Triumeq

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/10075 /202301	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	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/10075/202301.
IG/1655/G	This was an application for a group of variations.	10/08/2023	n/a		

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

	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.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation				
WS/2458	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	01/06/2023	n/a		
IA/0113	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	19/04/2023	n/a		
X/0101/G	This was an application for a group of variations. C.I.6.a - Change(s) to therapeutic indication(s) -	15/12/2022	20/02/2023	SmPC, Annex II, Labelling and PL	

	Addition of a new therapeutic indication or modification of an approved one Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form				
WS/2334	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 in order to update information on pregnancy and breast-feeding based on supporting published medical literature data on DolPHIN-1 (Dolutegravir in pregnant HIV mothers and their neonates, NCT02245022). The requested worksharing procedure proposed amendments to the Summary of Product Characteristics. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/09/2022	20/02/2023	SmPC	Section 4.6. Pregnancy Dolutegravir crosses the placenta in humans. In pregnant women living with HIV, the median foetal umbilical cord concentration of dolutegravir was approximately 1.3-fold greater compared with the maternal peripheral plasma concentration. There is insufficient information on the effects of dolutegravir on neonates. Breast-feeding A median dolutegravir breast milk to maternal plasma ratio of 0.033 has been shown. For more information, please refer to the Summary of Product Characteristics.
WS/2310	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	01/09/2022	n/a		

	or addition) for the AS or a starting material/intermediate				
WS/2323	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from study 200336 listed as a category 3 study in the RMP. This is a prospective, interventional pharmacokinetic and safety study of DTG/ABC/3TC in pregnant women. The summary of objective of this PASS study is to investigate the use of DTG during pregnancy and address the safety concerns of pregnant/breastfeeding women. The RMP versions 18.0, 20.0 and 4.0 for Tivicay, Triumeq and Juluca, respectively, have also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	01/09/2022	n/a		
WS/2268	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	01/09/2022	20/02/2023	SmPC and PL	To update section 4.8 of the SmPC and section 4 of the PL to include the ADR "weight increased" with a frequency "common".
IG/1532	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/08/2022	20/02/2023	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.
IG/1537/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 B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	09/08/2022	n/a		
WS/2246	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	21/07/2022	n/a		
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	20/02/2023	Annex II and PL	
WS/2255	This was an application for a variation following a worksharing procedure according to Article 20 of	30/06/2022	n/a		

	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				
IB/0102	B.II.z - Quality change - Finished product - Other variation	12/03/2022	n/a		
WS/2210	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Following the finalisation of procedure EMEA/H/C/WS1810 concerning submission of EuroSIDA (category 3 PASS) study, this Type II worksharing variation was proposed to address the removal of three important risks (Dolutegravir Hypersensitivity reactions, Hepatobiliary reactions and Serious rash) from all four dolutegravir-containing product EU-RMPs; Tivicay (dolutegravir), Triumeq (dolutegravir/abacavir/lamivudine), Dovato (dolutegravir/lamivudine) and Juluca (dolutegravir/rilpivirine) - i.e. deletion of safety concerns. In addition, the MAH took opportunity to propose a harmonisation of the risks across all four dolutegravir-containing product EU-RMPs and other minor updates (including study details and epidemiology data). The requested worksharing procedure proposed	10/03/2022	n/a		

	amendments to the Risk Management Plan (RMP). C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
WS/2192	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC to add "completed suicide" to the list of adverse drug reactions (ADRs) with frequency "rare" in the dolutegravir (Tivicay), dolutegravir/ abacavir/lamivudine (Triumeq) and dolutegravir/lamivudine (Dovato) following the finalisation of PSUSA procedure EMEA/H/C/PSUSA/00010075/202101 (reporting period 17 Jan 2020 to 16 Jan 2021) based on reports of completed suicide from participants exposed to dolutegravir containing regimen in ViiV Healthcare-sponsored clinical trials. As the changes impact all dolutegravir containing products, the MAH submitted a worksharing procedure to include Dolutegravir/Rilpivirine (Juluca) product in accordance with Article 20 (worksharing procedure) of Commission Regulation (EC) 1234/2008. The Package Leaflet is updated in section 4 with a rather identical wording.	10/02/2022	20/02/2023	SmPC and PL	

