# Epivir

## 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 |
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| IAIN/0110 | 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 | 27/02/2019 | | Annex II and PL | |
| II/0108 | Update of section 4.2 of the SmPC in order to revise the posology in paediatric patients with renal impairment weighing less than 25 kg and aged at least | 13/12/2018 | 06/02/2019 | SmPC and PL | As part of a previous type II variation (II-104), section 4.2 of the SmPC of Epivir oral solution was updated to recommend a 25% dose increase in children at least 3 months of age and |

[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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| | 3 months.<br>In addition, the Marketing authorisation holder (MAH) took the opportunity to amend the SmPC and Package Leaflet with regards to details of the product composition in line with QRD requirements and to introduce minor editorial changes.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | weighing less than 25 kg. This update was based on interactions with sorbitol-containing antiretroviral drugs which may be co-administered with Epivir.<br>The current dosing recommendations for children aged at least 3 months and weighing less than 25 kg with renal impairment are not based on clinical data, but on PK extrapolations. Applying the same method of dose estimation, the CHMP considered that the doses in children with renal insufficiency should also be increased by 25%.<br>In order to provide additional guidance to the prescriber, the MAH also introduced a statement indicating that patients changing between oral solution and tablets should follow the dosing recommendations that are specific to the respective formulation. |
| T/0109 | Transfer of Marketing Authorisation | 21/11/2018 | 17/12/2018 | SmPC, Labelling and PL | |
| IAIN/0107 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 28/09/2018 | 17/12/2018 | SmPC | |
| IG/0923/G | This was an application for a group of variations.<br><br>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<br>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 | 22/05/2018 | n/a | | |

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| | manufacturer of a novel excipient | | | | |
| II/0104 | Update of section 4.2 of the SmPC of Epivir oral solution to recommend a 25% dose increase in children from 8 to 10 mg/kg/day, section 4.5 of the SmPC of both Epivir tablets and oral solution, and section 4.4 of the SmPC for Epivir oral solution only, to add information regarding the interaction between lamivudine and sorbitol based on the results of Study 204857. The Package Leaflet was updated accordingly. Further, a minor amendment has been implemented throughout the SmPC to update the clinical terminology for 'Pneumocystis carinii pneumonia' to 'Pneumocystis jiroveci pneumonia'. In addition, the MAH has taken the opportunity to align the product information with the QRD template version 10, to make minor editorial changes in the annexes and to update the contact details of the local representative in Norway in the Package Leaflet.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 25/01/2018 | 05/03/2018 | 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.<br>When possible, avoid chronic coadministration of Epivir 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 HIV-1 viral load when chronic coadministration cannot be avoided.<br>Whenever possible in children, an all-tablet regimen should preferably be used. Epivir oral solution given concomitantly with sorbitol-containing medicines should be used only when an all-tablet regimen cannot be used and the benefits of treatment outweigh possible risks including lower virological suppression. Consider more frequent monitoring of HIV-1 viral load when Epivir is used with chronically-administered, sorbitol-containing medicines [e.g. Ziagen oral solution]. Although not studied, the same effect would be expected with other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol. |
| WS/1334/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.<br><br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting | 15/02/2018 | n/a | | |

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| | material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | | | | |
| PSUSA/9207/ 201511 | Periodic Safety Update EU Single assessment - lamivudine (HIV infections), lamivudine / zidovudine | 02/09/2016 | n/a | | PRAC Recommendation - maintenance |
| II/0101 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 07/07/2016 | 24/05/2017 | SmPC | |
| IG/0670/G | This was an application for a group of variations.<br><br>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<br>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 | 13/04/2016 | n/a | | |

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| WS/0769 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>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 Mitochondrial Toxicity in Children (MITOC) Study (WE027/WWE112888). The Package leaflet is updated accordingly.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 01/04/2016 | 17/05/2016 | 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, 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.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation<br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 28/01/2016 | 17/05/2016 | SmPC and PL | |
| WS/0755 | This was an application for a variation following a worksharing procedure according to Article 20 of | 17/09/2015 | 17/05/2016 | SmPC | This procedure update section 5.1 of the SmPC in order to include information regarding the absence of antagonist |

