Ziagen

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IG/1532	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/08/2022		SmPC and PL	To update sections 4.4 and 4.6 of the SmPC and section 2 of the PL to implement the recommendation of the CHMP to remove the disease information relating to sexual transmission of HIV and to amend the sections related to breast-feeding.

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

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IG/1504	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	20/07/2022		Annex II and PL	
N/0122	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/12/2021	04/03/2022	PL	
WS/2116/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	11/11/2021	n/a		
IG/1388	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	21/05/2021	n/a		
IG/1361	A.7 - Administrative change - Deletion of manufacturing sites	04/03/2021	04/03/2022	Annex II and PL	
IG/1360	A.7 - Administrative change - Deletion of manufacturing sites	02/03/2021	04/03/2022	Annex II and PL	

IG/1333	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	20/01/2021	n/a		
IG/1326	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	18/01/2021	n/a		
WS/1917	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.5 of the SmPC (for Ziagen, Kivexa, Trizivir and Triumeq) and 5.2 (for Triumeq only) to add new information about the drug-drug interactions between abacavir and riociguat. The Package Leaflet is updated accordingly. Furthermore, the MAH took the opportunity to introduce an excipient update for Ziagen, Kivexa and Trizivir in line with the SmPC guideline, a syringe instruction update in the Package Leaflet of Ziagen and a revised statetment in section 6.6 of the SmPC for Triumeq in line with the QRD template. Moreover, minor editorial updates have been introduced throughout the Product Information of all four products.	14/01/2021	09/03/2021	SmPC and PL	In vitro, abacavir inhibits CYP1A1. Concomitant administration of a single dose (0.5 mg) of riociguat (CYP1A1 substrate) to HIV patients receiving the combination of abacavir/dolutegravir/lamivudine (600mg/50mg/300mg once daily) led to an approximately three-fold higher riociguat AUC(0-∞) when compared to historical riociguat AUC(0-∞) reported in healthy subjects. Therefore, when riociguat is co-administered with abacavir, its dose may need to be reduced. Consult the riociguat prescribing information for dosing recommendations.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/1307	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	08/01/2021	n/a		
WS/1864/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	22/10/2020	n/a		
PSUSA/10/201912	Periodic Safety Update EU Single assessment - abacavir	03/09/2020	n/a		PRAC Recommendation - maintenance
IG/1237	A.1 - Administrative change - Change in the name and/or address of the MAH	11/06/2020	09/03/2021	SmPC, Labelling and PL	
WS/1713	This was an application for a variation following a worksharing procedure according to Article 20 of	12/03/2020	09/03/2021	SmPC and	

	Commission Regulation (EC) No 1234/2008. Submission of updated RMPs (Kivexa, Trizivir, Ziagen version 2.0 and Triumeq version 17.0) in order to remove the additional risk minimisation measure of provision of abacavir hypersensitivity education materials for healthcare professionals. Annex II is updated accordingly. In addition, the MAH took the opportunity to introduce an editorial update in the SmPC of Triumeq. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required			Annex II	
IA/0110/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	22/11/2019	04/02/2020	Annex II and PL	

IG/1150	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	07/11/2019	n/a		
WS/1521	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	11/04/2019	n/a		
WS/1545	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	14/02/2019	n/a		
IAIN/0107	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	12/02/2019	04/02/2020	Annex II and PL	

T/0104	Transfer of Marketing Authorisation	21/11/2018	07/12/2018	SmPC, Labelling and PL	
IG/0993	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	18/10/2018	n/a		
IAIN/0102	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/09/2018	07/12/2018	SmPC	
II/0101/G	This was an application for a group of variations. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological product) of a specification parameter wit its corresponding test method as a result of a safety or quality issue	01/03/2018	07/12/2018	SmPC and PL	The Ziagen oral solution is a clear to slightly opalescent yellowish, aqueous solution which may turn into a brown colour over time.
PSUSA/10/20 1612	Periodic Safety Update EU Single assessment - abacavir	01/09/2017	n/a		PRAC Recommendation - maintenance
N/0100	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/06/2017	07/12/2018	Labelling	

