Dovato

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
R/0045	Renewal of the marketing authorisation.	25/01/2024	21/03/2024	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Dovato in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. Only changes to the Product information (PI) to bring it

[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).

					in line with the current QRD template version 10.3 and SmPC guidelines are introduced with this renewal procedure.
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.
IB/0041/G	This was an application for a group of variations. B.II.e.1.b.1 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Solid, semi-solid and non-sterile liquid pharmaceutical forms B.II.e.1.b.1 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Solid, semi-solid and non-sterile liquid pharmaceutical forms	06/09/2023	21/03/2024	SmPC, Labelling and PL	
IB/0042/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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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	22/08/2023	n/a		

	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 B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.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				
IG/1655/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.a.1.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	10/08/2023	n/a		

	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IAIN/0043/G	This was an application for a group of variations. B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	02/08/2023	n/a		
II/0040/G	This was an application for a group of variations. Submission of the final reports from study 204861 (GEMINI-1) and study 205543 (GEMINI-2) listed as category 3 studies in the RMP; these are phase 3, randomised, double-blind, multicentre, parallel group, non-inferiority studies evaluating the efficacy, safety and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults. The RMP version 4.1 has 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 C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	20/07/2023	n/a		

	of studies to the competent authority				
IA/0039	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	24/04/2023	n/a		
IB/0037	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	24/04/2023	n/a		
IB/0036	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/12/2022	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 DolPHIN-1 (Dolutegravir in pregnant HIV mothers and their neonates, NCT02245022). The requested worksharing procedure proposed amendments to the Summary of Product Characteristics. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/09/2022	15/03/2023	SmPC	Section 4.6. Pregnancy Dolutegravir crosses the placenta in humans. In pregnant women living with HIV, the median foetal umbilical cord concentration of dolutegravir was approximately 1.3-fold greater compared with the maternal peripheral plasma concentration. There is insufficient information on the effects of dolutegravir on neonates. Breast-feeding A median dolutegravir breast milk to maternal plasma ratio of 0.033 has been shown. For more information, please refer to the Summary of

					Product Characteristics.
WS/2310	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	01/09/2022	n/a		
WS/2268	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/09/2022	15/03/2023	SmPC and PL	To update section 4.8 of the SmPC and section 4 of the PL to include the ADR "weight increased" with a frequency "common".
IG/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		

IB/0032	B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	14/06/2022	n/a		
II/0029	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/06/2022	15/03/2023	SmPC and PL	
IB/0030	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	02/05/2022	n/a		
WS/2210	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Following the finalisation of procedure EMEA/H/C/WS1810 concerning submission of EuroSIDA (category 3 PASS) study, this Type II worksharing variation was proposed to address the removal of three important risks (Dolutegravir Hypersensitivity reactions, Hepatobiliary reactions and Serious rash) from all four dolutegravir-containing product EU-RMPs; Tivicay (dolutegravir), Triumeq (dolutegravir/abacavir/lamivudine), Dovato (dolutegravir/lamivudine) and Juluca (dolutegravir/rilpivirine) - i.e. deletion of safety concerns. In addition, the MAH took opportunity to propose a harmonisation of the risks across all four	10/03/2022	n/a		

	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 a worksharing procedure to include Dolutegravir/Rilpivirine (Juluca) product in	10/02/2022	15/03/2023	SmPC and PL	

	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				
IB/0027	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	21/12/2021	n/a		

PSUSA/10075 /202101	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	16/09/2021	15/11/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10075/202101.
IA/0025	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	12/10/2021	n/a		
WS/1990	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.4 and 5.2 of the SmPC of the fixed-dose combination products Combivir, Dovato, Kivexa, Triumeq and Trizivir to include new information about use of the products in patients with renal impairment. Furthermore, minor editorial changes have been implemented throughout the Product Information and the lists of local representatives have been updated for all products. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/07/2021	20/08/2021	SmPC and PL	Patients with a creatinine clearance between 30 and 49 mL/min receiving Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir may experience a 1.6-to 3.3-fold higher lamivudine exposure (AUC) than patients with a creatinine clearance ≥50 mL/min. There are no safety data from randomized, controlled trials comparing Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir to the individual components in patients with a creatinine clearance between 30 and 49 mL/min who received dose-adjusted lamivudine. In the original lamivudine registrational trials in combination with zidovudine, higher lamivudine exposures were associated with higher rates of haematologic toxicities (neutropenia and anaemia), although discontinuations due to neutropenia or anaemia each occurred in <1% of subjects. Other lamivudine-related adverse events (such as gastro-intestinal and hepatic disorders) may occur. The CHMP considered that, with the exception of Epivir, the previous recommendations to adjust the dose in patients with a sustained creatinine clearance between

