Zeffix

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
IA/0088	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)	15/03/2024	n/a		

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

II/0087	Update of section 4.4 of the SmPC in order to amend an existing warning on HIV/HBV co-infection, particularly regarding the importance of HIV testing and the risk of HIV resistance with subtherapeutic doses of lamivudine and/or monotherapy in patients with HIV/HBV co-infection. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/02/2024		SmPC and PL	The following update of section 4.4 of the SmPC was considered to further contribute to the adequate management of patients co-infected with hepatitis B virus (HBV) and HIV: The 100 mg usual dose of lamivudine used for the treatment of HBV is not appropriate for patients who acquire HIV or are co infected with HBV and HIV. If a patient with unrecognised or untreated HIV infection is prescribed the dose of lamivudine recommended for the treatment of HBV, rapid emergence of HIV resistance and a limitation of treatment options is likely to result because of the subtherapeutic dose and the inappropriate use of monotherapy for HIV treatment. HIV counselling and testing should be offered to all patients before beginning treatment with lamivudine for HBV and periodically during treatment.
IB/0086/G	This was an application for a group of variations. B.II.c.z - Change in control of excipients in the Finished Product - Other variation B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	25/10/2023	n/a		
IB/0085/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	20/10/2023	n/a		

	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				
IAIN/0084	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	18/07/2022	17/07/2023	Annex II and PL	
II/0083	Update of sections 4.9 of the SmPC in order to update the Overdosage of the GDS for lamivudine-human immunodeficiency virus (HIV) information based on the safety database. The section 3 of 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	23/09/2021	18/11/2021	SmPC and PL	Based on safety database, the overdose symptoms and signs text of the SmPC has been updated. Accordingly the package leaflet has been updated as well. For more information, please refer to the Summary of Product Characteristics.
II/0082	Update of section 5.2 of the SmPC in order to update pharmacokinetic information based on results from bioavailability studies (204993 and 204994) with lamivudine-containing products. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/09/2021	18/11/2021	SmPC	Based on observed results from bioavailability studies with lamivudine-containing products, the lamivudine elimination half-life values have been updated. For more information, please refer to the Summary of Product Characteristics.

N/0081	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/09/2021	18/11/2021	PL	
PSUSA/1824/202007	Periodic Safety Update EU Single assessment - lamivudine (chronic hepatitis B)	11/03/2021	n/a		PRAC Recommendation - maintenance
IAIN/0080/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 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	25/01/2021	18/11/2021	Annex II and PL	
IAIN/0079/G	This was an application for a group of variations. 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 A.7 - Administrative change - Deletion of manufacturing sites	25/01/2021	18/11/2021	Annex II and PL	
IA/0078	A.5.b - Administrative change - Change in the name	08/01/2021	n/a		

	and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
IB/0076	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/10/2020	18/11/2021	SmPC, Annex II, Labelling and PL	
IA/0075	A.7 - Administrative change - Deletion of manufacturing sites	08/11/2019	11/02/2020	Annex II and PL	
IAIN/0074	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	15/02/2019	11/02/2020	Annex II and PL	
T/0073	Transfer of Marketing Authorisation	12/10/2018	26/11/2018	SmPC, Labelling and PL	
IA/0072/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.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	25/05/2018	n/a		

