Tivicay

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
II/0093	Submission of the final study report for Study ING112578 (IMPAACT P1093) (Category 3 PASS); an open-label, Phase 1/2 study designed to select a DTG dose for chronic dosing of infants, children, and adolescents based on PK, safety, and tolerability. As a consequence, a revised RMP version 21 to remove	28/11/2024	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).

	long-term safety data as an area of missing information has been approved. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
WS/2751/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.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 A.7 - Administrative change - Deletion of manufacturing sites 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	31/10/2024	n/a		

	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.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				
WS/2620	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 about the use of DTG-containing regimens in pregnancy and at conception based on final results from non-interventional Tsepamo study and the Eswatini Birth Outcomes Surveillance study. In addition, data from other cohort studies and pregnancy registries, including the APR, DOLOMITE-EPPICC (Study 208613) and DOLOMITE-NEAT-ID Network study (Study 208759) both listed as category 3 studies in the RMP; and the US Chart Review (Study 212976) as well as data from literature are included. DOLOMITE-EPPICC (Study 208613) is a non-interventional study to assess "real-world" maternal and foetal outcomes following	31/10/2024		SmPC and PL	SmPC new text At the light of the updated information about the use of dolutegravir (DTG)-containing regimens in pregnancy and at conception based on final results from two large non-interventional studies (Tsepamo and Eswatini Birth Outcomes Surveillance studies), data from other cohort studies and pregnancy registries (including the Antiretroviral Pregnancy Registry (APR), final results from DOLOMITE-EPPICC and data from ongoing DOLOMITE-NEAT-ID Network study), the US Chart Review as well as data from literature, section 4.6 of the SmPC has been updated. The recommendation for use of these products during pregnancy has also been amended. The package leaflet has been updated accordingly. For more information, please refer to the Summary of Product Characteristics.

	DTG use during pregnancy and to describe patterns of DTG utilization; DOLOMITE NEAT ID Network Study (208759) is a non-interventional, multi-site observational study to define the safety and effectiveness of dolutegravir use in HIV positive pregnant women. In addition, the MAH took the opportunity to implement editorial changes to sections 4.4 and 4.5 of the SmPC. The package leaflet is updated accordingly. The RMP version 19.0 (Tivicay), version 23.1 (Triumeq), version 5.0 (Dovato) and version 8.0 (Juluca) have also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10075 /202301	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	14/09/2023	14/09/2023	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. 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.b.2.a - Change in test procedure for AS or	10/08/2023	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
II/0089	Update of section 5.2 of the SmPC in order to update Tmax data for the dolutegravir tablet formulations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2023	20/06/2024	SmPC	The information on pharmacokinetic properties has been updated to state that dolutegravir is rapidly absorbed following oral administration, with median Tmax at 1 to 3 hours post dose for film-coated tablet or dispersible tablet formulations. For more information, please refer to the Summary of Product Characteristics.
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		
IB/0086	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/03/2023	n/a		
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	22/09/2022	06/02/2023	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.

	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				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/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	01/09/2022	06/02/2023	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

	Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				"common".
IB/0083	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/08/2022	06/02/2023	SmPC and PL	Sections 4.4 and 4.6 of the SmPC were revised to remove information related to sexual transmission and update the text regarding HIV transmission in breast-feeding women, following CHMP recommendation. The PL was updated accordingly.
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	06/02/2023	Annex II and PL	
WS/2255	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	30/06/2022	n/a		
II/0077	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/03/2022	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	10/03/2022	n/a		

	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 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	10/02/2022	06/02/2023	SmPC and PL	

	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. 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	12/11/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10075/202101.

