Trizivir

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
PSUSA/3144/ 202212	Periodic Safety Update EU Single assessment - abacavir / lamivudine / zidovudine	14/09/2023	15/11/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3144/202212.
IG/1532	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/08/2022	02/12/2022	SmPC and PL	To update sections 4.4 and 4.6 of the SmPC and section 2 of the PL to implement the recommendation of the CHMP to

[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).

					remove the disease information relating to sexual transmission of HIV and to amend the sections related to breast-feeding.
IG/1504	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	20/07/2022	02/12/2022	Annex II and PL	
IG/1425/G	This was an application for a group of variations. 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.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	31/03/2022	n/a		
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	16/12/2021	02/12/2022	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.

	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				
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. 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	11/11/2021	n/a		
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,	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/

	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				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.
WS/1989	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 4.9 of the SmPC to revise the overdose information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/06/2021	20/08/2021	SmPC	No specific symptoms or signs have been identified following acute overdose with abacavir, zidovudine or lamivudine apart from those listed as adverse reactions.
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		
IA/0124	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	17/03/2021	n/a		
IG/1361	A.7 - Administrative change - Deletion of manufacturing sites	04/03/2021	20/08/2021	Annex II and PL	
IG/1333	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 -	20/01/2021	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/3144/ 201912	Periodic Safety Update EU Single assessment - abacavir / lamivudine / zidovudine	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		
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 variation	14/02/2019	n/a		
IA/0111	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate	20/11/2018	n/a		

	from an already approved manufacturer				
IAIN/0110	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2018	24/10/2019	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/0108	Transfer of Marketing Authorisation	10/09/2018	28/09/2018	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	28/09/2018	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/3144/ 201612	Periodic Safety Update EU Single assessment - abacavir / lamivudine / zidovudine	01/09/2017	n/a		PRAC Recommendation - maintenance
IB/0103/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	16/06/2017	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				
IG/0688	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	19/05/2016	n/a		
IB/0100	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	20/04/2016	n/a		
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	13/04/2016	n/a		

	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				
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. 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	01/04/2016	25/04/2016	SmPC, Annex II and PL	

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	25/04/2016	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	25/04/2016	SmPC 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 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	17/09/2015	25/04/2016	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.
IB/0095/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.	02/07/2015	25/04/2016	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".

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0089	Update of section 5.1 of the SmPC, upon request by the CHMP following the PRAC assessment of EMEA/H/C/PSUSA/3144/201312, to delete the description of outdated clinical data regarding the comparison between bitherapy and tritherapy. Further, a paragraph in section 5.1 of the SmpC concerning the comparison with nelfinavir has also been deleted. In addition, the MAH has taken this opportunity to implement minor editorial changes in the product information, to align the SmPC and Package Leaflet with the latest QRD template (version 9), and to update the lactic acidosis description in the Package Leaflet in line with the description provided for Ziagen (abacavir) and Kivexa (abacavir/lamivudine). C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	21/05/2015	25/04/2016	SmPC and PL	The MAH has submitted a type II variation application to delete two obsolete paragraphs concerning comparative data between bitherapy and tritherapy from the description of the clinical experience in SmPC section 5.1. These data are not clinically relevant given the current clinical HIV management. An additional short paragraph concerning the comparison with nelfinavir has also been deleted since it is considered of limited value and as nelfinavir is no longer available on the EU market (the MA was withdrawn in 2007).
IG/0537/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate	13/05/2015	n/a		

	from an already approved manufacturer B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				
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	25/04/2016	SmPC and PL	

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		
IB/0088/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of	04/03/2015	13/05/2015	SmPC and Labelling	

	the finished or intermediate product - Minor change in the manufacturing process B.II.d.1.i - Change in the specification parameters and/or limits of the finished product - Ph. Eur. 2.9.40 uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 or Ph. Eur. 2.9.6 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms 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				
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 starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	25/09/2014	n/a		