IB/0098/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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	10/01/2017	n/a		
WS/0956/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.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	21/07/2016	09/03/2017	Annex II	

	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/0948	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.5 of the SmPC to remove the current information regarding a potential interaction between abacavir and ribavirin. The Package Leaflet has been updated accordingly. In addition, updated RMPs were agreed during the procedure: Ziagen RMP version 13; Kivexa RMP version 5; Triumeq RMP version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/07/2016	09/03/2017	SmPC and PL	PK study COL112055 did not show apparent impact of ABC on the intracellular concentrations of ribavirin triphosphate after 56 days of treatment (RBV alone: 15.93 pmol/106 cells; RBV+ABC: 15.87 pmol/106 cells). Although the variability of these measures is too high (80-100%) to achieve adequate statistical power (a difference between these 2 arms only >40% can be excluded), the data are nonetheless reassuring, the intracellular values being quite similar in between arms. In addition, 3 retrospective studies performed in a large number of HCV/HIV coinfected subjects do not support a potential impact of ABC on the sustained virologic response with Peg-IFN+ribavirin. Moreover, the potential interaction of ABC on RBV is currently not considered in the European guidelines for the treatment of HIV/HCV coinfected subjects.
IB/0095	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/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	13/04/2016	n/a		

	manufacturer of a novel excipient				
WS/0845	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, 4.3, 4.4 and 5.2 of the SmPC in order to align the Hepatic Impairment wording for the 3 older abacavir-containing products (ZIAGEN™, KIVEXA™ and TRIZIVIR™) with the TRIUMEQ™ SmPC. The Package Leaflet is updated accordingly. In addition, the MAH has taken the opportunity to correct some minor administrative errors in the labelling for the 3 products. The requested worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	09/03/2017	SmPC, Annex II and PL	
WS/0769	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC in order to revise the wording regarding mitochondrial dysfunction following assessment of responses to a relevant LEG and after analysis of the final CSR of the	01/04/2016	09/03/2017	SmPC and PL	Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia,

	Mitochondrial Toxicity in Children (MITOC) Study (WE027/WWE112888). The Package leaflet is updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed in utero to nucleos(t)ide analogues, that present with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.
WS/0888/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/01/2016	07/04/2016	SmPC and PL	
IA/0093	A.7 - Administrative change - Deletion of manufacturing sites	12/01/2016	n/a		
WS/0755	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 5.1 of the SmPC in order to include information regarding the absence of antagonist	17/09/2015	07/04/2016	SmPC	This procedure update section 5.1 of the SmPC in order to include information regarding the absence of antagonist effects in vitro between the active substances and other retrovirals.

	effects in vitro between the active substances and other retrovirals. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0090	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	11/09/2015	n/a		
IB/0089/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	14/08/2015	n/a		
IB/0088	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	10/07/2015	n/a		
WS/0733	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 4.1, 4.2, 4.3, 4.4 and 4.8 of the SmPC to revise the information on hypersensitivity reactions in line with a recent revision of the Triumeq	02/07/2015	07/04/2016	SmPC and PL	In this worksharing variation, the information related to hypersensitivity reactions (HSR) to abacavir sulfate (ABC) has been revised to provide a more condensated and less redundant description of the HSR to abacavir. The most detailed description of the HSR have been kept in section 4.8 of the SmPC under the "description of the selected adverse reactions".