II/0073/G	This was an application for a group of variations. Update of section 5.1 of the Tivicay SmPC in order to add new information on efficacy and safety based on data from studies 204861 (GEMINI-1) and 205543 (GEMINI-2). These are Phase III, identical, ongoing, randomized, double-blind, parallel group studies, to provide longer term efficacy and safety data on the use of dolutegravir (DTG) for the treatment of HIV-1 infection. The Package Leaflet is updated accordingly. The grouping includes a Type IA variation to update the ATC code for both Film Coated and Dispersible Tablets. In addition, the MAH took the opportunity to include an editorial correction to the list of excipients in the SmPC and Package Leaflet and to update the list of local representatives in the Package Leaflet. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/09/2021	31/01/2022	SmPC and PL	SmPC new text […] 5.1 Pharmacodynamic properties Pharmacotherapeutic group: Antivirals for systemic use, other antivirals, ATC code: J05AJ03 […] Resistance in vivo In previously untreated patients receiving dolutegravir + 2 NRTIs in Phase IIb and Phase III, no development of resistance to the integrase class, or to the NRTI class was seen (n=1118 follow-up of 48-96 weeks). In previously untreated patients receiving dolutegravir + lamivudine in the GEMINI studies through week 144 (n=716), no development of resistance to the integrase class, or to the NRTI class was seen. […] Clinical efficacy and safety Previously untreated patients The efficacy of dolutegravir in HIV-infected, therapy naïve subjects is based on the analyses of 96-week data from two randomized, international, double-blind, active-controlled trials, SPRING-2 (ING113086) and SINGLE (ING114467). This is supported by 96 week data from an open-label, randomized and active-controlled study FLAMINGO (ING114915) and additional data from the open-label phase of SINGLE to 144 weeks. The efficacy of dolutegravir in combination with lamivudine in adults is supported by 144-week data from two identical 148-week, randomised, multicentre, double-blind, non-inferiority studies GEMINI-1 (204861) and GEMINI-2 (205543). […] For more information, please refer to the Summary of

					Product Characteristics.
IG/1417	A.7 - Administrative change - Deletion of manufacturing sites	03/08/2021	n/a		
IB/0070	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	12/04/2021	n/a		
IA/0072	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	07/04/2021	n/a		
IB/0067/G	This was an application for a group of variations. 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	25/02/2021	n/a		
IA/0069	A.7 - Administrative change - Deletion of manufacturing sites	24/02/2021	n/a		
IG/1362	A.7 - Administrative change - Deletion of manufacturing sites	22/02/2021	n/a		
IG/1332	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer	18/01/2021	n/a		

	responsible for importation and/or batch release - Not including batch control/testing				
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	12/11/2021	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				
X/0058/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/11/2020	11/01/2021	SmPC, Annex II, Labelling and PL	Please refer to scientific discussion Tivicay-H-C-002753-X-0058-G.
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	07/01/2021	n/a		
PSUSA/10075/202001	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	17/09/2020	16/11/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10075/202001.
II/0064	Update of section 5.1 in order to add long-term efficacy and safety data, following the week 96 results from studies 204861 (GEMINI-1) and 205543 (GEMINI-2), listed as specific Category 3 studies in the RMP. These are two identical ongoing pivotal, randomised, double-blind, parallel group, 148-week, phase III studies to evaluate the efficacy, safety and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-	15/10/2020	11/01/2021	SmPC	At 96 weeks the dolutegravir plus lamivudine group (86% with plasma HIV-1 RNA < 50 copies/mL [pooled data]) remained non-inferior to the dolutegravir plus tenofovir/emtricitabine FDC group (90% with plasma HIV-1 RNA < 50 copies/mL [pooled data]). The adjusted difference in proportions and 95% CI was -3.4% (-6.7, 0.0). The results of the pooled analysis were in line with those of the individual studies, for which the secondary endpoint (difference in proportion <50 copies/mL plasma

	infected treatment naïve patients. In addition, the MAH took the opportunity to introduce minor editorial changes in the Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				HIV-1 RNA at Week 96 based on the Snapshot algorithm for dolutegravir plus lamivudine versus dolutegravir plus tenofovir/emtricitabine FDC) was met. The adjusted differences of -4.9 (95% CI: -9.8; 0.0) for GEMINI-1 and -1.8 (95% CI: -6.4; 2.7) for GEMINI-2 were within the prespecified non-inferiority margin of -10%. The mean increase in CD4+ T-cell counts was 269 in the DTG+3TC arm and 259 in the DTG+FTC/TDF arm, at week 96. For more information, please refer to the Summary of Product Characteristics.
IB/0063	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/08/2020	16/11/2020	SmPC and PL	
II/0052	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. C.I.4 - Change(s) in the SPC, Labelling or PL due to	23/07/2020	16/11/2020	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 time of conception compared to 21 cases in 19,361 (0.11%: 95% CI 0.07%, 0.17%) women exposed to non-

	new quality, preclinical, clinical or pharmacovigilance data				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	16/11/2020	SmPC, Labelling and PL	
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),	06/02/2020	08/04/2020	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