					30 and 49 mL/min can be removed. Patients with a sustained creatinine clearance between 30 and 49 mL/min who receive Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir should be monitored for lamivudine-related adverse events, notably haematologic toxicities. If new or worsening neutropenia or anaemia develop, a dose adjustment of lamivudine, per lamivudine prescribing information, is indicated, which cannot be achieved with Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir. Combivir/Dovato/ Kivexa/ Triumeq/ Trizivir should be discontinued and the individual components should be used to construct the treatment regimen. The existing dose recommendations for Epivir have been maintained. The CHMP considered the lack of impact on pill burden when the lamivudine dose is adjusted for a monocomponent product and the fact that dose adjustments may be still used for subjects initially treated with lamivudine-containing fixed dose combinations, but requiring dose-adjusted individual components administration for safety reasons. For more information, please refer to the Summary of Product Characteristics.
IB/0023	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)	18/08/2021	15/11/2021	SmPC	To extend the shelf-life of the finished product as packaged for sale from 2 years to 3 years.
IG/1417	A.7 - Administrative change - Deletion of manufacturing sites	03/08/2021	n/a		

II/0020	Update of section 4.8 in order to add new safety information regarding hepatic safety and section 5.1 to include long-term efficacy and safety information, based on studies 204861 (GEMINI-1) and 205543 (GEMINI-2), listed as category 3 studies in the RMP. GEMINI-1 and GEMINI-2 were Phase III, randomised, double-blind, multicentre, parallel group, non-inferiority studies evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of 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	20/05/2021	20/08/2021	SmPC and PL	
II/0019	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/05/2021	20/08/2021	SmPC	
IA/0022	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		
PSUSA/10075 /202001	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine,	17/09/2020	18/11/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing

	dolutegravir / lamivudine				Authorisation(s)' for PSUSA/10075/202001.
II/0001	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 new quality, preclinical, clinical or pharmacovigilance data	23/07/2020	18/11/2020	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-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.

IG/1238	A.1 - Administrative change - Change in the name and/or address of the MAH	17/06/2020	18/11/2020	SmPC, Labelling and PL	
IA/0016	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	15/06/2020	n/a		
IA/0015	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	15/06/2020	n/a		
IB/0014	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	30/04/2020	n/a		
WS/1762	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.3 and 4.5 of the SmPC in order to add a new contraindication in relation to the co-administration of dolutegravir with medicinal products with narrow therapeutic windows that are substrates of organic cation transporter 2 (OCT2), including but not limited to fampridine (also known as dalfampridine).The Package Leaflet is updated accordingly. In addition, the products information have been updated to reflect the following changes: - remove the drug-drug interactions for products no longer authorised in the EU (boceprevir,	06/02/2020	01/04/2020	SmPC and PL	A new contraindication is added to the Product information for dolutegravir containing products namely dolutegravir (DTG; TIVICAY), dolutegravir/abacavir/lamivudine (DTG/ABC/3TC; TRIUMEQ), dolutegravir/rilpivirine fixed dose combination (DTG/RPV FDC; JULUCA), and dolutegravir/lamivudine (DTG/3TC; DOVATO), to warn of concurrent administration of dolutegravir with medicinal products with narrow therapeutic windows, that are substrates of OCT-2, including but not limited to fampridine (also known as dalfampridine). Fampridine is a substrate of OCT2 with a narrow therapeutic index and could show an increased risk of seizures at elevated concentrations. While the proposed interaction has not been formally

	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				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 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	20/02/2020	n/a		

	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				
II/0009	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/02/2020	18/11/2020	SmPC	
II/0008	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/02/2020	18/11/2020	SmPC	
PSUSA/10075 /201907	Periodic Safety Update EU Single assessment - dolutegravir, dolutegravir / abacavir / lamivudine, dolutegravir / lamivudine	13/02/2020	n/a		PRAC Recommendation - maintenance
IB/0012/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	10/01/2020	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.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				
IB/0010	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	04/12/2019	n/a		
IAIN/0006	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	22/11/2019	n/a		
IB/0003	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	29/10/2019	n/a		
IB/0004	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)	18/10/2019	n/a		
IA/0002/G	This was an application for a group of variations.	13/09/2019	n/a		

	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				