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| | Commission Regulation (EC) No 1234/2008.<br><br>Update of 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.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | effects in vitro between the active substances and other retrovirals. |
| N/0099 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 28/07/2015 | 17/05/2016 | Labelling | |
| 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 | 17/05/2016 | Annex II and PL | |
| IG/0552 | 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 | | |
| WS/0645 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>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 | 23/04/2015 | 17/05/2016 | SmPC and PL | |

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| | 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).<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | |
| IB/0094 | B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation | 08/04/2015 | n/a | | |
| WS/0578 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>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. | 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.<br><br>Virological Response Based on Plasma HIV-1 RNA less than |

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| | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | 80 copies/ml at Week 48 and Week 96 in the Once Daily versus Twice Daily abacavir + lamivudine randomisation of ARROW (Observed Analysis):<br>Week 0 (After ≥36 Weeks on Treatment):<br>Plasma HIV-1 RNA <80 c/mL Twice daily N(%): 250/331 (76) Once daily N(%): 237/335 (71)<br>Risk difference (once daily-twice daily) -4.8% (95% CI -11.5% to +1.9%), p=0.16<br>Week 48:<br>Plasma HIV-1 RNA <80 c/mL Twice daily N(%): 242/331 (73) Once daily N(%): 236/330 (72)<br>Risk difference (once daily-twice daily) -1.6% (95% CI -8.4% to +5.2%), p=0.65<br>Week 96:<br>Plasma HIV-1 RNA <80 c/mL Twice daily N(%): 234/326 (72) Once daily N(%): 230/331 (69)<br>Risk difference (once daily-twice daily) -2.3% (95% CI -9.3% to +4.7%), p=0.52<br><br>No additional safety issues have been identified in paediatric subjects receiving either once or twice daily dosing compared to adults.<br><br>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.<br><br>The abacavir + lamivudine once daily dosing group was demonstrated to be non-inferior to the twice daily group |

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| | | | | | 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.<br><br>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 c respectively, p=0.07). |
| II/0084 | 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) and the list of local representatives in the Package Leaflet is also updated. | 23/10/2014 | 26/02/2015 | SmPC and PL | The MAH 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 Epivir remains unchanged. |

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| | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | |
| IA/0091 | A.7 - Administrative change - Deletion of manufacturing sites | 07/07/2014 | n/a | | |
| IB/0087/G | This was an application for a group of variations.<br><br>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<br>B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold | 20/06/2014 | n/a | | |
| WS/0393/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.<br><br>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>B.I.a.1.z - Change in the manufacturer of intermediate used in the manufacturing process of the active substance<br>B.I.a.1.z - Change in the manufacturer of intermediates used in the manufacturing process of | 22/05/2014 | n/a | | |

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| | the active substance<br>A.4 - Administrative change - Change in the name of a manufacturer of the intermediates used in the manufacture of the active substance<br>A.7 - Administrative change - Deletion of multiple manufacturing sites<br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>B.I.a.3.a - Change in batch size (including batch size ranges) of intermediate - Up to 10-fold increase compared to the originally approved batch size<br>B.I.a.3.a - Change in batch size (including batch size ranges) of intermediate - Up to 10-fold increase compared to the originally approved batch size<br>B.I.a.3.a - Change in batch size (including batch size ranges) of intermediate - Up to 10-fold increase compared to the originally approved batch size<br>B.I.b.1.b - Change in the specification limit of a reagent – Tightening of specification limits<br>B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation<br>B.I.b.1.b - Change in the specification limits of a reagent - Tightening of specification limits<br>B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation | | | | |

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| | B.I.b.2.c - Change in test procedure for reagent - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS<br>B.I.b.1.z - Change in the specification limits of a reagent - Other variation<br>B.I.b.2.c - Change in test procedure for reagent - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS<br>B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation<br>B.I.b.1.z - Change in the specification limit of a reagent - Other variation<br>B.I.b.2.c - Change in test procedure for reagent - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS<br>B.I.b.1.z - Change in the specification limits of a reagent - Other variation<br>B.I.b.1.z - Change in the specification limit of a reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation<br>B.I.b.1.z - Change in the specification limit of a reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation | | | | |

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| | B.I.b.1.d - Change in the specification parameters and/or limits of a reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)<br>B.I.b.1.d - Change in the specification parameters and/or limits of a starting material - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)<br>B.I.b.1.b - Change in the specification parameters and/or limits of a starting material - Tightening of specification limits<br>B.I.b.1.z - Change in the specification parameters and/or limits of a starting material – Other variation<br>B.I.b.2.e - Change in test procedure for intermediate - Other changes to a test procedure (including replacement or addition) for the intermediate<br>B.I.b.1.z - Change in the specification limit of an intermediate - Other variation<br>B.I.b.1.z - Change in the specification limit of an intermediate - Other variation<br>B.I.b.1.b - Change in the specification parameters and/or limits of an intermediate - Tightening of specification limits<br>B.I.b.1.z - Change in the specification parameters and/or limits of an intermediate - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an intermediate - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an intermediate - Other variation<br>B.I.b.1.z - Change in the specification limit of an intermediate - Other variation<br>B.I.b.1.z - Change in the specification limit of an | | | | |

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| | intermediate - Other variation<br>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation<br>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation<br><br>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation<br>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation<br>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<br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>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<br>B.I.a.3.a - Change in batch size (including batch size | | | | |

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| | ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size<br>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<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>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<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>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<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | | | | |

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| | of an obsolete parameter)<br>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)<br>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits<br>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits<br>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<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters | | | | |

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| | and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation<br>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation<br>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | | | | |
| 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 | | |
| IA/0089 | B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process | 05/05/2014 | 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.<br><br>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 | 26/02/2015 | 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 |

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| | addition, minor corrections are made to translations and an editorial change is implemented in Trizivir PL.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | | | | SmPC in Dutch. |
| IA/0088/G | This was an application for a group of variations.<br><br>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process<br>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<br>B.II.d.2.e - Change in test procedure for the finished product - Update of the test procedure to comply with the updated general monograph in the Ph. Eur.<br>B.II.d.2.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number<br>B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method<br>B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition) | 02/04/2014 | n/a | | |

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| | B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products | | | | |
| IA/0086 | B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 26/03/2014 | n/a | | |
| N/0082 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 03/12/2013 | 26/02/2015 | PL | |
| WS/0361 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>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.<br>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.<br><br>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 | 25/04/2013 | 30/05/2013 | 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).<br>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 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. |

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| | NO new additional data are submitted by the MAH | | | | |
| 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.<br><br>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.<br>In addition, the list of local representatives was updated in the Package Leaflet.<br>Furthermore, the product information is being brought in line with the latest QRD template version 8.3.<br><br>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.<br>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. | 21/06/2012 | 23/07/2012 | Annex II | Update of the Detailed Description of the Pharmacovigilance System (DDPS) to ViiV Healthcare Ltd version 4 dated May 2012. |

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| | 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.<br><br>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 | | | | |
| IAIN/0077 | A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release | 29/11/2011 | 15/06/2012 | Annex II and PL | |
| IA/0076 | 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 | 14/04/2011 | n/a | SmPC | |
| II/0074 | Update of Summary of Product Characteristics and Package Leaflet<br>Update of section 4.8 of the SmPC to add 'angioedema' as a new adverse event in fulfilment of PSU049 (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 | 23/09/2010 | 25/10/2010 | 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). Moreover the frequency category for undesirable effects was reworded to be in line with the latest SmPC guideline. PL was modified accordingly and aligned to QRD template. Moreover minor corrections were introduced |

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| | guideline. The PL has been revised accordingly and aligned to QRD template. In addition the MAH took this opportunity to amend contact details of local representatives in the PL, to update Annex II and to correct the EMA website address.<br><br>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 | | | | to the local representatives list in the PL and in Annex II. |
| N/0073 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 30/07/2010 | n/a | PL | |
| T/0072 | Transfer of Marketing Authorisation | 22/03/2010 | 29/04/2010 | SmPC, Labelling and PL | |
| II/0071 | To update sections 4.4, 4.5 and 4.6 of the Epivir SPC to harmonise the content with the Zeffix SPC in order to fulfil the MAH commitment during the Zeffix renewal procedure. Section 2 (Taking other medicines) of the PL was updated accordingly.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 24/09/2009 | 28/10/2009 | 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 Epivir (lamivudine) 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 |

