Combivir

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
IG/1532	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/08/2022		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 remove the disease information relating to sexual transmission of HIV and to amend the sections related to breast-feeding.

[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).

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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		Annex II and PL	
IB/0106	B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	14/07/2022	n/a		
PSUSA/9207/ 202111	Periodic Safety Update EU Single assessment - lamivudine (HIV infections), lamivudine / zidovudine	07/07/2022	n/a		PRAC Recommendation - maintenance
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	16/12/2021		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

	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				reviewed indicated a terminal elimination half-life for lamivudine of 18-19 hours.
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.	22/07/2021	26/08/2021	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

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				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.	24/06/2021	26/08/2021	SmPC	No specific symptoms or signs have been identified following acute overdose with abacavir, zidovudine or

	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				lamivudine apart from those listed as adverse reactions.
IG/1361	A.7 - Administrative change - Deletion of manufacturing sites	04/03/2021	12/08/2021	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 - Not including batch control/testing	20/01/2021	n/a		
WS/1951	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/12/2020	12/08/2021	SmPC and PL	
IG/1237	A.1 - Administrative change - Change in the name and/or address of the MAH	11/06/2020	12/08/2021	SmPC, Labelling and PL	
PSUSA/9207/ 201811	Periodic Safety Update EU Single assessment - lamivudine (HIV infections), lamivudine / zidovudine	11/07/2019	n/a		PRAC Recommendation - maintenance

T/0094	Transfer of Marketing Authorisation	21/11/2018	31/01/2019	SmPC, Labelling and PL	
IA/0095	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	23/11/2018	n/a		
IAIN/0093	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/09/2018	31/01/2019	SmPC	
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. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	15/02/2018	n/a		

	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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/01/2018	31/01/2019	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.

PSUSA/9207/201511	Periodic Safety Update EU Single assessment - lamivudine (HIV infections), lamivudine / zidovudine	02/09/2016	n/a		PRAC Recommendation - maintenance
IB/0089	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/07/2016	03/03/2017	SmPC, Labelling and PL	
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		
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		
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	01/04/2016	03/03/2017	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

	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				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	02/05/2016	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	17/09/2015	02/05/2016	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.

	other retrovirals. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0084	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/07/2015	02/05/2016	SmPC and PL	
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 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	13/05/2015	n/a		
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	23/04/2015	02/05/2016	SmPC and PL	

	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				
II/0078	Submission of the final study report for an observational multi-cohort study on the use and safety of Combivir scored tablets among HIV-infected children and adolescent using the EPPICC data as mentioned in the version 4 of Combivir EU Risk Management Plan (RMP). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	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.	22/05/2014	n/a		

	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 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				

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	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 (including contact details) and/or changes in the PSMF location	16/05/2014	n/a		
WS/0544	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC with a revised wording on the risk of transmission as requested by the CHMP. The PL has been updated accordingly. In 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	20/04/2015	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.
N/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/11/2013	20/04/2015	PL	
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 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.
IB/0066/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	25/02/2013	n/a		

	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				
IA/0068	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	05/02/2013	n/a		
IA/0067/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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter	20/12/2012	n/a		
IG/0205	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	30/07/2012	n/a		

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		
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				
II/0059	Update of sections 4.4, 4.5, 4.6 and 5.1 of the SmPC in fulfilment of commitments (FUM 034) 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 introduce minor corrections in section 4.2, 4.4 and in Annex IIIA, 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	02/05/2011	SmPC, Annex II, Labelling and PL	A warning statement has been added in section 4.4 that Combivir 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 Antiretroviral Pregnancy Registry (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. Minor corrections were introduced in sections 4.2, 4.4 and in Annex II and IIIA. The PL was updated accordingly as well as the local representatives details.
II/0060	Update of section 4.8 of the SmPC to add 'angioedema' as a new adverse event in fulfilment of PSU033 (covering period 01.12.06 - 30.11.09 and concerning all lamivudine-containing products). The PL has been revised accordingly and aligned to QRD template. In addition the MAH took this opportunity to update the contact details of local representatives, the EMA website address and some minor mistakes in Annex II, Labelling and PL. C.I.3.b - Implementation of change(s) requested	23/09/2010	03/11/2010	SmPC, Annex II, Labelling and PL	Section 4.8 of the SmPC has been amended with the addition of the new adverse event "angioedema" and the calculation of its frequency (rare). PL was modified accordingly. Moreover minor corrections were introduced to amend the local representatives list in the PL, the EMA website address in Annex II and some mistakes in Annex IIIA and PL.