	SmPC. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0082	Submission of updated RMP (version 9) in order to remove the important potential risk of viral resistance in children 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	21/05/2015	n/a		
IG/0530	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	20/05/2015	07/04/2016	Annex II and PL	
IAIN/0083	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	29/04/2015	07/04/2016	SmPC	
WS/0645	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	23/04/2015	07/04/2016	SmPC and PL	

	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 data				
WS/0673/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its	26/03/2015	n/a		

	corresponding test method				
WS/0578	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 4.2 of the SmPC with extended posology recommendations with reference to the once daily vs twice daily oral dosing regimen of ABC + 3TC in HIV-1–infected paediatric patients aged 3 months and older, and amended weight ranges for scored tablets according to the WHO recommendations, as well as sections 4.8, 5.1 and 5.2 of the SmPC with further data on pharmacokinetics, safety and efficacy based on the results of the ARROW study (COL105677), its PK substudy and the PK studies PENTA 13 and PENTA 15. The Package Leaflet has been updated accordingly. Further, an updated RMP version 5 was agreed for Ziagen during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/01/2015	26/02/2015	SmPC and PL	A randomised comparison of a regimen including once daily vs twice daily dosing of abacavir and lamivudine was undertaken within a randomised, multicentre, controlled study of HIV-infected, paediatric patients. 1206 paediatric patients aged 3 months to 17 years enrolled in the ARROW Trial (COL105677) and were dosed according to the weight - band dosing recommendations in the World Health Organisation treatment guidelines (Antiretroviral therapy of HIV infection in infants and children, 2006). After 36 weeks on a regimen including twice daily abacavir and lamivudine, 669 eligible subjects were randomised to either continue twice daily dosing or switch to once daily abacavir and lamivudine for at least 96 weeks. Of note, from this study clinical data were not available for children under one year old. Virological Response Based on Plasma HIV-1 RNA less than 80 copies/ml at Week 48 and Week 96 in the Once Daily versus Twice Daily abacavir + lamivudine randomisation of ARROW (Observed Analysis): Week 0 (After ≥36 Weeks on Treatment): Plasma HIV-1 RNA <80 c/mL Twice daily N(%): 250/331 (76) Once daily N(%): 237/335 (71) Risk difference (once daily-twice daily) -4.8% (95% CI -11.5% to +1.9%), p=0.16 Week 48: Plasma HIV-1 RNA <80 c/mL Twice daily N(%): 242/331 (73) Once daily N(%): 236/330 (72) Risk difference (once daily-twice daily) -1.6% (95%

					CI -8.4% to +5.2%), p=0.65 Week 96: Plasma HIV-1 RNA <80 c/mL Twice daily N(%): 234/326 (72) Once daily N(%): 230/331 (69) Risk difference (once daily-twice daily) -2.3% (95% CI -9.3% to +4.7%), p=0.52 No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults. In a pharmacokinetic study (PENTA 15), four virologically controlled subjects less than 12 months of age switched from abacavir plus lamivudine oral solution twice daily to a once daily regimen. Three subjects had undetectable viral load and one had plasmatic HIV-RNA of 900 copies/ml at Week 48. No safety concerns were observed in these subjects. The abacavir + lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group according to the pre-specified non-inferiority margin of -12%, for the primary endpoint of <80 c/mL at Week 48 as well as at Week 96 (secondary endpoint) and all other thresholds tested (<200c/mL, <400c/mL, <1000c/mL), which all fell well within this non-inferiority margin. Subgroup analyses testing for heterogeneity of once vs twice daily demonstrated no significant effect of sex, age, or viral load at randomisation. Conclusions supported non-inferiority regardless of analysis method. In a separate study comparing the unblinded NRTI

					combinations (with or without blinded nelfinavir) in children, a greater proportion treated with abacavir and lamivudine (71%) or abacavir and zidovudine (60%) had HIV-1 RNA □400 copies/ml at 48 weeks, compared with those treated with lamivudine and zidovudine (47%)[p=0.09, intention to treat analysis]. Similarly, greater proportions of children treated with the abacavir containing combinations had HIV-1 RNA □50 copies/ml at 48 weeks (53%, 42% and 28% respectively, p=0.07).
WS/0543	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To add an alternative test method for the active substance. 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	25/09/2014	n/a		
WS/0542	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Change of specification of abacavir sulphate to comply with the Ph.Eur.. B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply	25/09/2014	n/a		

	with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS				
PSUV/0079	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
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		
IG/0410/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 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.b.2.a - Change in test procedure for AS or 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	28/03/2014	n/a		
R/0071	Renewal of the marketing authorisation.	23/01/2014	21/03/2014	SmPC, Annex II and PL	Based on the review of the available information and on the basis of a re-evaluation of the benefit risk balance, the

					CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Ziagen continues to be favourable. The CHMP is of the opinion that the renewal can be granted with unlimited validity.
IA/0072/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.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.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.1.i - Change in the specification parameters and/or limits of the finished product - Ph. Eur. 2.9.40 uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 or Ph. Eur. 2.9.6	05/03/2014	n/a		
IB/0070	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	26/09/2013	n/a		

IB/0069	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	24/08/2013	21/03/2014	SmPC, Annex II and PL	
IG/0295	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	29/04/2013	n/a		
WS/0338	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to expand existing warning about immune reactivation syndrome with information on autoimmune disorders. The Package Leaflet is updated accordingly. In addition, the list of local representatives was updated in the Package Leaflet. Furthermore, the product information is being brought in line with the latest QRD template version 8.3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/02/2013	26/03/2013	SmPC, Annex II, Labelling and PL	The review performed by the Marketing Authorisation Holder identified 75 cases of different autoimmune disorders occurring in the setting of immune reconstitution. These included Basedow's/Graves' disease, systemic lupus erythematosus, sarcoidosis, rheumatoid arthritis, polymyositis, Guillain-Barré syndrome, Still's syndrome and myasthenia gravis. Cases involving zidovudine, lamivudine, abacavir and fosamprenavir were identified. These disorders all developed when CD4 count was increased or increasing and viral load undetectable. The autoimmune disorders resolved (or improved) spontaneously or with specific therapy and while Anti-Retroviral Therapy was continued. Most of cases had a relatively late onset following Anti-Retroviral Therapy initiation except cases of Guillain-Barré syndrome and adult onset Still's disease. The time to onset ranged from 2 weeks to 37 months. While it was recognised that the number of cases is small, the long and variable time to onset probably causes underreporting of such adverse reactions and therefore little is known on the exact pathogenesis and the risk factors. The CHMP agreed that information about

					autoimmune disorders occurring in the context of immune reconstitution should be reflected in the product information.
WS/0163	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Introduction of a new Detailed Description of the Pharmacovigilance System (DDPS), following the transfer of the marketing authorisation/scientific opinion from GSK to ViiV Healthcare Ltd. This DDPS had previously been assessed for another product of the same MAH/SOH. Annex IIB of Epivir, Kivexa, Lamivudine ViiV and Trizivir have consequently been updated in line with the new QRD template wording for the DDPS. In addition the MAH corrected a minor mistake in the French Annex for Epivir. C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH	21/06/2012	21/06/2012	Annex II	Update of the Detailed Description of the Pharmacovigilance System (DDPS) to ViiV Healthcare Ltd version 4 dated May 2012.
IAIN/0065	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	18/11/2011	21/06/2012	Annex II and PL	
II/0062	Update of sections 4.4 and 4.5 of the SmPC to alert on the possible reduction of SVR in ABC/RBV co-treated patients as requested by the CHMP (RMP084). The MAH took the opportunity to reorganize the existing information on Liver Disease	22/09/2011	24/10/2011	SmPC, Annex II, Labelling and PL	Section 4.4 of the SmPC has been updated with a warning that caution should be exercised when ABC and RBV are co-administered. Conflicting clinical findings are reported in the literature with some data suggesting that HIV/HCV co-infected patients receiving abacavir-containing ART may be

