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
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	18/10/2018	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).

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	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				
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	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 data	12/07/2018	12/12/2018	SmPC and PL	n/a

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 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	17/05/2018	n/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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	06/04/2018	n/a		
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	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.

	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				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 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	01/03/2018	12/12/2018	SmPC and PL	n/a

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. 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	10/01/2018	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				
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	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	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. 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	10/01/2017	n/a		

	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 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	04/01/2017	26/06/2017	Annex II and PL	
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 -	24/11/2016	n/a		

	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 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	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

	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				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	06/10/2016	n/a		N/A

	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				
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	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	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.

	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				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	06/07/2016	n/a		

	manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of 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	13/04/2016	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IG/0674	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	13/04/2016	n/a		
PSUSA/10075 /201507	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / 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	22/10/2015	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/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

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 and/or limits of an AS, starting material/intermediate/reagent - Other variation	06/08/2015	n/a		

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 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	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.

	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 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	23/04/2015	07/03/2016	SmPC and PL	

	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 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	26/03/2015	07/03/2016	SmPC and Labelling	

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		