	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				
N/0058	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/07/2010	n/a	PL	
T/0057	Transfer of Marketing Authorisation	29/03/2010	10/05/2010	SmPC, Labelling and PL	
II/0056	Update of the Detailed Description of the Pharmacovigilance System (DDPS) including change of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II has been updated with the new version number. Update of DDPS (Pharmacovigilance)	17/12/2009	25/01/2010	Annex II	The DDPS has been updated (version 7.2) to reflect the change of the QPPV as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements.
II/0055	Update of the Detailed Description of Pharmacovigilance Systems (DDPS) in order to include the change of the Qualified Person for Pharmacovigilance (QPPV). In addition, the Marketing Authorisation Holder (MAH) took the opportunity to notify other minor changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.	19/02/2009	02/04/2009	Annex II	The DDPS has been updated (version 6.2) to reflect the change of the Qualified Person for Pharmacovigilance (QPPV) as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.

	Update of DDPS (Pharmacovigilance)				
II/0051	To update sections 4.2 "Posology and method of administration" and 5.2 "Pharmacokinetic properties" of the Summary of Product Characteristics relating to administration of crushed tablets with food and liquid further to CHMP request following assessment of the FUM 28 in February 2008. Section 3 of the Package Leaflet was updated accordingly. The MAH also took the opportunity to update section 6 of the Package Leaflet with new contact details for the local representative in Latvia. In addition, the Labelling has been updated with the inclusion of Braille. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/07/2008	16/09/2008	SmPC, Labelling and PL	Studies concerning the administration of crushed tablets with a small amount of semi-solid food or liquid show that the tablets can be crushed and then administered with small amount of semi-solid food or liquid without pharmaceutical quality impact. This information is useful for the treatment of paediatric patients who cannot swallow tablets and also for adults in difficulties in swallowing.
IA/0054	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	29/07/2008	n/a		
IA/0053	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	29/07/2008	n/a		
IA/0052	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	29/07/2008	n/a		
R/0049	Renewal of the marketing authorisation.	13/12/2007	13/02/2008	SmPC, Annex II, Labelling	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy

				and PL	of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Combivir continues to be favorable. The renewal was granted with unlimited validity.
II/0050	Change(s) to the manufacturing process for the active substance	24/01/2008	29/01/2008		
II/0044	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 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	18/10/2007	23/11/2007	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 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.
II/0043	Update of summary of product characteristics, annex II, labelling and package leaflet Extension of indication to paediatric patients and replacement of film coated tablets by scored film coated tablets. Furthermore, the MAH took the opportunity of this variation to split the outer carton and bottle label. Extension of Indication	20/09/2007	13/11/2007	SmPC, Annex II, Labelling and PL	This will refer to the scientific discussion of this assessment report.
II/0048	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/48 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	Quality changes	22/02/2007	01/03/2007		
IA/0047	IA_06_a_Change in ATC code: Medicinal products for human use	27/02/2007	n/a	SmPC	
IA/0046	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/0041	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) and changed the format according to the latest EMEA/QRD template. Update of Summary of Product Characteristics, Labelling and Package Leaflet	14/12/2006	26/01/2007	SmPC, Annex II, Labelling 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.
IB/0039	IB_17_a_Change in re-test period of the active substance	09/08/2006	n/a		
IA/0040	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	26/07/2006	n/a		
IA/0038	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	19/07/2006	n/a	Annex II and PL	
IA/0037	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	19/07/2006	n/a		
IB/0034	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	06/01/2006	n/a		

IB/0035	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	05/01/2006	n/a		
IA/0036	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	08/12/2005	n/a		
IA/0033	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	14/09/2005	n/a		
IA/0032	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	14/06/2005	n/a		
II/0031	Update of Summary of Product Characteristics and Package Leaflet	18/11/2004	05/01/2005	SmPC and PL	
IB/0030	IB_37_b_Change in the specification of the finished product - add. of new test parameter	07/12/2004	n/a		
IA/0029	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	03/09/2004	n/a		
IA/0028	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/0026	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	24/03/2004	26/05/2004	SmPC and PL	

