Lamivudine 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	
II/0024	Update to section 4.6 of the SmPC to reflect updated exposure data relating to the use of lamivudine in the treatment of HIV-1 in pregnant women. In addition, the MAH took this opportunity to include a warning in section 4.5 of the SmPC regarding drug interaction with cytidine analogues and other medicinal products containing lamivudine, in line with the existing warning in section 4.4. Moreover, the SmPC and the Package Leaflet are updated in line with the latest QRD template (version 9.0). C.I.4 - Change(s) in the SPC, Labelling or PL due to	23/10/2014		SmPC and PL	The SOH produced a bibliographic research (especially clinical studies and data from the Antiretroviral Pregnancy Registry) to gather additional safety data about the use of lamivudine in pregnant women. Overall, these data confirmed the lack of impact on birth defects, birth weight and prematurity when a lamivudine-containing regimen is used compared to other ARV regimen. This supports the lamivudine product information about HIV-infected pregnant women, which states that lamivudine can be used during pregnancy if clinically needed. The benefit/risk balance of Lamivudine ViiV remains unchanged.

	new quality, preclinical, clinical or pharmacovigilance data				
IG/0438	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	16/05/2014	n/a		
WS/0544	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC with a revised wording on the risk of transmission as requested by the CHMP. The PL has been updated accordingly. In addition, minor corrections are made to translations and an editorial change is implemented in Trizivir PL. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/04/2014		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.
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	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

	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 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				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 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.
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.
II/0018	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) and to update the AE frequency category in line with the latest SmPC guideline. The PL has been revised accordingly. Moreover the PSUR cycle in Annex II was updated.	23/09/2010	n/a	SmPC, Annex II and PL	Section 4.8 of the SmPC has been amended with the addition of the new adverse event “angioedema” and the calculation of its frequency (rare). The frequency category for undesirable effects was reworded to be in line with the latest SmPC guideline. The PL was modified accordingly. Moreover the PSUR cycle in Annex II was updated to a three yearly cycle.

	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				
T/0017	Request for a change of Article 58 Scientific Opinion Holder for LamivudineGSK from GSK Group Ltd. to ViiV Healthcare UK Ltd. Transfer of Marketing Authorisation	24/06/2010	24/06/2010	SmPC, Labelling and PL	
II/0016	To update sections 4.4, 4.5 and 4.6 of the Lamivudine GSK SPC to harmonise the content with the Zeffix SPC in order to fulfil the SOH commitment during the Zeffix renewal procedure. Section 2 (Taking other medicines) of the PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	n/a	SmPC and PL	Since the active substance of Zeffix is lamivudine (approved for the treatment of Hepatitis B), the changes of the product information adopted during the Zeffix renewal were reflected in the Lamivudine GSK product information. These changes include: the revision of section 4.6 to give consistent message regarding the clinical experience gained on the use of lamivudine during pregnancy; the addition of information that lamivudine should not be taken with drugs containing lamivudine or emtricitabine in section 4.4 and the deletion of information regarding the co-administration of lamivudine with ganciclovir or foscarnet in section 4.5. Furthermore, reference to zalcitabine was removed from the product information since this medicine is no longer marketed.
II/0015	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	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.

	FUM 28 in February 2008. Section 3 of the Package Leaflet was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				This information is useful for the treatment of paediatric patients who cannot swallow tablets and also for adults in difficulties in swallowing.
II/0014	Change(s) to the manufacturing process for the active substance	24/01/2008	n/a		
IB/0013	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/0011	Update of Summary of Product Characteristics and Package Leaflet To update sections 3, 4.2 and 5.2 of the SPC to replace film coated tablets by scored film coated tablets for use by paediatric patients. Sections 3 and 6 of the PL were updated accordingly. Furthermore, the SOH took the opportunity of this variation to split the outer carton and bottle label and to introduce a minor change in the PL. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	20/09/2007	SmPC and PL	In order to address the need in children on anti-HIV medicines, the MAH has further developed the Epivir tablet to include a score line. Due to the new form the tablet can now be halved (or broken in two) for use by paediatric patients.
II/0012	To update section 5.1 of the SPC concerning the emergence of M184V mutation following CHMP request dated 18 October 2006.	19/07/2007	n/a	SmPC	The SOH submitted this type II variation II/12 (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

	Update of Summary of Product Characteristics				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/0008	Update of or change(s) to the pharmaceutical documentation	22/03/2007	n/a		
IB/0009	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	22/03/2007	n/a		
IA/0010	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 section 5.2 of the SPC to include additional wording relating to the reduced exposure to lamivudine in children less than 6 years of age, following the CHMP request in September 2006. Update of Summary of Product Characteristics	24/01/2007	24/01/2007	SmPC	The lower exposure to lamivudine observed in younger children (<6 years old) when compared to older children (?6 years old) in pharmacokinetic studies conducted in children together with data from re-analysis of a clinical trial in HIV infected children tend to show that a better virologic suppression was achieved in children aged ?6 years old. The CHMP acknowledge that no statistically significant difference was observed in this clinical study. However, the results are not so far from statistical significance and the small sample size should be taken into account. Overall these data cannot be regarded as reassuring on the

					lamivudine regimens to recommend in children aged from 3 months to 6 years. The CHMP considers that these data should prompt a cautious attitude with regard to the clinical impact of the lower lamivudine exposure identified in younger children (<6 years old) when compared to older children. Therefore, the CHMP requested in September 2006 that section 5.2 of the SPC should be updated to include some additional wording illustrating this finding.
II/0006	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. Update of Summary of Product Characteristics and Package Leaflet	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 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.
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	02/03/2006	n/a		