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| | | | | | information since this medicine is no longer marketed. |
| II/0069 | 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.<br>Section 3 of the Package Leaflet was updated accordingly.<br>The MAH also took the opportunity to update section 6 of the Package Leaflet with new contact details for the local representative in Latvia and the Labelling with inclusion of Braille for all pharmaceutical forms.<br><br>Update of Summary of Product Characteristics, Labelling and Package Leaflet | 24/07/2008 | 05/09/2008 | SmPC, Labelling 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.<br>This information is useful for the treatment of paediatric patients who cannot swallow tablets and also for adults in difficulties in swallowing. |
| IA/0070 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 03/07/2008 | n/a | | |
| IA/0068 | IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms | 22/02/2008 | n/a | | |
| II/0067 | Change(s) to the manufacturing process for the active substance | 24/01/2008 | 28/01/2008 | | |
| IA/0066 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 19/11/2007 | n/a | Annex II and PL | |
| IA/0065 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site | 15/11/2007 | n/a | | |

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| II/0063 | Update of Summary of Product Characteristics, labelling and Package Leaflet<br><br>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.<br>Furthermore, the MAH took the opportunity of this variation to split the outer carton and bottle label and to introduce a minor change in the PL.<br><br>Update of Summary of Product Characteristics, Labelling and Package Leaflet | 20/09/2007 | 30/10/2007 | SmPC, Labelling 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/0064 | To update section 5.1 of the SPC concerning the emergence of M184V mutation following CHMP request dated 18 October 2006.<br><br>Update of Summary of Product Characteristics | 19/07/2007 | 31/08/2007 | SmPC | The MAH submitted this type II variation II/64 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 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). |
| II/0061 | 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.<br><br>Update of Summary of Product Characteristics | 24/01/2007 | 01/03/2007 | 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 acknowledges that no statistically significant difference was observed in this clinical study. However, the results are not so far from statistical significance and the |

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| | | | | | small sample size should be taken into account.<br>Overall these data cannot be regarded as reassuring for the lamivudine recommended regimens 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. |
| IA/0062 | 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 | | |
| II/0060 | 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.<br><br>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.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 14/12/2006 | 25/01/2007 | 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. |
| IA/0058 | IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing | 20/10/2006 | n/a | Annex II and PL | |

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| IA/0059 | IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms | 16/10/2006 | n/a | | |
| IA/0057 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site<br>IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms | 16/10/2006 | n/a | | |
| IB/0054 | IB_17_a_Change in re-test period of the active substance | 08/08/2006 | n/a | | |
| IA/0056 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site | 02/08/2006 | n/a | | |
| R/0052 | Renewal of the marketing authorisation. | 01/06/2006 | 28/07/2006 | SmPC, Annex II, Labelling and PL | Based on the CHMP 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 Epivir continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity. The MAH will submit yearly PSURs, unless otherwise specified by the CHMP. |
| IA/0055 | IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold | 26/07/2006 | n/a | | |
| IA/0053 | IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer | 11/07/2006 | n/a | | |
| IB/0048 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 06/01/2006 | n/a | | |