	(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				
IA/0027	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	09/03/2004	n/a		
IB/0025	IB_10_Minor change in the manufacturing process of the active substance	10/02/2004	n/a		
II/0021	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 PL is amended accordingly. Furthermore, the MAH has taken this opportunity to update the PL in section 4 to revise the wording on lipodystrophy as recommended by the CPMP in March 2003 and in section 6 to update the telephone number of the local representative in Germany. Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	05/02/2004	SmPC and PL	
II/0023	Update of the section 5.3 " Preclincal safety data" of the Summary of Prduict Characteristics (SPC) to illustrate the results of a cohort pilot study showing	25/09/2003	14/01/2004	SmPC	

	that zidovudine may be incorporated into leucocyte DNA. Update of Summary of Product Characteristics				
II/0022	Update of section 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics (SPC) to characterise the role of a "fixed combination" product based on resistance data, as requested by the CPMP further to the opinion on the first five year renewal of the Marketing Authorisation. Update of Summary of Product Characteristics	25/09/2003	14/01/2004	SmPC	
IA/0024	15a_Change in IPCs applied during the manufacture of the product	20/10/2003	n/a		
I/0020	24_Change in test procedure of active substance	05/08/2003	20/08/2003		
I/0018	34b_Manufacturing process for PhEur components verified by certificate of suitability from PhEur	08/08/2003	20/08/2003		
I/0019	01_Withdrawal of the manufacturing authorisation for a site of manufacture	18/07/2003	22/07/2003		
R/0016	Renewal of the marketing authorisation.	19/03/2003	11/06/2003	SmPC, Annex II and PL	
I/0015	11_Change in or addition of manufacturer(s) of active substance	23/08/2002	29/08/2002		

II/0012	To update the Summary of Product Characteristics (SPC) section 5.1 (“Pharmacodynamic Properties”) relating to the use of lamivudine and zidovudine as part of HAART and relating to an update of virological information. Furthermore, to update section 4.8 (“Undesirable Effects”) to include pure red cell aplasia, aplastic anaemia and hepatitis and to reflect the frequencies of the adverse drug reactions in accordance with the SPC guideline. Also, to update section 4.4 (“ Special warnings and special precautions”) to reflect the class labelling statement for nucleoside analogues regarding lactic acidosis as revised by the CPMP. The relevant sections of the package leaflet have been amended accordingly. Furthermore, some minor changes have been incorporated in the SPC and Package Leaflet, in order to bring the text in line with the latest QRD/ EMEA templates. In addition, the list of the Local Representatives has been updated. Update of Summary of Product Characteristics and Package Leaflet	30/05/2002	22/08/2002	SmPC and PL	
I/0014	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	08/05/2002	15/05/2002		
I/0013	15_Minor changes in manufacture of the medicinal product 12a_Change in specification of starting material/intermediate used in manuf. of the active	05/03/2002	13/03/2002		

	substance				
II/0011	The Marketing Authorisation Holder applied for an update of the Summary of Product Characteristics, (sections 4.4 "Special warnings and special precautions for use", 4.5 "Interactions" and 4.8 "Undesirable effects", and as a consequence an update of 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 Package Leaflet	29/03/2001	31/07/2001	SmPC, Labelling and PL	
II/0010	The Marketing Authorisation Holder applied for an update of the Summary of Product Characteristics (section "Undesirable effects" and as a consequence an update of 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 Package Leaflet	28/08/2000	27/12/2000	SmPC, Labelling and PL	
I/0009	12_Minor change of manufacturing process of the active substance 11b_Change in supplier of an intermediate compound used in manufacture of the active substance	20/10/1999	20/12/1999	Labelling	

I/0008	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	20/10/1999	20/12/1999		
I/0007	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	20/10/1999	20/12/1999		
II/0006	Update of Summary of Product Characteristics and Package Leaflet	23/06/1999	16/11/1999	SmPC, Labelling and PL	
I/0005	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	25/05/1999	03/06/1999		
I/0004	11_Change in or addition of manufacturer(s) of active substance	19/08/1998	n/a		
I/0003	13_Batch size of active substance	19/08/1998	n/a		
I/0002	11_Change in or addition of manufacturer(s) of active substance	19/08/1998	n/a		
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/06/1998	17/08/1998	Labelling and PL	