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		
PSUSA/3144/ 201312	Periodic Safety Update EU Single assessment - abacavir / lamivudine / zidovudine	11/09/2014	n/a		PRAC Recommendation - maintenance
IA/0085	A.7 - Administrative change - Deletion of manufacturing sites	15/07/2014	n/a		
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 the active substance	22/05/2014	n/a		

	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 Pharmacovigilance system - Changes in QPPV	16/05/2014	n/a		

	(including contact details) and/or changes in the PSMF location				
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 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	25/04/2014	13/05/2015	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.
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	28/03/2014	n/a		

	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
N/0077	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/01/2014	13/05/2015	PL	Inclusion of additional local representative of the MAH for the new member state Croatia. In addition the MAH took this opportunity to update the PL in line with the current information in the SmPC on paraesthesia as a symptom of abacavir hypersensitivity (Section 4 of the PL). Furthermore, the contact details for the local representative in the Czech Republic was also updated.
IG/0348	B.III.1.a.4 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Deletion of certificates (in case multiple certificates exist per material)	21/08/2013	n/a		
IG/0342	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	21/08/2013	n/a		
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	25/04/2013	23/05/2013	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

	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				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	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

	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				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/0070	To put in place a Risk Management Plan (RMP) following CHMP request during procedure PSU085. Annex II has been modified accordingly, to include 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	21/02/2013	26/03/2013	Annex II	Following the assessment of Trizivir PSU 085 (MAH's 24th PSUR) the CHMP requested the MAH to produce a risk management plan (RMP) for Trizivir. The MAH submitted the present type II variation to fulfill this request and update Annex IIB to reflect that an RMP is now in place for Trizivir, 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 Trizivir 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	21/06/2012	06/07/2012	Annex II	Update of the Detailed Description of the Pharmacovigilance System (DDPS) to ViiV Healthcare Ltd

	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 NCA/EMA for another product of the same MAH				version 4 dated May 2012.
IG/0191/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.7 - Administrative change - Deletion of manufacturing sites B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	25/06/2012	n/a		
IB/0068	C.I.3.a - Implementation of change(s) requested	22/05/2012	06/07/2012	SmPC, Annex	

	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			II and PL	
IA/0064	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	19/10/2011	n/a		
II/0062	Update of sections 4.4, 4.5 and 4.6 of the SmPC in fulfilment of commitments (FUM 081) 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. The MAH took this opportunity to bring the SmPC in line with the latest QRD template and to update the local representatives details 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	17/03/2011	07/06/2011	SmPC, Labelling and PL	A warning statement has been added in section 4.4 that Trizivir should not be used with other products containing lamivudine or emtricitabine. Section 4.6 has been revised to reflect the clinical data provided by the APR and to align it with other antiretroviral products. Section 4.5 has been updated with new information on interaction and restructured in line with the tabular format described in the HIV guideline. The information on carcinogenic risk in section 5.3 was amended in line with the revised section 4.6. The PL was revised accordingly.
R/0063	Renewal of the marketing authorisation.	23/09/2010	29/11/2010	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the

					benefit/risk profile of Trizivir continues to be favorable. The CHMP was also of the opinion that the renewal can be granted with unlimited validity.
T/0061	Transfer of Marketing Authorisation	16/04/2010	26/05/2010	SmPC, Labelling and PL	
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.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	10/03/2010	12/05/2010	SmPC, Annex II, Labelling and PL	
IB/0059	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	28/01/2010	n/a		
IB/0058	IB_10_Minor change in the manufacturing process of the active substance	25/01/2010	n/a		

II/0057	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. Sections 2 "Before you take Trizivir" and 4 "Possible side effects" of the PL were updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	22/10/2009	23/11/2009	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.
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/09/2009	n/a	PL	
IA/0056	IA_09_Deletion of manufacturing site	23/07/2009	n/a		
II/0049	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 Trizivir tablets to include information regarding abacavir use and the potential increased risk of myocardial infarction. Annex IIIA was updated with information in Braille.	23/04/2009	27/05/2009	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

