s) to the manufacturing process for the active substance	24/01/2008	29/01/2008		
IB/0017	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	16/11/2007	16/11/2007	SmPC, Labelling and PL	
IB/0019	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	08/11/2007	n/a		
II/0016	To update section 5.1 of the SPC concerning the emergence of M184V mutation following CHMP request dated 18 October 2006. Update of Summary of Product Characteristics	19/07/2007	27/08/2007	SmPC	The MAH submitted this type II variation II/16 to update section 5.1 of the SPC by adding information to discourage the maintenance of lamivudine in presence of M184V mutation when other active NRTIs are available following CHMP request dated 18 October 2006. This request was driven by the renewal of the Marketing Authorisation (R/52) for Epivir (lamivudine), which is another NRTIs indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection.
II/0015	To update section 5.2 of the SPC to include the results from a study evaluating abacavir intracellular pharmacokinetics in HIV infected patients in relation	19/07/2007	27/08/2007	SmPC	The MAH provided the results of studies to support the once daily regimen for abacavir and lamivudine. For abacavir it was demonstrated that the pharmacokinetic

	to FUM 17.1. Update of Summary of Product Characteristics				parameters of CBV-TP (carbovir thiphospate, active metabolite of abacavir) where higher with the abacavir once daily regimen than with the abacavir twice daily regimen. Regarding lamivudine it was found that intracellular lamivudine-TP pharmacokinetic parameters were similar or lower for the lamivudine 300 mg once daily regimen compared to the lamivudine 150 mg twice daily regimen.
II/0013	To update section 5.1 of the SPC with information on resistance to abacavir, based on an analysis of resistance data derived from pertinent clinical trials. The MAH took the opportunity of this change to update the ATC code for Kivexa. Update of Summary of Product Characteristics	22/02/2007	30/05/2007	SmPC	Based on results from the available relevant studies, the SPC has been updated with information on the resistance pattern of abacavir, in particular on the mutation pejorative to the virological response of abacavir, since this information could be clinically helpful. The information is now presented for in vitro resistance and for in vivo resistance in therapy naïve patients as well as therapy experienced patients. Concerning in vivo resistance in therapy naïve patients, isolates from most patients experiencing virological failure with a regimen containing abacavir in pivotal clinical trials showed either no NRTI-related changes from baseline or only M184V or M184I selection. Concerning in vivo resistance in therapy experienced patients, a clinically significant reduction of susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors. Phenotypic resistance to abacavir requires M184V with at least one other abacavir-selected mutation, or M184V with multiple thymidine analogue mutations. The currently recommended resistance algorithms can help in the appropriate use of abacavir.

IA/0014	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	20/02/2007	n/a		
II/0012	Update of section 4.4 and section 4.8 of the SPC and section 2 of the PL to implement the class labelling text on osteonecrosis, agreed by the CHMP in September 2006. In addition the MAH completed the list of local representatives in the PL to include the two new EU Member States (Bulgaria and Romania) according to the latest EMEA/QRD template. The contact details for the local representatives in Portugal have been updated. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	17/01/2007	SmPC and PL	Cases of osteonecrosis (death of the bone tissue resulting from an insufficient blood supply) have been reported in HIV-infected patients since the end of the 80's. Although the cause of this disease could be due to multi factors (including the use of corticosteroids, alcohol consumption, severe immunosuppression, higher body mass index) it has occurred specially in patients with HIV advanced disease and/or in patients with long term use of combination antiretroviral therapy (CART). Further to the review of all available data the CHMP agreed that this information should now be included in the SPC and PL of all antiretroviral medicinal products. Patients should be warned to seek medical advice in case they experience joint stiffness, aches and pain especially of the hip, knee and shoulder or if they experienced any difficulty in movement.
II/0009	To update section 4.4 of the SPC and section 2 of the PL with new information relating to genetic and clinical risk factors for the abacavir hypersensitivity reaction. The MAH also took the opportunity to update the product information according to the QRD template version 7.1. Update of Summary of Product Characteristics, Labelling and Package Leaflet	18/10/2006	28/11/2006	SmPC, Annex II, Labelling and PL	A review of genetic risk factors for the hypersensitivity to abacavir has shown that Caucasian patients with the HLA-B*5701 allele are more likely to develop a hypersensitivity reaction to abacavir. Analyses of clinical risk factors for the hypersensitivity to abacavir have identified the risk for Black patients to be approximately half the risk for other racial groups combined. However, since approximately 5% of patients receiving abacavir develop a hypersensitivity reaction, the risk for Black patients is of the same magnitude as for other racial groups and the same close monitoring should apply to patients of all racial groups.
IB/0010	IB_17_a_Change in re-test period of the active	10/08/2006	n/a		

	substance				
IA/0011	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	26/07/2006	n/a		
II/0008	Change(s) to the manufacturing process for the active substance	01/06/2006	07/06/2006		
IB/0005	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	06/01/2006	n/a		
IB/0006	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	05/01/2006	n/a		
IB/0004	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	22/12/2005	n/a		
IA/0007	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	08/12/2005	n/a		
II/0003	To update section 5.3 “Preclinical safety data” of the Summary of Product Characteristics (SPC) to include data from the oral rat micronucleus study report as requested by CHMP in April 2005. Update of Summary of Product Characteristics	15/09/2005	07/11/2005	SmPC	To update section 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics (SPC) to introduce the 48 week results of the study ESS30008 as requested by CHMP in April 2005. Also the Marketing Authorisation Holder took the opportunity to update the address of the Polish and Swedish representatives in the Package Leaflet
II/0002	To update section 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics (SPC) to introduce the 48 week results of the study ESS30008 as requested by CHMP in April 2005.	15/09/2005	07/11/2005	SmPC and PL	To update section 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics (SPC) to introduce the 48 week results of the study ESS30008 as requested by CHMP in April 2005.

	Also the Marketing Authorisation Holder took the opportunity to update the address of the Polish and Swedish representatives in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet				Also the Marketing Authorisation Holder took the opportunity to update the address of the Polish and Swedish representatives in the Package Leaflet
II/0001	To update section 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics (SPC) to introduce the 48 week results of the study CAL30001 as requested by CHMP in March 2005. In addition, the Marketing Authorisation Holder took the opportunity of this variation to update the address of the local representative in Slovenia in the Package Leaflet (PL). Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	08/09/2005	SmPC and PL	