	in section 4.4 to improve clarity. The address of the local representative for Spain and Cyprus was corrected in the PL. Minor corrections were made in the German labelling and PL, and in the Greek PL. Annex II was amended to reflect the three yearly PSUR cycle, as requested following PSU083. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				at risk of a lower response rate to pegylated interferon/ribavirin therapy. A possible intracellular mechanism has been postulated that ABC and RBV (two guanosine analogues) may be competing for the enzymes of a shared phosphorylation pathway. This could lead to a reduction in intracellular phosphorylated metabolites of ribavirin and, as a potential consequence, a reduced chance of sustained virological response (SVR) for Hepatitis C (HCV) in HCV co-infected patients treated with pegylated interferon plus RBV. Section 4.5 has also been updated accordingly.
IA/0063	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 currently approved batch size	19/10/2011	n/a		
IA/0061	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	09/03/2011	n/a	SmPC, Annex II, Labelling and PL	
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/07/2010	05/08/2010	PL	
T/0058	Transfer of Marketing Authorisation	29/03/2010	10/05/2010	SmPC, Labelling and PL	

IB/0057	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	03/02/2010	n/a		
IB/0056	IB_10_Minor change in the manufacturing process of the active substance	27/01/2010	n/a		
II/0055	The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "steps after the authorisation" will be updated as follows: Changes to QPPV Update of DDPS (Pharmacovigilance)	17/12/2009	20/01/2010	Annex II	The DDPS has been updated (version 7.2) to reflect the change of the QPPV as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements.
II/0054	Update of section 4.1 "Therapeutic indications", section 4.4 "Special warnings and precaution for use" and section 4.8 "Undesirable Effects" of the SPC to improve clarity for prescribers on HLA-B*5701 screening and the clinical management of abacavir (ABC) hypersensitivity reaction (HSR), as requested in the CHMP's assessment of the abacavir PSUR covering the period 01 January 2008 to 31 December 2008. The information on the HSR incidence was revised. Section 2 "Before you take Ziagen" of the PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	22/10/2009	20/11/2009	SmPC and PL	There has been one report of a case of hypersensitivity reaction (HSR) against the active substance abacavir at re-initiation of treatment in a patient who previously had well tolerated this medicinal product. However afterwards, this patient was tested positive for the gene HLA-B*5701, which is associated with a higher HSR risk. There have also been case reports of HSR in patients who already had shown HSR symptoms before, but were tested HLA-B*5701 negative. Based on these facts, it was regarded as necessary to amend the recommendation for HLA-B*5701 testing before re-initiation of abacavir treatment and to highlight that HSR can also occur in HLA-B*5701 negative patients in the Product Information. Regarding the latter issue, also the information on HSR incidence was updated and is now reflecting the still significant HSR incidence obtained for HLA-B*5701 negative patients in recent studies which differentiated between HLA-B*5701 negative

					and positive patients.
IA/0053	IA_09_Deletion of manufacturing site	23/07/2009	n/a		
II/0049	Update of Summary of Product Characteristics, Labelling and Package Leaflet To update section 4.4 of the SPC and section 2 of the Package Leaflet for Ziagen Tablets and Ziagen Oral Solution to include information regarding abacavir use and the potential increased risk of myocardial infarction. Annex IIIA was updated with information in Braille. Furthermore, the contact details for Denmark and Slovakia were updated in the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/04/2009	08/06/2009	SmPC, Labelling and PL	In April 2008 EMEA issued a press release on an association between the use of abacavir and the risk of myocardial infarction shown in an observational study (DAD study). Since then additional data derived from observational studies and clinical trials have become available on this issue including FHDH study. Observational studies have shown an association between myocardial infarction and the use of abacavir. The patients studied have generally received antiretroviral treatment prior inclusion in the study (experienced patients). There were limited numbers of myocardial infarction in data from clinical trials and a small increase in risk could not be excluded. The data available so far present some inconsistencies and can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there is no established biological mechanism to explain a potential increase in risk. The CHMP concluded that on the basis of the data available no recommendation could be made for changing the therapeutic management of patients. When prescribing Ziagen action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). The SPC and package leaflet of abacavir-containing medicinal products will be updated to reflect this information.