	Furthermore, the contact details for Denmark, Latvia and Slovakia were updated in the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet				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 Trizivir action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).
IA/0053	IA_06_a_Change in ATC code: Medicinal products for human use	20/08/2008	n/a	SmPC	
IA/0052	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	29/07/2008	n/a		
IA/0051	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	29/07/2008	n/a		
IA/0050	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	29/07/2008	n/a		
II/0046	To update sections 4.1 and 4.4 of the SPC to inform prescribers that before initiating treatment with	24/01/2008	28/02/2008	SmPC and PL	Hypersensitivity reaction (HSR) is a potential life-threatening adverse reaction which occurs in approximately

	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				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/0048	Change(s) to the manufacturing process for the active substance	24/01/2008	28/01/2008		
II/0043	Update of Summary of Product Characteristics and Package Leaflet. To update sections 4.4 "Special warnings and precautions for use" and 4.5 "Interaction with other medicinal products and other forms of interaction" of	18/10/2007	21/11/2007	SmPC and PL	Following the European Mutual Recognition renewal application for zidovudine (Retrovir), the Summary of Products Characteristics (SPC) and the Package Leaflet (PL) of Retrovir were modified as regards the interaction with ribavirin and clarithromycin. The interaction between ribavirin and zidovudine was removed and a statement

	the Summary of Product Characteristics (SPC) concerning interactions relevant to zidovudine: clarithromycin and ribavirin. The CHMP took the opportunity of this variation to harmonise the information on interactions for all zidovudine containing products. Section 2 of the Package Leaflet (PL) was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				referring that clarithromycin tablets reduce the absorption of zidovudine was introduced. The MAH has submitted type II variation applications for the other medicinal products containing zidovudine (Combivir, Lamivudine/Zidovudine GSK and Trizivir) to update the information to be in line with the Retrovir SPC and PL. Furthermore, there is now a lot of evidence from clinical trials and from literature that concomitant use of zidovudine and ribavirin is associated with a greater risk of anaemia. The consensus conference on the treatment of HCV/HIV co-infected patients already recommended that the use of zidovudine should be avoided due to an excess risk of anaemia. The CHMP took the opportunity of this variation to check the consistency concerning the information on interactions relevant to zidovudine and to harmonise the product information of the products containing zidovudine.
IB/0047	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	08/11/2007	n/a		
II/0045	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	03/09/2007	SmPC	The MAH submitted this type II variation II/45 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/0042	Update of Summary of Product Characteristics 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 and in response to the MAH commitment made in variation II/39. The MAH took the opportunity of this change to update the ATC code for Trizivir. Update of Summary of Product Characteristics	26/04/2007	04/06/2007	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.
II/0041	Quality changes	22/02/2007	28/02/2007		
IA/0044	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/0040	Update of section 4.4 and section 4.8 of the SPC and section 2 of the PL to implement the class labelling	14/12/2006	24/01/2007	SmPC and PL	Cases of osteonecrosis (death of the bone tissue resulting from an insufficient blood supply) have been reported in

	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. Update of Summary of Product Characteristics and Package Leaflet				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/0039	To update section 5.1 of the SPC with new information relating to study ACTG5095. The MAH also took the opportunity to introduce minor QRD changes to the SPC and package leaflet (PL). Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	22/11/2006	SmPC and PL	ACTG5095 is a randomised, double-blind, placebo controlled study performed in antiretroviral-naïve HIV-1 infected adults and aiming at comparing 3 regimens: zidovudine/ lamivudine/ abacavir/ efavirenz vs zidovudine/ lamivudine/ efavirenz vs zidovudine/ lamivudine/ abacavir (Trizivir). The triple nucleoside reverse transcriptase inhibitor (NRTI) fixed-dose combination, Trizivir, was shown to induce a significantly higher rate of virologic failure as compared to a tritherapy with efavirenz. Furthermore, it was demonstrated that there is no benefit of adding abacavir to a tritherapy with efavirenz
II/0036	To update sections 4.4 and 4.8 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 contact details for Sweden in the PL.	18/10/2006	22/11/2006	SmPC 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