	The proposed wording should be as follows (identical with the suggested wording by the MAH regarding Dovato (footnote instead of brackets for the explanatory wording is acceptable to be in line with already included footnote on suicidal ideation and suicide attempt), Triumeq and Juluca. Nevertheless, the wording in section 4 for Tivicay is not exactly the same as for the other three products and should be therefore adapted accordingly). Furthermore, it could be considered to add a statement for patients in section of the PL that they should consult their doctor especially if neuropsychiatric side effects occur, since only under this condition an adequate reaction by the HCPs (knowledge of the adverse effects) is possible. 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				
PSUSA/10075 /202101	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	16/09/2021	15/11/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10075/202101.
WS/2116/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	11/11/2021	n/a		

	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IA/0098	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	02/11/2021	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, Dovato, Kivexa, Triumeq and Trizivir to include new information about use of the products in patients with renal impairment. Furthermore, minor editorial changes have been implemented throughout the Product Information and the lists of local representatives have been updated for all products. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/07/2021	22/09/2021	SmPC and PL	Patients with a creatinine clearance between 30 and 49 mL/min receiving Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir may experience a 1.6-to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥50 mL/min. There are no safety data from randomized, controlled trials comparing Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir to the individual components in patients with a creatinine clearance between 30 and 49 mL/min who received dose-adjusted lamivudine. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of haematologic toxicities (neutropenia and anaemia), although discontinuations due to neutropenia or anaemia each occurred in <1% of subjects. Other lamivudine-related adverse events (such as gastro-intestinal and hepatic disorders) may occur. The CHMP considered that, with the exception of Epivir, the previous recommendations to adjust the dose in patients

					with a sustained creatinine clearance between 30 and 49 mL/min can be removed. Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir should be monitored for lamivudine-related adverse events, notably haematologic toxicities. If new or worsening neutropenia or anaemia develop, a dose adjustment of lamivudine, per lamivudine prescribing information, is indicated, which cannot be achieved with Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir. Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir should be discontinued and the individual components should be used to construct the treatment regimen. The existing dose recommendations for Epivir have been maintained. The CHMP considered the lack of impact on pill burden when the lamivudine dose is adjusted for a monocomponent product and the fact that dose adjustments may be still used for subjects initially treated with lamivudine-containing fixed dose combinations, but requiring dose-adjusted individual components administration for safety reasons. For more information, please refer to the Summary of Product Characteristics.
IB/0095	B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	09/09/2021	n/a		
IG/1417	A.7 - Administrative change - Deletion of manufacturing sites	03/08/2021	n/a		

II/0091	Update of sections 4.2, 4.4 and 4.5 of the SmPC to include information on administration of an additional dose of 50 mg dolutegravir when Triumeq is co-administered with strong enzyme inducing drugs, sections 4.4 and 4.5 to include information on co-administration of Triumeq and supplements or multivitamins containing calcium, iron or magnesium when taken with food and section 5.2 to include information on the elimination half-life of lamivudine. The Package Leaflet is updated accordingly. These changes follow the CHMP request to align the Product Information of Triumeq and Dovato, made at the time of recommending the initial marketing authorisation of Dovato. In addition, the MAH took the opportunity to update the details of the Northern Ireland local representative in line with the QRD template v. 10.2. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/05/2021	25/06/2021	SmPC and PL	
IA/0094	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	25/05/2021	n/a		
IA/0093	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	07/04/2021	n/a		

	size				
IG/1362	A.7 - Administrative change - Deletion of manufacturing sites	22/02/2021	n/a		
IG/1332	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	18/01/2021	n/a		
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	14/01/2021	25/06/2021	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.