R/0051	Renewal of the marketing authorisation.	19/03/2009	29/05/2009	SmPC and Labelling	Based on the CHMP review of the available information , the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Ziagen continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation for Ziagen. However due to the abacavir safety profile (hypersensitivity reaction and the concerns currently being evaluated: potential association with myocardial infarction and shorter time to virological failure observed with lamivudine-abacavir fixed dose combination) the CHMP is of the opinion that one additional five-year renewal on the basis of pharmacovigilance grounds is required.
II/0052	Update of DDPS (Pharmacovigilance)	19/02/2009	07/04/2009	Annex II	The DDPS has been updated (version 6.2) to reflect the change of the Qualified Person for Pharmacovigilance (QPPV) as well as to notify other changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
II/0048	To update sections 4.2 "Posology and method of administration" and 5.2 "Pharmacokinetic properties" of the Summary of Product Characteristics relating to administration of crushed tablets with food and liquid further to CHMP request following assessment of the FUM 28 in February 2008. Section 3 of the Package Leaflet was updated accordingly. The MAH also took the opportunity to update section 6 of the Package Leaflet with new contact details for	24/07/2008	02/09/2008	SmPC and PL	Studies concerning the administration of crushed tablets with a small amount of semi-solid food or liquid show that the tablets can be crushed and then administered with small amount of semi-solid food or liquid without pharmaceutical quality impact. This information is useful for the treatment of paediatric patients who cannot swallow tablets and also for adults in difficulties in swallowing.

	the local representative in Latvia in both pharmaceutical forms. Update of Summary of Product Characteristics and Package Leaflet				
IA/0050	IA_05_Change in the name and/or address of a manufacturer of the finished product	03/07/2008	n/a		
II/0045	Update of Summary of Product Characteristics and Package Leaflet	24/01/2008	29/02/2008	SmPC and PL	
IB/0047	IB_33_Minor change in the manufacture of the finished product	31/01/2008	n/a		
II/0042	Update of Summary of Product Characteristics, Annnex II, labelling and Package Leaflet To update sections 3 and 4.2 to replace film coated tablets by scored film coated tablets for use by paediatric patients. Sections 3 and 6 of the PL and labelling were updated accordingly. Furthermore, the MAH has submitted a detailed description of the Pharmacovigilance System. Update of Summary of Product Characteristics, Labelling and Package Leaflet	18/10/2007	20/11/2007	SmPC, Annex II, Labelling and PL	In order to address the need in children of anti-HIV medicines, the MAH has further developed the Ziagen scored tablet to include a score line. Due to the new form the tablet can be now halved (or broken in two) for paediatric use. The MAH has substantiated the safety and efficacy of this regimen. Moreover, an independent study (to evaluating the management of antiretroviral therapy in symptomatic HIV infected infants and children in Africa) is ongoing that is expected to give further reassurance in this field. Furthermore, The MAH committed to perform a proactive pharmacovigilance survey to detect any signal towards a deterioration of the safety profile of zidovudine and to complete a safety review on a 6 monthly basis on paediatric data for the scored tablets.
IB/0046	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	08/11/2007	n/a		

IA/0044	IA_05_Change in the name and/or address of a manufacturer of the finished product	03/09/2007	n/a	Annex II and PL	
II/0043	To update section 5.2 of the SPC to include the results from a study evaluating abacavir pharmacokinetics in HIV infected patients in relation to FUM 52.1. Update of Summary of Product Characteristics	19/07/2007	27/08/2007	SmPC	The MAH provided the results of a study to support the once daily regimen for abacavir. This study demonstrated that the pharmacokinetic parameters of CBV-TP (carbovir triphospate, active metabolite of abacavir) where higher with the abacavir once daily regimen than with the abacavir twice daily regimen.
II/0041	Update of Summary of Product Characteristics To update section 5.1 of the Summary of Product Characteristics (SPC) with information on resistance to abacavir, based on an analysis of resistance data derived from pertinent clinical trials and in response to the MAH commitment made in variation II/38. Update of Summary of Product Characteristics	24/04/2007	30/05/2007	SmPC	Based on results from the available relevant studies, the SPC has been updated with information on the resistance pattern of abacavir, in particular on the mutation pejorative to the virological response of abacavir, since this information could be clinically helpful. The information is now presented for in vitro resistance and for in vivo resistance in therapy naïve patients as well as therapy experienced patients. Concerning in vivo resistance in therapy naïve patients, isolates from most patients experiencing virological failure with a regimen containing abacavir in pivotal clinical trials showed either no NRTI-related changes from baseline or only M184V or M184I selection. Concerning in vivo resistance in therapy experienced patients, a clinically significant reduction of susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors. Phenotypic resistance to abacavir requires M184V with at least one other abacavir-selected mutation, or M184V with multiple thymidine analogue