	manufacturer of a novel excipient				
II/0069	Update of section 4.5 of the SmPC to add information regarding the interaction between lamivudine and sorbitol-containing medicines based on the results of Study 204857. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement a minor change in the labelling in line with the QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/01/2018	26/11/2018	SmPC, Labelling and PL	Study 204857 was undertaken to evaluate the effect of sorbitol on the pharmacokinetics of lamivudine. The study concluded that concomitant use of lamivudine with chronic administration of sorbitol containing medicines may reduce the exposure of lamivudine, possibly resulting in reduced virologic suppression or viral resistance. Co-administration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose (Adult HIV daily dose) of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC) and 28%, 52%, and 55% in the Cmax of lamivudine in adults. When possible, avoid chronic co-administration of Zeffix with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HBV viral load when chronic co-administration cannot be avoided.
IB/0071/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters	11/01/2018	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IB/0070	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	27/04/2017	n/a		
II/0068	Update of sections 4.4 and 4.6 of the SmPC to reflect pregnancy clinical outcome data from the Antiretroviral Pregnancy Registry (APR). In addition, an introductory paragraph for pregnancy has been added to section 4.6 of the SmPC in line with Epivir (lamivudine for Human Immunodeficiency Virus Indication) (variation II/84). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/02/2017	22/05/2017	SmPC	There is limited information available on maternal-foetal transmission of hepatitis B virus in pregnant women receiving treatment with lamivudine. Animal studies with lamivudine showed an increase in early embryonic deaths in rabbits but not in rats. Placental transfer of lamivudine has been shown to occur in humans. Available human data from the Antiretroviral Pregnancy Registry reporting more than 1000 outcomes from first trimester and more than 1000 outcomes from second and third trimester exposure in pregnant women indicate no malformative and foeto/neonatal effect. Less than 1% of these women have been treated for HBV, whereas the majority was treated for HIV at higher doses and with other concomitant medications. Zeffix can be used during pregnancy if clinically needed. For patients who are being treated with lamivudine and subsequently become pregnant consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of lamivudine.
IB/0067	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/06/2016	22/05/2017	SmPC and PL	
PSUSA/1824/201507	Periodic Safety Update EU Single assessment - lamivudine (chronic hepatitis B)	01/04/2016	26/05/2016	SmPC, Annex II, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1824/201507.

IAIN/0066/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.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.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	21/12/2015	26/05/2016	Annex II and PL	
IA/0064	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	08/05/2015	n/a		
IB/0063/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 A.4 - Administrative change - Change in the name	08/08/2014	n/a		

	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.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.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 B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.z - Change in the specification parameters				

	and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters				

	and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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) 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)				

	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters				

	and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
R/0062	Renewal of the marketing authorisation.	25/04/2014	23/06/2014	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of Zeffix remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/10/2013	10/01/2014	SmPC and PL	
IB/0055/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size	12/06/2013	n/a		

IA/0060	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	06/06/2013	n/a		
IB/0058	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	30/04/2013	n/a		
IAIN/0059	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/04/2013	n/a		
IG/0279	A.1 - Administrative change - Change in the name and/or address of the MAH	18/04/2013	10/01/2014	SmPC, Labelling and PL	
IA/0056	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	15/04/2013	n/a		
II/0053	The MAH proposed the update of sections 4.5 and 4.4. of the SPC, following the changes requested by CHMP AR of November 2011 concerning FUM 050.2 to specify that concomitant use of lamivudine and cladribine is not recommended. The package Leaflet is updated in accordance. Furthermore the MAH took this opportunity to make other updates required for full compliance with QRD template. Minor updates to the local representative contact information in Belgium, Czech Republic, Cyprus, Poland and Luxembourg were also introduced. The requested variation proposed amendments to	17/01/2013	20/12/2013	SmPC, Annex II, Labelling and PL	In the last PSUR a literature article (Chtioui et al 2008 Brit J Haematol 144: 131-142) relating a possible interaction between cladribine and lamivudine was provided. A patient with chronic lymphocytic leukaemia (CLL) receiving lamivudine showed no effect from cladribine until lamivudine was discontinued. The authors suspected a potential interaction based on intracellular phosphorylation of the two medicines and an in vitro study was carried out using peripheral blood mononuclear cells isolated from a healthy volunteer. This in vitro study showed that phosphorylated cladribine levels were decreased with increasing lamivudine concentrations, in line with what expected as per cladribine Product