	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				(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/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 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	20/02/2020	n/a		

	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
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		
PSUSA/10075 /201901	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	05/09/2019	n/a		PRAC Recommendation - maintenance

WS/1572	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.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)	16/05/2019	n/a		
IAIN/0050/G	This was an application for a group of variations. C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	18/04/2019	04/11/2019	SmPC and PL	
WS/1580	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	11/04/2019	n/a		
IA/0048	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	21/03/2019	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IA/0047	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		
IA/0045/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	09/01/2019	n/a		
IB/0043/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	09/01/2019	04/11/2019	SmPC and PL	
IG/1032/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	18/12/2018	n/a		

	the AS - Minor change in the manufacturing process of the AS				
IAIN/0042	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/11/2018	04/11/2019	SmPC	
II/0041/G	This was an application for a group of variations. Update of sections 4.4, 4.8 and 5.1 of the SmPC based on week 24 data (secondary analysis) from the pivotal Phase III studies, 204861 [GEMINI-1] and 205543 [GEMINI-2] in ART-naïve adult subjects. 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/11/2018	04/11/2019	SmPC and PL	The two-drug regimen of dolutegravir 50 mg once daily and lamivudine 300 mg once daily was explored in two large randomized and blinded studies, GEMINI-1 and GEMINI-2. This regimen is only suitable for the treatment of HIV-1 infection where there is no known or suspected resistance to the integrase inhibitor class, or to lamivudine. In GEMINI-1 (204861) and GEMINI-2 (205543), identical 148-week, randomised, double-blind studies, 1433 adult HIV-1 infected antiretroviral naïve subjects were randomised to either a two-drug regimen of dolutegravir 50 mg plus lamivudine 300 mg once daily, or to a three-drug regimen of dolutegravir 50 mg once daily with fixed dose TDF/FTC. Subjects were enrolled with a screening plasma HIV-1 RNA of 1000 c/mL to ≤500,000 c/mL. At baseline, in the pooled analysis, median patient age was 33 years, 15% were female, 32% non-white, 6% had hepatitis C co-infection and 9% were CDC Stage 3. Approximately one third of the patients were infected with an HIV non-B subtype; these characteristics were similar between treatment groups. Virologic suppression (HIV-1 RNA <50 copies/mL) in the dolutegravir plus lamivudine group was non-inferior to the dolutegravir plus TDF/FTC group at 48 weeks. The results of the pooled analysis were in line with those of the individual studies, for which the primary endpoint (difference in proportion <50 copies/mL plasma HIV-1 RNA at week 48 based on the Snapshot algorithm)

					was met. The adjusted difference was -2.6% (95% CI: -6.7; 1.5) for GEMINI-1 and -0.7% (95% CI: -4.3; 2.9) for GEMINI-2 with a prespecified non-inferiority margin of 10%. Through 48 weeks in the GEMINI-1 and GEMINI-2 studies, no cases of emergent resistance to the integrase- or NRTI-class were seen in either the DTG+3TC or comparator DTG+ TDF/FTC arms. There are no data available on the use of dolutegravir plus lamivudine as a two-drug regimen in paediatric patients.
R/0040	Renewal of the marketing authorisation.	26/07/2018	21/09/2018	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Tivicay in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10075 /201801	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	06/09/2018	n/a		PRAC Recommendation - maintenance
II/0034	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. 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	21/09/2018	SmPC and PL	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	17/05/2018	n/a		

	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 test procedure (including replacement or addition) for the AS or a starting material/intermediate				
T/0039	Transfer of Marketing Authorisation	23/04/2018	08/05/2018	SmPC, Labelling and PL	
IB/0038/G	This was an application for a group of variations. 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	07/05/2018	n/a		

	compared to the originally approved batch size				
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/0031	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	08/05/2018	SmPC and PL	n/a