					mutations. The currently recommended resistance algorithms can help in the appropriate use of abacavir.
II/0040	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.4 and section 4.8 of the SPC and section 2 of the PL to implement the class labelling text on osteonecrosis, agreed by the CHMP in September 2006. In addition the MAH completed the list of local representatives in the PL to include the two new EU Member States (Bulgaria and Romania) according to the latest EMEA/QRD template. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	17/01/2007	SmPC and PL	Cases of osteonecrosis (death of the bone tissue resulting from an insufficient blood supply) have been reported in HIV-infected patients since the end of the 80's. Although the cause of this disease could be due to multi factors (including the use of corticosteroids, alcohol consumption, severe immunosuppression, higher body mass index) it has occurred specially in patients with HIV advanced disease and/or in patients with long term use of combination antiretroviral therapy (CART). Further to the review of all available data the CHMP agreed that this information should now be included in the SPC and PL of all antiretroviral medicinal products. Patients should be warned to seek medical advice in case they experience joint stiffness, aches and pain especially of the hip, knee and shoulder or if they experienced any difficulty in movement.
II/0038	To update section 5.1 of the SPC with new information relating to study ACTG5095 Update of Summary of Product Characteristics	18/10/2006	28/11/2006	SmPC	ACTG5095 is a randomised, double-blind, placebo controlled study performed in antiretroviral-naïve HIV-1 infected adults and aiming at comparing 3 regimens: zidovudine/ lamivudine/ abacavir/ efavirenz vs zidovudine/ lamivudine/ efavirenz vs zidovudine/ lamivudine/ abacavir (Trizivir). The tritherapy with zidovudine/ lamivudine/ abacavir (Trizivir) was shown to induce a significantly higher rate of virologic failure as compared to a tritherapy with efavirenz. Furthermore, it was demonstrated that there is no benefit of adding abacavir to a tritherapy with efavirenz.
II/0037	To update sections 4.4 and 4.8 of the SPC and	18/10/2006	28/11/2006	SmPC, Annex	A review of genetic risk factors for the hypersensitivity to

	section 2 of the PL with new information relating to genetic and clinical risk factors for the abacavir hypersensitivity reaction. The MAH also took the opportunity to update the product information according to the QRD template version 7.1. Update of Summary of Product Characteristics, Labelling and Package Leaflet			II, Labelling and PL	abacavir has shown that Caucasian patients with the HLA-B*5701 allele are more likely to develop a hypersensitivity reaction to abacavir. Analyses of clinical risk factors for the hypersensitivity to abacavir have identified the risk for Black patients to be approximately half the risk for other racial groups combined. However, since approximately 5% of patients receiving abacavir develop a hypersensitivity reaction, the risk for Black patients is of the same magnitude as for other racial groups and the same close monitoring should apply to patients of all racial groups.
IA/0039	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	31/10/2006	n/a		
II/0033	Change(s) to the manufacturing process for the active substance	01/06/2006	07/06/2006		
IA/0036	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	24/05/2006	n/a		
IA/0035	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	31/03/2006	n/a	Annex II and PL	
IA/0034	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	31/03/2006	n/a		
IA/0032	IA_09_Deletion of manufacturing site	06/01/2006	n/a	Annex II and PL	
IB/0031	IB_14_b_Change in manuf. of active substance	22/12/2005	n/a		