	the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet. C.I.3.z - 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 - Other variation				Information. While the robustness of the findings and their clinical relevance remain unclear (this concomitant use in clinical practice is likely to be very rare, a literature research only retrieved this single case report, and no other haematological parameters as red blood cells or platelets count were evaluated) the potential for this drug interaction supported by the in vitro study justifies updating the Product Information.
N/0052	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/12/2012	20/12/2013	PL	
IAIN/0051	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	24/11/2011	27/06/2012	Annex II and PL	
IA/0050	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	26/04/2011	n/a	SmPC	
II/0049	IIn fulfilment of FUM 044.1, section 4.4 of the SmPC has been amended to improve clarity around the current text on exacerbation of hepatitis, in line with other nucleoside agents for CHB, and section 4.8 has been updated with regards to the frequency category of ADR based on the SmPC Guideline rev. 2. The PL has been revised accordingly. The MAH took this opportunity to amend the contact details of the Danish representative in the PL, to implement a change in section 4.4 following the linguistic review	21/10/2010	26/11/2010	SmPC and PL	Section 4.4 of the SmPC has been amended to improve clarity around the text on exacerbation of hepatitis, in line with other nucleoside agents for CHB. The approved text i) differentiate information related to development of resistance and post-treatment exacerbations of ALT flares, ii) better reflects data on post-treatment ALT elevations. Section 4.8 has been updated with regards to the frequency category of ADR based on the rule of 3/X recommended in the latest SmPC Guideline. The PL has

	of variation II-47 and to align SmPC and PL to the latest QRD template. 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				been modified accordingly.
II/0047	To update sections 4.2, 4.4, 4.6 and 5.1 of the SPC as a response to the commitments made by the MAH as part of the Zeffix licence renewal. The PL was revised accordingly. The MAH took the opportunity of this variation to update the contact details for the Danish, German and Cypriot local representatives and to introduce minor changes in the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	20/05/2010	02/07/2010	SmPC, Annex II and PL	
R/0046	Renewal of the marketing authorisation.	29/05/2009	27/08/2009	SmPC, Annex II, Labelling and PL	
II/0045	Change(s) to the manufacturing process for the active substance	24/01/2008	28/01/2008		
IA/0044	IA_09_Deletion of manufacturing site	18/12/2007	n/a	Annex II and PL	
IA/0043	IA_05_Change in the name and/or address of a	18/12/2007	n/a	Annex II and	

	manufacturer of the finished product			PL	
II/0040	To update sections 4.2 and 5.1 of the SPC to increase the continuation of therapy from HbeAg seroconversion from 3 months to at least 3-6 months and to include a wording relating to the rate of late virological relapses, as requested by the CHMP in August 2006. This follows the assessment of an epidemiological clinical study over five years in patents with or without YMDD mutants together with a comparative literature review. Update of Summary of Product Characteristics	24/01/2007	27/02/2007	SmPC	A 5-year open off-treatment epidemiologic study was performed to provide data on the durability of post-treatment responses. The final results of this study show that late virological relapses occur in 39% of HBeAg+ve patients who seroconverted post lamivudine treatment. These results together with data from a comprehensive literature review performed by the MAH indicate that the HBeAg seroconversion is not sufficient to ensure that a sustained response could be obtained and section 5.1 of the SPC was revised to include this information. Furthermore, according to data from a literature review and in line with the current international treatment guidelines, section 4.2 of the SPC was amended to allow continuation of treatment with Zeffix for at least 3-6 months from HBeAg seroconversion instead of the currently recommended duration of 3 months.
IA/0042	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	20/02/2007	n/a		
IA/0041	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	13/11/2006	n/a		
IB/0038	IB_17_a_Change in re-test period of the active substance	08/08/2006	n/a		
IA/0039	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	26/07/2006	n/a		