	Update of Summary of Product Characteristics and Package Leaflet				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/0037	IB_17_a_Change in re-test period of the active substance	09/08/2006	n/a		
IA/0038	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	26/07/2006	n/a		
II/0035	Change(s) to the manufacturing process for the active substance	01/06/2006	07/06/2006		
R/0029	Renewal of the marketing authorisation.	17/11/2005	10/04/2006	SmPC, Annex II, Labelling and PL	
IB/0032	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	06/01/2006	n/a		
IB/0033	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	05/01/2006	n/a		
IB/0031	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	22/12/2005	n/a		
IA/0034	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	08/12/2005	n/a		
IA/0030	IA_15_a_Submission of Ph. Eur. certificate for active	14/09/2005	n/a		

	substance - approved manufacturer				
IA/0028	IA_15_b_02_Submission of Ph. Eur. certificate for active substance - new manuf./other substances	14/06/2005	n/a		
II/0026	To update section 4.4 "Special warnings and special precautions for use" and 4.8 "Undesirable effects" of the Summary of Product Characteristics and section 2 "Before you take Trizivir" of the Package Leaflet, to implement the class labelling text regarding the Immune Reactivation Syndrome, as adopted by the CHMP in July 2004. For consistency with other abacavir containing medicinal products the Marketing Authorisation Holder (MAH) took the opportunity of this variation to include some minor amendments to the annexes I and IIIB. Additionally, the MAH added side-headings to section 4.4 of the SPC. Update of Summary of Product Characteristics and Package Leaflet	18/11/2004	05/01/2005	SmPC and PL	
II/0025	To update section 4.4 "Special warnings and special precautions for use" and section 4.8 "Undesirable effects" of the Summary of Product Characteristics (SPC) and sections 2 "Before you take Trizivir" and 4 "Possible side effects" of the Package Leaflet (PL) for Trizivir tablets to increase the percentage of patients receiving abacavir containing products who develop a hypersensitivity reaction from 4% to 5%, further to the assessment of PSUR 12 covering the period from 1 January 2003 – 30 June 2003. Furthermore, the	21/10/2004	17/11/2004	SmPC and Labelling	

	Marketing Authorisation Holder took the opportunity of this variation to amend the address of the Estonian local representative in the PL and to correct some errors in the Polish translation of the SPC and PL. Update of Summary of Product Characteristics and Package Leaflet				
IA/0027	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	27/10/2004	n/a		
IA/0024	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	03/09/2004	n/a		
IA/0023	IA_05_Change in the name and/or address of a manufacturer of the finished product	29/07/2004	n/a	Annex II and PL	
II/0021	Update of the section 4.4 (Special warnings and special precaution for use) of the Summary of Product Characteristics (SPC) and section 2 of the Package Leaflet (PL) under subheading "Pregnancy" , to implement the class labelling for nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) regarding mitochondrial toxicity in children with in utero and post-natal exposure, as adopted by the CPMP in November 2003 Update of Summary of Product Characteristics and Package Leaflet	24/03/2004	26/05/2004	SmPC and PL	

IA/0022	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	09/04/2004	n/a		
IB/0018	IB_10_Minor change in the manufacturing process of the active substance	13/02/2004	n/a		
IB/0020	IB_10_Minor change in the manufacturing process of the active substance	10/02/2004	n/a		
II/0016	Update of the section 4.4 "Special warnings and special precautions of use" of the Summary of Product Characteristics (SPC) to implement the class labelling on liver impairment adopted by the CPMP for all anti-retroviral medicinal products in April 2003. The section 2 of the Package Leaflet (PL) is amended accordingly. Furthermore, the MAH has taken this opportunity to update the section 4.8 "Undesirable effects" of the SPC by reordering the wording on skin reactions and the PL in section 4 to revise the wording on lipodystrophy as adopted by the CPMP in March 2003 and in section 6 to update the adress of the local representative in Germany. The MAH also updated the SPC and PL accortding to the latest EMEA / QRD templates. Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	30/01/2004	SmPC and PL	
N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/01/2004	05/02/2004	Labelling	