	new quality, preclinical, clinical or pharmacovigilance data				
WS/1810	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from study EuroSIDA (Study 201177) listed as a category 3 study in the RMP. This is a prospective observational cohort study to monitor and compare the occurrence of hypersensitivity reaction and hepatotoxicity in patients receiving dolutegravir (with or without abacavir) and other integrase inhibitors (with or without abacavir). Update of section 4.8 of the SmPC of Triumeq and Tivicay to include elevated bilirubin levels in combination with increased transaminases in patients treated with DTG-containing regimens (data from EuroSIDA and 14 other clinical trials), classified as 'rare' (≥1/10,000 to <1/1,000) and labelled under the SOC "Hepatobiliary disorders". In addition, the MAH updated the Package Leaflet of Triumeq and Tivicay to include increase in bilirubin levels as rare side effect. Furthermore, in line with the SmPC guideline, all laboratory findings related to hepatitis / acute hepatic failure, i.e. including ALT and AST elevations currently listed under the SOC "Investigations", were moved to the SOC "Hepatobiliary disorders" in section 4.8 of the SmPC of Triumeq and Tivicay.	14/01/2021	25/06/2021	SmPC and PL	Final results of study EuroSIDA (Study 201177), a prospective observational cohort study to monitor and compare the occurrence of hypersensitivity reaction and hepatotoxicity in patients receiving dolutegravir (with or without abacavir) and other integrase inhibitors (with or without abacavir) has been submitted. In addition to the data from EuroSIDA, the MAH submitted and 14 other clinical trials to establish the incidence of clinically relevant elevated bilirubin levels in combination with increased transaminases in patients treated with DTG-containing regimens For more details please refer to section 4.8 of the SmPC and section 4 of the PI.

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IA/0088	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	11/01/2021	n/a		
IA/0086	A.7 - Administrative change - Deletion of manufacturing sites	22/12/2020	n/a		
PSUSA/10075 /202001	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	17/09/2020	25/11/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10075/202001.
II/0069	Update of section 4.6 of the SmPC in order to update the safety information regarding the occurrence of neural tube defects with the dolutegravir -containing regimens based on the interim analysis from the Tsepamo study. This is a birth outcomes surveillance study being conducted in Botswana that was designed to evaluate adverse birth outcomes by HIV status and antiretroviral regimen, and to determine if there is an increased risk of neural tube defects among infants exposed to efavirenz at conception. This surveillance system captures all antiretroviral exposure including dolutegravir. The PL is updated accordingly.	23/07/2020	25/11/2020	SmPC	Section 4.6 of the SmPC of Tivicay, Triumeq, Juluca and Dovato (dolutegravir-based products) has been updated to include safety information regarding the occurrence of neural tube defects (NTDs) with dolutegravir (DTG)-containing regimens based on interim analysis from a birth outcomes surveillance study being conducted in Botswana (the Tsepamo study). This is an observational cohort study focusing on the safety of antiretroviral therapy during pregnancy and was designed to evaluate adverse birth outcomes by HIV status and antiretroviral regimen. The assessment of the latest results (July 2020) from the study shows a small increase of neural tube defects; 7 cases in 3,591 deliveries (0.19%; 95% CI 0.09%, 0.40%) to mothers taking dolutegravir-containing regimens at the

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				time of conception compared to 21 cases in 19,361 (0.11%: 95% CI 0.07%, 0.17%) women exposed to non-DTG regimens at the time of conception. The SmPC has been updated to include advice for women of childbearing potential to be counselled about the potential risk of NTD with DTG, including consideration of effective contraceptive measures. In addition, a recommendation to discuss the benefits and risks of continuing DTG versus switching to another antiretroviral regimen has been added in the case when a pregnancy is confirmed in the first trimester while on DTG.
WS/1806	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	02/07/2020	n/a		
IG/1238	A.1 - Administrative change - Change in the name and/or address of the MAH	17/06/2020	25/11/2020	SmPC, Labelling and PL	
IB/0083/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	15/06/2020	n/a		

	variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
WS/1762	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.3 and 4.5 of the SmPC in order to add a new contraindication in relation to the co-administration of dolutegravir with medicinal products with narrow therapeutic windows that are substrates of organic cation transporter 2 (OCT2), including but not limited to fampridine (also known as dalfampridine).The Package Leaflet is updated accordingly. In addition, the products information have been updated to reflect the following changes: - remove the drug-drug interactions for products no longer authorised in the EU (boceprevir, dofetilide, nelfinavir) - remove the inverted triangle for additional monitoring for Dovato only. Editorial changes have been made to the product information. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflets. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/02/2020	01/04/2020	SmPC and PL	A new contraindication is added to the Product information for dolutegravir containing products namely dolutegravir (DTG; TIVICAY), dolutegravir/abacavir/lamivudine (DTG/ABC/3TC; TRIUMEQ), dolutegravir/rilpivirine fixed dose combination (DTG/RPV FDC; JULUCA), and dolutegravir/lamivudine (DTG/3TC; DOVATO), to warn of concurrent administration of dolutegravir with medicinal products with narrow therapeutic windows, that are substrates of OCT-2, including but not limited to fampridine (also known as dalfampridine). Fampridine is a substrate of OCT2 with a narrow therapeutic index and could show an increased risk of seizures at elevated concentrations. While the proposed interaction has not been formally investigated in a drug interaction study for dolutegravir, the contradiction is accepted given the information stated in the approved product labelling for fampridine, and the understanding of dolutegravir potential to inhibit OCT2. The SmPC section 4.3 and 4.5 and the PL have been updated accordingly.

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 by new additional data to be submitted by the MAH where significant assessment is required	12/03/2020	25/11/2020	SmPC and Annex II	
WS/1738/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.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	20/02/2020	n/a		

	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 B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation 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				
WS/1729	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	13/02/2020	n/a		
PSUSA/10075 /201907	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	13/02/2020	n/a		PRAC Recommendation - maintenance
IB/0079/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	08/01/2020	n/a		

	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer 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.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				
WS/1685	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	14/11/2019	n/a		
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	07/11/2019	n/a		

	manufacturer of a novel excipient				
IB/0070	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	24/09/2019	n/a		
IA/0071/G	This was an application for a group of variations. B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/09/2019	n/a		
PSUSA/10075 /201901	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	05/09/2019	n/a		PRAC Recommendation - maintenance
IB/0068	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)	30/08/2019	n/a		
R/0063	Renewal of the marketing authorisation.	26/04/2019	20/06/2019	SmPC, Labelling and PL	
IAIN/0067/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	21/05/2019	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 B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
IA/0065	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	27/02/2019	n/a		
IB/0064/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/02/2019	20/06/2019	SmPC and PL	
T/0061	Transfer of Marketing Authorisation	23/10/2018	12/12/2018	SmPC, Labelling and PL	
IB/0062	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	10/12/2018	n/a		

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		
IAIN/0059	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/09/2018	12/12/2018	SmPC	
PSUSA/10075 /201801	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	06/09/2018	n/a		PRAC Recommendation - maintenance
IA/0058/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	03/08/2018	n/a		
II/0053	Update of section 4.8 of the SmPC to add the new ADR 'acute hepatic failure' with a frequency of rare based on post-marketing and clinical trial data, and to implement minor changes for increased clarity. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	12/07/2018	12/12/2018	SmPC and PL	n/a