IA/0037	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	11/07/2006	n/a		
II/0035	To update section 4.4 and 4.8 of the SPC of Zeffix tablets and oral solution to re-organise information on exacerbation of hepatitis as requested by CHMP following the evaluation of PSUR 17 covering the period from 1 August 2004 to 31 July 2005. Additionally the MAH proposed to update section 4.8 of the SPC to introduce rhabdomyolysis as a very rare side effect. The PL was updated accordingly. Furthermore, the MAH updated the product information according to QRD v07. Update of Summary of Product Characteristics, Labelling and Package Leaflet	01/06/2006	04/07/2006	SmPC, Annex II, Labelling and PL	Exacerbations of hepatitis During the year covered by PSUR n. 17 (from 1 August 2004 to 31 July 2005), four fatal cases with hepatic events occurring after lamivudine withdrawal were recorded. Severe post-treatment flares, which can be fatal are recognised to occur following withdrawal of lamivudine and such events are currently described in section 4.4 "Special warnings and precautions for use" of the SPC. Given the importance of this information, the CHMP concluded that section 4.4 of the SPC should be re-organized so as to have a sub-title "exacerbation of hepatitis" reflecting the possibility of per-treatment and post-treatment exacerbation of hepatitis whether or not associated with viral resistance. Furthermore, such serious adverse events so far not listed in section 4.8 "Undesirable effects" of the SPC have been added. Rhabdomyolysis Following the assessment of PSUR n. 17, and given the medical seriousness of rhabdomyolysis (can induce serious and life threatening renal damage), a cumulative review of available data was considered warranted and was provided by the MAH. Therefore, rhabdomyolysis has been added as a very rare adverse reaction in section 4.8 under the heading of "Musculoskeletal and connective tissue disorders" of the SPC.
IA/0036	IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	30/03/2006	n/a		

IA/0034	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	21/03/2006	n/a	Annex II and PL	
IA/0033	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	21/03/2006	n/a		
IB/0031	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	15/02/2006	n/a		
IB/0030	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	15/02/2006	n/a		
IA/0032	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	18/01/2006	n/a		
II/0029	Update of Summary of Product Characteristics	16/03/2005	25/04/2005	SmPC	
II/0028	Update of Summary of Product Characteristics	16/03/2005	25/04/2005	SmPC	
II/0027	Update of Summary of Product Characteristics	17/02/2005	29/03/2005	SmPC	
R/0024	Renewal of the marketing authorisation.	29/07/2004	20/10/2004	SmPC, Annex II, Labelling and PL	
IA/0026	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	03/09/2004	n/a		
N/0025	To update the list of local representatives in the Package Leaflet (PL) , to include the local	25/06/2004	n/a	PL	

	representatives of the ten new European Member States and to update the format of the PL according to the latest EMEA/QRD template. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
IA/0023	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	01/03/2004	n/a		
IB/0022	IB_10_Minor change in the manufacturing process of the active substance	10/02/2004	n/a		
II/0015	To update the Summary of Product Characteristics (SPC) further to the CPMP assessment of the PSUR covering 1 June - 30 November 2002. This includes reformatting section 4.8 "Undesirable effects" presenting the adverse drug reactions by MedDRA system organ class and ranked by frequency and the inclusion of the adverse reactions thrombocytopenia and muscle disorders, including myalgia and cramps. Furthermore, the SPC has been updated in line with the latest EMEA/QRD templates. The package Leaflet (PL) has been updated accordingly. Furthermore, the name of manufacturer has been corrected in the Danish PL. Update of Summary of Product Characteristics and Package Leaflet	22/10/2003	20/01/2004	SmPC and PL	

I/0016	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	29/10/2003	n/a		
I/0014	24_Change in test procedure of active substance	05/08/2003	19/08/2003		
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/01/2003	17/02/2003	Labelling and PL	
II/0006	Update of Summary of Product Characteristics	19/09/2002	19/12/2002	SmPC	
I/0008	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	30/07/2002	09/09/2002	Annex II and PL	
I/0011	16_Change in the batch size of finished product	30/07/2002	n/a		
I/0010	15_Minor changes in manufacture of the medicinal product	30/07/2002	n/a		
I/0009	08_Change in the qualitative composition of immediate packaging material	30/07/2002	n/a		
I/0007	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	30/07/2002	n/a		
I/0005	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	08/05/2002	17/05/2002		
II/0004	Update of Summary of Product Characteristics and Package Leaflet	13/12/2001	02/04/2002	SmPC, Labelling and PL	

II/0002	Update of Summary of Product Characteristics and Package Leaflet	14/12/2000	23/04/2001	SmPC, Labelling and PL	