	without Ph. Eur. certificate - new manufacturer				
II/0030	Update of Summary of Product Characteristics and Package Leaflet	15/09/2005	07/11/2005	SmPC and PL	
II/0029	Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	08/09/2005	SmPC and PL	
IA/0028	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	13/05/2005	n/a		
II/0027	Update of Summary of Product Characteristics and Package Leaflet	18/11/2004	17/12/2004	SmPC, Annex II and PL	
II/0026	Update of Summary of Product Characteristics and Package Leaflet	16/09/2004	28/10/2004	SmPC and PL	
II/0020	Update of Summary of Product Characteristics and Package Leaflet	16/09/2004	28/10/2004	SmPC and PL	
R/0025	Renewal of the marketing authorisation.	03/06/2004	18/08/2004	SmPC, Annex II, Labelling and PL	
II/0024	Update of Summary of Product Characteristics and Package Leaflet	22/04/2004	26/05/2004	SmPC and PL	
IB/0022	IB_10_Minor change in the manufacturing process of the active substance	13/02/2004	n/a		
IA/0023	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	10/02/2004	n/a		

II/0019	Update of the section 4.4 "Special warnings and special precautions of use" of the Summary of Product Characteristics (SPC) to implement the class labelling on liver impairment adopted by the CPMP for all anti-retroviral medicinal products in April 2003. The section 2 of the Package Leaflet (PL) is amended accordingly. Furthermore, the MAH has taken this opportunity to update the section 4.8 "Undesirable effects" of the SPC by reordering the wording on skin reactions and the PL in section 4 to revise the wording on lipodystrophy as adopted by the CPMP in March 2003 and in section 6 to update the local representative in Luxembourg. The MAH also updated the SPC and PL accortding to the latest EMEA / QRD templates. Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	30/01/2004	SmPC and PL	
IA/0021	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	29/10/2003	n/a		
II/0018	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	14/07/2003	SmPC and PL	
I/0015	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	25/02/2003	08/04/2003	Annex II and PL	
I/0016	08_Change in the qualitative composition of immediate packaging material	19/03/2003	26/03/2003		

I/0017	25_Change in test procedures of the medicinal product	14/02/2003	26/02/2003		
I/0014	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	14/02/2003	26/02/2003		
II/0009	Update of Summary of Product Characteristics and Package Leaflet	25/07/2002	28/10/2002	SmPC and PL	
I/0013	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	02/07/2002	11/07/2002		
I/0012	13_Batch size of active substance	02/07/2002	11/07/2002		
I/0011	12_Minor change of manufacturing process of the active substance	02/07/2002	11/07/2002		
I/0010	11_Change in or addition of manufacturer(s) of active substance	02/07/2002	11/07/2002		
II/0006	Update of Summary of Product Characteristics and Package Leaflet	27/06/2001	24/10/2001	SmPC, Labelling and PL	
II/0005	Extension of Indication	27/06/2001	24/10/2001	SmPC, Labelling and PL	
I/0008	24a_Change in test procedure for starting material/intermediate used in manuf. of active	09/10/2001	23/10/2001		

	substance				
I/0007	12_Minor change of manufacturing process of the active substance 12a_Change in specification of starting material/intermediate used in manuf. of the active substance	09/10/2001	23/10/2001		
I/0004	20_Extension of shelf-life as foreseen at time of authorisation	19/01/2001	26/03/2001	SmPC	
II/0003	Update of Summary of Product Characteristics and Package Leaflet	19/10/2000	22/02/2001	SmPC, Labelling and PL	
II/0002	Update of Summary of Product Characteristics, Labelling and Package Leaflet	25/05/2000	25/05/2000	SmPC, Labelling and PL	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/11/1999	15/02/2000	Labelling and PL	