	data				
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/1320/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.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 B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for	17/05/2018	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place 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				
WS/1341/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 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	19/04/2018	n/a		
IG/0911/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	06/04/2018	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
II/0047	Update of sections 4.5 and 5.2 of the SmPC based on new in vitro studies conducted for abacavir (ABC) and lamivudine (3TC). In addition, the MAH took the opportunity to implement minor corrections in section 5.1 of the SmPC and minor editorial changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/03/2018	12/12/2018	SmPC	Abacavir inhibited the MATE1-mediated transport of 14C-metformin with a calculated IC50 value of 40.4 µM but did not inhibit CYP enzymes, OATP1B1 or OATP1B3. Lamivudine did not inhibit CYP enzymes, OATP1B1, OATP1B and MATE2-K. Neither abacavir nor lamivudine was a substrate of CYP enzymes. Abacavir was not a substrate of the investigated transporters OATP1B1, OATP1B3, MATE1 or MATE2-K, whereas active renal secretion of lamivudine in the urine is mediated through OCT2 as well as MATE1 and MATE2-K. Trimethoprim (an inhibitor of these drug transporters) has been shown to increase lamivudine plasma concentrations; however, the resulting increase was not clinically significant. Data from literature showed that lamivudine was an OCT1 and OCT2 inhibitor. As hepatic elimination plays a minor role in the clearance of lamivudine, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance. Although abacavir and lamivudine are substrates of BCRP and P-gp in vitro, given the high absolute bioavailability of abacavir and lamivudine, inhibitors of these efflux transporters are unlikely to result in a clinically relevant impact on abacavir or lamivudine concentrations. For more information, please refer to the Summary of Product Characteristics.
II/0049	Update of section 4.8 of the SmPC to add the new ADR 'anxiety' with a frequency of 'common' based on post-marketing and clinical trial data. The Package	01/03/2018	12/12/2018	SmPC and PL	n/a

	Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make some editorial changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
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	12/12/2018	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.
IB/0050/G	This was an application for a group of variations.	10/01/2018	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				
IB/0051	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/01/2018	n/a		
IG/0873	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	08/12/2017	n/a		
PSUSA/10075 /201701	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	01/09/2017	n/a		PRAC Recommendation - maintenance
IAIN/0045	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	17/05/2017	n/a		

IB/0043	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/03/2017	n/a		
PSUSA/10075 /201607	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	09/02/2017	n/a		PRAC Recommendation - maintenance
IB/0041	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/02/2017	n/a		
II/0037	Update of section 4.8 of the SmPC to add the ADR myalgia with a frequency of common, and to update the source of observed ADRs with the combination of dolutegravir + abacavir/lamivudine, based on post-marketing experience with dolutegravir. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/01/2017	26/06/2017	SmPC	N/A
II/0036	Update of section 5.1 of the SmPC to include Week 24 (primary analysis) and Week 48 data from the Phase IIIb clinical study 201147 (STRIIVING), to support the use of Triumeq in HIV-infected antiretroviral (ART)-experienced adults. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/01/2017	26/06/2017	SmPC	The STRIIVING study (201147) was a 48-week, randomized, open-label, active-controlled, multicentre, non-inferiority switch study in virologically suppressed subjects without any prior treatment failure, and with no documented history of resistance to any class. Virologically suppressed (HIV-1 RNA <50 c/mL) subjects were randomly assigned (1:1) to continue their current ART regimen (2 NRTIs plus either a PI, NNRTI, or INI), or switch to ABC/DTG/3TC FDC once daily (Early Switch). Hepatitis B

