EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Lamivudine / Zidovudine ViiV

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
WS/0755	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/09/2015		SmPC	

[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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WS/0645	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.6 of the SmPC to include the WHO guidelines on breastfeeding. The Package Leaflet has been updated accordingly. In addition, the WSA has taken the opportunity to promote consistency across products by updating where relevant (i.e. for Trizivir, Combivir, Lamivudine/Zidovudine ViiV and Triumeq), the pharmacokinetic statements in section 4.6 of the SmPC to reflect the most recently approved wording for the components abacavir and lamivudine (Kivixa EMEA/H/C/581/R/0051 and Epivir EMEA/H/C/107/II/0084). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/04/2015		SmPC and PL	
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	25/04/2014		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.

	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				
IG/0348	B.III.1.a.4 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Deletion of certificates (in case multiple certificates exist per material)	21/08/2013	n/a		
IG/0342	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	21/08/2013	n/a		
IG/0295	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	29/04/2013	n/a		
WS/0361	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 in order to reflect a potential drug-drug interaction between lamivudine and cladribine. This labelling update has been assessed via a separate Type II variation procedure (Zeffix; EMEA/H/C/242/II/53) with confirmation that the change should also be implemented for other lamivudine containing ViiV marketed HIV products as listed above. The Package Leaflet was updated accordingly and an error in Trizivir SmPC in one of the sub-headings in	25/04/2013	25/04/2013	SmPC and PL	The drug-drug interaction between lamivudine and cladribine (CdA) was assessed in a type II variation of Zeffix (EMEA/H/C/242/II/53) based on a publication by Chtioui et al (Concomitant treatment with lamivudine renders cladribine inactive by inhibition of its phosphorylation. Br.J.Haematology. 2008; 144: 136-137). This article described a patient with chronic lymphoid leukaemia who was treated with CdA and Zeffix. No decrease of the peripheral blood lymphocyte count was observed after the first cycle of CdA. Zeffix was discontinued and the lymphocyte count decreased following the second and third cycles of CdA. The authors suspected a potential interaction based on intracellular phosphorylation when both medicines are administered

	the tabular summary of interaction information was also amended. 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				concomitantly. In addition, an in vitro study was carried out using peripheral blood mononuclear cells isolated from a healthy volunteer. This in vitro study showed that phosphorylated CdA levels were decreased with increasing 3TC concentrations.
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	25/04/2013	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.

IG/0205	B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions	30/07/2012	n/a		
IG/0191/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.7 - Administrative change - Deletion of manufacturing sites B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	25/06/2012	n/a		
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.	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.

	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				
II/0027	Update of sections 4.4, 4.5, 4.6 and 5.1 of the SmPC in fulfilment of commitments (FUM 006) related to all antiretroviral agents containing lamivudine based on clinical experience gained on the use of lamivudine during pregnancy and on new information available on interactions. The PL was updated accordingly. In addition, minor corrections have been made to section 4.4 in line with the new QRD guideline. 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	17/03/2011	n/a	SmPC, Annex II and PL	
II/0028	Update of section 4.8 of the SmPC to add 'angioedema' as a new adverse event in fulfilment of PSU 007 (covering period 01.12.06 - 30.11.09 and concerning all lamivudine-containing products). The PL has been revised accordingly. 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	23/09/2010	n/a	SmPC and PL	

T/0026	Request for a change of Article 58 Scientific Opinion Holder for Lamivudine/Zidovudine GSK from GSK Group Ltd. to ViiV Healthcare UK Ltd. Transfer of Marketing Authorisation	24/06/2010	24/06/2010	SmPC, Labelling and PL	
II/0025	Changes to QPPV Update of DDPS (Pharmacovigilance)	17/12/2009	n/a	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 SOH fulfils the requirements.
II/0024	Update of DDPS (Pharmacovigilance)	19/02/2009	n/a	SmPC and 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.
IA/0023	IA_06_a_Change in ATC code: Medicinal products for human use	27/08/2008	n/a	SmPC	
IA/0022	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	28/07/2008	n/a		
IA/0021	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	28/07/2008	n/a		
IA/0020	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	28/07/2008	n/a		