II/0015	The Marketing Authorisation Holder applied for an update of section 5.3 "Preclinical safety data" of the SPC to illustrate the results of a cohort pilot study showing that zidovudine may be incorporated into leukocyte DNA. Furthermore, the SPC has been updated in line with the latest EMEA/QRD template. Update of Summary of Product Characteristics	25/09/2003	14/01/2004	SmPC	
IA/0017	15a_Change in IPCs applied during the manufacture of the product	20/10/2003	n/a		
I/0012	34b_Manufacturing process for PhEur components verified by certificate of suitability from PhEur	08/08/2003	18/09/2003		
I/0014	24_Change in test procedure of active substance	05/08/2003	12/09/2003		
I/0013	01_Withdrawal of the manufacturing authorisation for a site of manufacture	18/07/2003	22/07/2003		
II/0010	The Marketing Authorisation Holder (MAH) applied for an update of the Summary of Product Characteristics to include the class labelling on Lipodystrophy in sections 4.4 (“Special warnings and special precautions for use”) and 4.8 (“Undesirable Effects”). Relevant changes are equally proposed for the Package Leaflet. Additionally, the contact details of the local representatives for Finland, Greece, Ireland and Spain have been updated in Section 6 of the Package Leaflet.	19/03/2003	30/06/2003	SmPC and PL	

	Update of Summary of Product Characteristics and Package Leaflet				
II/0005	The Marketing Authorisation Holder applied for the update of the Summary of Product Characteristics (SPC) further to the revised class labelling relating to lactic acidosis, safety related changes further to analyses of Periodic Safety Update Reports (PSURs) and other safety reports and harmonisation with Ziagen, Epivir and Combivir product information. The changes consist in the update of symptoms and signs of hypersensitivity reactions in section 4.4 ("Special warnings and special precautions for use") and 4.8 ("Undesirable effects"), inclusion of skin and subcutaneous tissue disorders as undesirable effects not associated with hypersensitivity reactions in section 4.8, and the inclusion of pure red cell aplasia, aplastic anemia and hepatitis in section 4.8. As a consequence, the Package Leaflet has been updated according to the above and according to the latest EMEA/QRD template. In addition, the list of local representatives has been revised. Update of Summary of Product Characteristics and Package Leaflet	25/07/2002	17/10/2002	SmPC and PL	
I/0009	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	16/07/2002	22/07/2002		

I/0008	13_Batch size of active substance	16/07/2002	22/07/2002		
I/0007	12_Minor change of manufacturing process of the active substance	16/07/2002	22/07/2002		
I/0006	11_Change in or addition of manufacturer(s) of active substance	16/07/2002	22/07/2002		
I/0004	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	08/05/2002	15/05/2002		
I/0002	12_Minor change of manufacturing process of the active substance	21/11/2001	27/11/2001		
II/0001	The Marketing Authorisation Holder applied for an update of the Summary of Product Characteristics (SPC) (sections 4.2. "Posology and method of administration", 4.3. "Contraindications", 4.4 "Special warnings and special precautions for use", 4.5 "Interaction with other medicinal products and other forms of interaction" and 4.8 "Undesirable effects", 5.2. "Pharmacokinetic properties", 5.3. "Preclinical safety data" and as a consequence, an update of the labelling and the Package Leaflet). Furthermore, the MAH proposed some minor changes in the SPC, Labelling and Package Leaflet in order to bring the text in line with the latest QRD/ EMEA templates. Update of Summary of Product Characteristics and	27/06/2001	09/11/2001	SmPC, Labelling and PL	

	Package Leaflet				
I/0003	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	12/10/2001	n/a		