					co-infection was one of the main exclusion criteria. Patients were mainly white (66%) or black (28%) of male sex (87%). Main prior transmission routes were homosexual (73%) or heterosexual (29%) contact. The proportion with a positive HCV serology was 7%. The median time from first starting ART was around 4.5 years. Virologic suppression (HIV-1 RNA <50 copies/mL) in the ABC/DTG/3TC FDC group (85%) was statistically non-inferior to the current ART groups (88%) at 24 weeks. The adjusted difference in proportion and 95% CI [ABC/DTG/3TC vs current ART] were 3.4%; 95% CI: [-9.1, 2.4]. After 24 weeks all remaining subjects switched to ABC/DTG/3TC FDC (Late Switch). Similar levels of virologic suppression were maintained in both the Early and Late Switch groups at 48 weeks. For the detailed results of the study, please refer to the updated SmPC.
II/0035	Update of section 5.1 of the SmPC to include Week 48 data from the Phase IIIb clinical study ING117172 (ARIA) to support the use of Triumeq in HIV-infected antiretroviral (ART)-naïve women. Further, a minor consequential change was implemented in section 4.8 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/01/2017	26/06/2017	SmPC	In ARIA (ING117172), a randomized, open-label, active-controlled, multicenter, parallel group, non-inferiority study; 499 HIV-1 infected ART naïve adult women were randomized 1:1 to receive either; DTG/ABC/3TC FDC 50 mg/600 mg/300 mg; or atazanavir 300 mg plus ritonavir 100 mg plus tenofovir disproxil fumarate/ emtricitabine 300 mg/200 mg (ATV+RTV+TDF/FTC FDC), all administered once daily. Please refer to the SmPC for information on demographics and Week 48 efficacy results.
IB/0040/G	This was an application for a group of variations.	10/01/2017	n/a		

	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				
IB/0038/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.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	04/01/2017	26/06/2017	Annex II and PL	

	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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 originally approved batch size				
WS/1042/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.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.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 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	24/11/2016	n/a		

	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				
II/0031	Update of section 4.2 of the SmPC with an amended recommendation related to dose reduction in patients with hepatic impairment and section 4.4 of the SmPC with revised wording related to mitochondrial dysfunction, in line with the SmPCs of other abacavir containing products. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor changes in Annex II and the labelling in line with the latest QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/10/2016	14/11/2016	SmPC, Annex II, Labelling and PL	Abacavir is primarily metabolised by the liver. No clinical data are available in patients with moderate or severe hepatic impairment, therefore the use of Triumeq is not recommended unless judged necessary. In patients with mild hepatic impairment (Child-Pugh score 5-6) close monitoring is required, including monitoring of abacavir plasma levels if feasible. Mitochondrial dysfunction following exposure in utero: Nucleoside and nucleotide 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 post-natally

					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 reactions have often been transitory. Some 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 nucleoside and nucleotide analogues, who presents 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/0977	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.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	06/10/2016	n/a		N/A

IB/0032	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	21/09/2016	14/11/2016	SmPC	
PSUSA/10075 /201601	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	02/09/2016	n/a		PRAC Recommendation - maintenance
IG/0714	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	12/08/2016	n/a		
WS/0948	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.5 of the SmPC to remove the current information regarding a potential interaction between abacavir and ribavirin. The Package Leaflet has been updated accordingly. In addition, updated RMPs were agreed during the procedure: Ziagen RMP version 13; Kivexa RMP version 5; Triumeq RMP version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/07/2016	14/11/2016	SmPC and PL	PK study COL112055 did not show apparent impact of ABC on the intracellular concentrations of ribavirin triphosphate after 56 days of treatment (RBV alone: 15.93 pmol/106 cells; RBV+ABC: 15.87 pmol/106 cells). Although the variability of these measures is too high (80-100%) to achieve adequate statistical power (a difference between these 2 arms only >40% can be excluded), the data are nonetheless reassuring, the intracellular values being quite similar in between arms. In addition, 3 retrospective studies performed in a large number of HCV/HIV coinfected subjects do not support a potential impact of ABC on the sustained virologic response with Peg-IFN+ribavirin. Moreover, the potential interaction of ABC on RBV is currently not considered in the European guidelines for the treatment of HIV/HCV coinfected subjects.