	Leaflet has been updated accordingly and minor editorial changes implemented. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0032	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
IB/0029/G	This was an application for a group of variations. 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) 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) 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)	04/07/2017	20/12/2017	SmPC	

X/0018/G	This was an application for a group of variations. An extension application to add two new strengths (10mg and 25mg tablets) to support the extension (variation type II C.I.6) of the target population covered by the authorised therapeutic indication for Tivicay to treat paediatric patients from 6 years of age infected with HIV. Data from cohort I and II A of the clinical trial ING112578 are presented in support of the new therapeutic indication. Annex I_2.(c) Change or addition of a new strength/potency C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/12/2016	23/02/2017	SmPC, Labelling and PL	Please refer to the Scientific Discussion Tivicay EMEA/H/C/002753/X/0018/G.
PSUSA/10075 /201607	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	09/02/2017	n/a		PRAC Recommendation - maintenance
II/0027	Update of section 4.8 of the SmPC to add the ADRs arthralgia and myalgia with a frequency of uncommon. The Package Leaflet has been updated accordingly. In addition, the MAH has taken the opportunity to make minor corrections in section 5.1 of the SmPC and to update the contact details of the local representative in Norway in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	19/01/2017	20/12/2017	SmPC and PL	N/A

	data				
IB/0026	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	24/11/2016	n/a		
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 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	24/11/2016	n/a		

	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				
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/0023/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	06/09/2016	23/02/2017	Annex II, Labelling and PL	

	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.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				
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		

PSUSA/10075 /201507	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	11/02/2016	n/a		PRAC Recommendation - maintenance
IB/0017/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	21/12/2015	n/a		
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/11/2015	26/09/2016	PL	
WS/0820	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	22/10/2015	n/a		
II/0014/G	This was an application for a group of variations.	24/09/2015	26/09/2016	SmPC	The efficacy of dolutegravir in HIV-infected, therapy naïve subjects is based on the analyses of 96-week data from

	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 8 has been agreed. 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				two randomized, international, double-blind, active-controlled trials, SPRING-2 (ING113086) and SINGLE (ING114467). This is supported by 96 week data from an open-label, randomized and active-controlled study FLAMINGO (ING114915) and additional data from the open-label phase of SINGLE to 144 weeks. At 144 weeks in the open-label phase of SINGLE, virologic suppression was maintained, the dolutegravir + 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].
PSUSA/10075 /201501	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	10/09/2015	n/a		PRAC Recommendation - maintenance
II/0008/G	This was an application for a group of variations. Update of section 5.1 of the SmPC with week-48 results (end of study) from Phase III Study ING116529 in antiretroviral therapy (ART)-experienced, INI-resistant subjects and update of section 5.1 of the SmPC with combined analyses of antiviral response at Week 24 and Week 48 by IN genotype and DTG phenotype in treatment-experienced, INI-resistant subjects from Study ING112574 and Study ING116529. In addition, the MAH took the opportunity to make an editorial change in section 5.1 of the SmPC.	25/06/2015	28/07/2015	SmPC	The VIKING-4 study examined dolutegravir (plus optimized background therapy) in subjects with primary genotypic resistance to INIs at Screening in 30 subjects. Treatment-emergent mutations observed were consistent with those observed in the VIKING-3 study. At baseline, median patient age was 49 years, 20% were female, 58% non-white, and 23% had hepatitis B and/or C co-infection. Median baseline CD4+ was 160 cells/mm3, median duration of prior ART was 13 years, and 63% were CDC Class C. Subjects showed multiple class ART resistance at baseline: 80% had ≥2 NRTI, 73% ≥1 NNRTI, and 67% ≥2 PI major mutations; 83% had non-R5 virus. Sixteen of 30 subjects (53%) harboured Q148 virus at