II/0019	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. Update of Summary of Product Characteristics and Package Leaflet	24/07/2008	n/a	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.
II/0018	Change(s) to the manufacturing process for the active substance	24/01/2008	n/a		
IB/0017	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	05/11/2007	n/a	Annex II and PL	
II/0012	Update of Summary of Product Characteristics and Package Leaflet. This variation relates to the update of sections 4.4 "Special warnings and precautions for use" and 4.5 "Interaction with other medicinal products and other forms of interaction" of the Summary of Product Characteristics (SPC) concerning interactions relevant to zidovudine with clarithromycin and ribavirin and to the harmonisation of the information on interactions for all zidovudine containing products. Section 2 of the Package Leaflet (PL) was updated accordingly.	18/10/2007	n/a	SmPC and PL	Following the European Mutual Recognition renewal application for zidovudine (Retrovir), the Summary of Products Characteristics (SPC) and the Package Leaflet (PL) of Retrovir were modified as regards the interaction with ribavirin and clarithromycin. The interaction between ribavirin and zidovudine was removed and a statement referring that clarithromycin tablets reduce the absorption of zidovudine was introduced. The SOH has submitted type II variation applications for the other medicinal products containing zidovudine (Combivir, Lamivudine/Zidovudine GSK and Trizivir) to update the information to be in line with the Retrovir SPC and PL.

	Update of Summary of Product Characteristics and Package Leaflet				Furthermore, there is now a lot of evidence from clinical trials and from literature that concomitant use of zidovudine and ribavirin is associated with a greater risk of anaemia. The consensus conference on the treatment of HCV/HIV co-infected patients already recommended that the use of zidovudine should be avoided due to an excess risk of anaemia. The CHMP took the opportunity of this variation to check the consistency concerning the information on interactions relevant to zidovudine and to harmonise the product information of the products containing zidovudine.
II/0011	Update of summary of product characteristics, annex II, labelling and package leaflet Extension of indication to paediatric patients and replacement of film coated tablets by scored film coated tablets. Furthermore, the SOH took the opportunity of this variation to split the outer carton and bottle label. Extension of Indication	20/09/2007	20/09/2007	SmPC, Annex II, Labelling and PL	This will refer to the scientific discussion of this assessment report.
II/0016	Update of Summary of Product Characteristics	19/07/2007	n/a	SmPC	The SOH submitted this type II variation II/16 (corresponding by analogy, to a Type II variation pursuant to Commission Regulation (EC) 1085/2003) to update the section 5.1 of the SPC by adding information to discourage the maintenance of lamivudine in presence of M184V mutation when other active Nucleoside Reverse Transcriptase Inhibitors (NRTIs) are available following CHMP request dated 18 October 2006. This request was driven by the renewal of the marketing authorisation (R/52) for Epivir (lamivudine), which is a centrally authorised NRTIs indicated in antiretroviral combination

					therapy for the treatment of Human Immunodeficiency Virus (HIV) infection.
II/0009	Update of or change(s) to the pharmaceutical documentation	22/03/2007	n/a		
IA/0014	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	26/02/2007	n/a		
II/0007	Update of or change(s) to the pharmaceutical documentation	22/02/2007	n/a		
IA/0015	IA_06_a_Change in ATC code: Medicinal products for human use	20/02/2007	n/a	SmPC	
IB/0010	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	16/02/2007	n/a		
IA/0008	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	23/01/2007	n/a		
II/0006	Update of Summary of Product Characteristics, Labelling 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. Furthermore, the SOH updated the PI according to the latest version of the QRD template.	14/12/2006	14/12/2006	SmPC, Labelling 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

	Update of Summary of Product Characteristics and Package Leaflet				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 experienced joint stiffness, aches and pain especially of the hip, knee and shoulder or if they experienced any difficulty in movement.
IB/0004	IB_17_a_Change in re-test period of the active substance	07/08/2006	n/a		
IA/0005	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	20/07/2006	n/a		
IB/0002	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	27/03/2006	n/a		
IB/0001	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	27/03/2006	n/a		
IA/0003	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	01/03/2006	n/a		