II/0026/G	This was an application for a group of variations. Update of annex IID and RMP in order to update the educational slide set and website. Furthermore, the Marketing authorisation holder (MAH) is taking this opportunity to align the information within the RMP with the recently approved changes to the SmPC concerning information on lactic acidosis and lipodystrophy. 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	21/07/2016	14/11/2016	Annex II	
IB/0028/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	06/07/2016	n/a		

	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 the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				
IB/0025	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 and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	13/04/2016	n/a		
IG/0674	A.4 - Administrative change - Change in the name	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				
PSUSA/10075 /201507	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	11/02/2016	n/a		PRAC Recommendation - maintenance
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	07/03/2016	SmPC and PL	
IA/0019/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	29/10/2015	n/a		
WS/0820	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	22/10/2015	n/a		

	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IB/0020	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	20/10/2015	n/a		
II/0015/G	This was an application for a group of variations. Update of section 5.1 of the SmPC in order to include additional, long-term efficacy and safety data from week 144 of the Phase III study ING114467 (SINGLE) and week 96 of the Phase IIIb study ING114915 (FLAMINGO). The consolidated RMP version 9 has been agreed. In addition, the MAH took the opportunity to include a minor correction in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	07/03/2016	SmPC and PL	At 144 weeks in the open-label phase of SINGLE, virologic suppression was maintained, the DTG +ABC/3TC arm (71%) was superior to the EFV/TDF/FTC arm (63%), treatment difference was 8.3% (2.0, 14.6). At 96 weeks, virologic suppression in the dolutegravir group (80%) was superior to the DRV/r group (68%), (adjusted treatment difference [DTG-(DRV+RTV)]: 12.4%; 95% CI: [4.7, 20.2]). Response rates at 96 weeks were 82% for DTG+ABC/3TC and 75% for DRV/r+ABC/3TC.
PSUSA/10075 /201501	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine,	10/09/2015	n/a		PRAC Recommendation - maintenance

	dolutegravir / lamivudine				
IB/0016/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		
IB/0014/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.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.1.z - Change in the specification parameters	06/08/2015	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Other variation				
II/0007/G	This was an application for a group of variations. Update of sections 4.4 and 4.5 of the SmPC to reflect: - Data from a drug:drug interaction study 200901 with dolutegravir (DTG) and carbamazepine (REC 2); - Metformin drug:drug interaction data from study 201167; - Daclatasvir drug:drug interaction data from study 201102; - PK modelling of DTG when co-administered with etravirine (ETV) without a ritonavir (RTV)-boosted protease inhibitor (PI); - PK modelling of DTG when co-administered with the metabolic inducers phenytoin, phenobarbital, oxcarbazepine, and St. John's Wort (hyperforin), and corresponding Package Leaflet changes. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	25/06/2015	07/03/2016	SmPC and PL	Since the recommended dose of dolutegravir is 50 mg twice daily when co-administered with etravirine (without boosted protease inhibitors), efavirenz, nevirapine, rifampicin, tipranavir/ritonavir, carbamazepine, phenytoin, phenobarbital and St. John's wort, the use of Triumeq is not recommended for patients taking these medicines. Dolutegravir increased metformin concentrations. A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin, to maintain glycaemic control. Metformin is eliminated renally and therefore it is of importance to monitor renal function when co-treated with dolutegravir. This combination may increase the risk for lactic acidosis in patients with moderate renal impairment (stage 3a creatinine clearance [CrCl] 45– 59 mL/min) and a cautious approach is recommended. Reduction of the metformin dose should be highly considered. Section 4.5 of the SmPC provides further detailed recommendations concerning co-administration with medicinal products by therapeutic areas.

	data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0013	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	17/06/2015	n/a		
IB/0012	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/06/2015	07/03/2016	SmPC and PL	
IA/0010	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	23/04/2015	07/03/2016	SmPC and PL	

	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				
IB/0008	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	09/04/2015	n/a		
IAIN/0009	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	01/04/2015	n/a		
II/0006	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/03/2015	n/a		
II/0005	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/03/2015	n/a		
II/0004/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/03/2015	07/03/2016	SmPC and Labelling	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
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/0003/G	This was an application for a group of variations. 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 originally approved batch size B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	14/01/2015	n/a		