	Further, the MAH provided an updated population PK analysis in treatment-experienced, INI-naïve and INI-resistant subjects using pooled PK data from Study ING111762, Study ING112961, Study ING112574 and Study ING116529 and also provided PK/pharmacodynamic (PD) modelling data for subjects with baseline integrase resistance. Upon request by the CHMP during the procedure, sections 4.2, 4.4, 4.5 and 5.2 of the SmPC were updated to reflect that an increased dose of dolutegravir may be considered for patients with limited treatment options (less than 2 active agents) due to advanced multi class resistance. 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.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				baseline. At week 48, 12/30 (40%) subjects had HIV-1 RNA <50 copies/mL (ITT-E, Snapshot algorithm). In a combined analysis of VIKING-3 and VIKING-4 (n=186, VO population), the proportion of subjects with HIV RNA <50 copies/mL at Week 48 was 126/186 (68%). The proportion of subjects with HIV RNA <50 copies/mL was 96/126 (76%) for No Q148 mutations, 22/41 (54%) for Q148+1 and 5/19 (26%) for Q148+≥2 secondary mutations. In the presence of documented resistance that includes Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I, modelling suggests that an increased dose may be considered for patients with limitedtreatment options (less than 2 active agents) due to advanced multi class resistance. PK/PD modelling using pooled data from clinical studies in integrase resistant patients suggests that increasing the dose from 50 mg twice daily to 100 mg twice daily may increase the effectiveness of dolutegravir in patients with integrase resistance and limited treatment options due to advanced multi class resistance. The proportion of responders (HIV-1 RNA <50 c/mL) at week 24 was predicted to increase around 4-18% in the subjects with Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I. Although these simulated results have not been confirmed in clinical trials, this high dose may be considered in the presence of the Q148 + ≥2 secondary mutations from G140A/C/S, E138A/K/T, L74I in patients with overall limited treatment options due to advanced multi

					class resistance. There is no clinical data on the safety or efficacy of the 100 mg twice daily dose. Co-treatment with atazanavir increases the exposure of dolutegravir markedly, and should not be used in combination with this high dose, since safety with the resulting dolutegravir exposure has not been established.
II/0012/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 takes 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	25/06/2015	28/07/2015	SmPC and PL	Factors that decrease dolutegravir exposure should be avoided in the presence of integrase class resistance. This includes co-administration with medicinal products that reduce dolutegravir exposure (e.g. magnesium/ aluminium-containing antacid, iron and calcium supplements, multivitamins and inducing agents, etravirine (without boosted protease inhibitors), tipranavir/ritonavir, rifampicin, St. John's wort and certain anti-epileptic drugs). 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10075 /201407	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	26/02/2015	24/04/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10075/201407.
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).	23/04/2015	28/07/2015	SmPC and PL	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0011	Submission of phototoxicity study reports (category 3) to assess phototoxicity in dolutegravir. 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/0010	Submission of a study to investigate the in vitro potential for dolutegravir to inhibit a series of melanocortin receptors. 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/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	25/09/2014	24/04/2015	SmPC	
IB/0006/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	28/08/2014	n/a		

	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				
II/0001	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/07/2014	24/04/2015	SmPC	
II/0003/G	This was an application for a group of variations. Update of section 4.8 and 5.1 of the SmPC based on a grouping of 4 Type II variations concerning the following data: Study ING113086, Study ING114467, Study ING114915 and Study ING112574. In addition, further minor amendments to the SmPC, the Annex IIIA and the PL were implemented.	26/06/2014	24/04/2015	SmPC, Labelling and PL	Long term data has been provided from Phase III Studies ING113086 (SPRING-2) and ING114467 (SINGLE). Data has also been provided from Phase IIIb Study ING114915 (FLAMINGO) in ART-naïve patients. Week 48 pharmacology and efficacy results from the completed cohort of 183 INI-resistant subjects in Study ING112574 (VIKING-3) has also been provided. The product information has been updated accordingly.

	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				
IG/0438	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/05/2014	n/a		
WS/0544	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC with a revised wording on the risk of transmission as requested by the CHMP. The PL has been updated accordingly. In addition, minor corrections are made to translations and an editorial change is implemented in Trizivir PL. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/04/2014	24/04/2015	SmPC and PL	The warnings in product information regarding the risk of transmission have been updated as requested by the CHMP in a class labelling request adopted in December 2013. Minor corrections are made to translations of Combivir SmPC in Danish and PL in Finnish and Slovenian, Celsentri SmPC and PL in Finnish and Hungarian, Telzir PL in Finnish, Tivicay SmPC in Dutch.