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| IA/0051 | IA_09_Deletion of manufacturing site | 06/01/2006 | n/a | Annex II and PL | |
| IB/0049 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer | 05/01/2006 | n/a | | |
| IA/0050 | IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold | 08/12/2005 | n/a | | |
| II/0047 | To update section 4.4 “Special warnings and special precautions for use” and 4.8 “Undesirable effects” of the Summary of Product Characteristics (SPC) and section 2 “Before you take Epivir” of the Package Leaflet (PL), to implement the class labelling text regarding the Immune Reactivation Syndrome, as adopted by the CHMP in July 2004. Furthermore, to update section 4.4 “Special warnings and special precautions for use” of Epivir oral solution, to move the sentence to advise diabetic patients on the amount of sucrose contained in each dose. Additionally, the MAH added side-headings, where appropriate to section 4.4 of the SPC to improve readability. The MAH took also the opportunity of this variation to amend the address of the Estonian local representative in the PL.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 18/11/2004 | 17/12/2004 | SmPC and PL | |
| II/0045 | To update section 4.4 “Special warnings and special precautions for use” of the Summary of Product Characteristics (SPC), to implement the class labelling | 21/10/2004 | 06/12/2004 | SmPC and PL | |

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| | text regarding the high rate of virological failure and emergence of resistance at an early stage with triple combinations involving tenofovir disoproxil fumarate (Tenofovir DF) and two Nucleoside Reverse Transcriptase Inhibitors (NRTI's), lamivudine and abacavir as adopted by the CHMP in July 2004. Furthermore, the MAH took the opportunity of this variation to amend the address of the Estonian local representative in the Package Leaflet.<br><br>Update of Summary of Product Characteristics and Package Leaflet | | | | |
| II/0044 | To update section 5.3 "Preclinical safety data" of the Summary of Product Characteristics (SPC) of Epivir 150 mg tablets, 300 mg tablets and 10 mg/ml oral solution to include information on NRTI incorporation into cellular DNA.<br><br>Update of Summary of Product Characteristics | 21/10/2004 | 06/12/2004 | SmPC | |
| IA/0046 | IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold | 03/09/2004 | n/a | | |
| IA/0043 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 29/07/2004 | n/a | Annex II and PL | |
| II/0041 | Update of the section 4.4 (Special warnings and special precaution for use) of the Summary of Product Characteristics (SPC) and section 2 of the Package Leaflet (PL) under subheading "Pregnancy" , to implement the class labelling for | 24/03/2004 | 01/06/2004 | SmPC and PL | |

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| | nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) regarding mitochondrial toxicity in children with in utero and post-natal exposure, as adopted by the CPMP in November 2003<br><br>Update of Summary of Product Characteristics and Package Leaflet | | | | |
| IA/0042 | IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer | 01/03/2004 | n/a | | |
| IB/0040 | IB_10_Minor change in the manufacturing process of the active substance | 10/02/2004 | n/a | | |
| II/0037 | Update of sections 4.4 “Special warnings and special precautions for use” and 5.2 "Pharmacokinetic properties" of the Summary of Product Characteristics (SPC) to implement the class labelling statement 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 implement minor changes in the sections 4.4 and 4.6 ”Pregnancy and Lactation” of the SPC and to update the PL, section 4, to revise the wording on lipodystrophy as adopted by the CPMP in March 2003.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 20/11/2003 | 29/01/2004 | SmPC and PL | |

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| IA/0039 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site | 19/12/2003 | n/a | | |
| IA/0038 | IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site | 29/10/2003 | n/a | | |
| I/0036 | 24_Change in test procedure of active substance | 05/08/2003 | 19/08/2003 | | |
| II/0034 | The Marketing Authorisation Holder (MAH) applied for an update of the Summary of Product Characteristics to include the class labelling on Lipodystrophy in sections 4.4 (“Special warnings and special precautions for use”) and 4.8 (“Undesirable Effects”). Relevant changes are equally proposed for the Package Leaflet.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 19/03/2003 | 09/07/2003 | SmPC and PL | |
| II/0033 | New presentation(s) | 19/03/2003 | 09/07/2003 | SmPC, Labelling and PL | |
| II/0032 | The Marketing Authorisation Holder (MAH) applied for an update of the Summary of Product Characteristics (SPC) sections 4.2 (“Posology and method of administration”) further to the CPMP assessment of 48 week data of a clinical study. In addition, the MAH proposed some minor linguistic changes to the language versions to improve the readability and to comply with the latest EMEA/ QRD templates. Relevant changes are also included in the Package | 20/02/2003 | 14/05/2003 | SmPC and PL | |

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| | Leaflet.<br><br>Update of Summary of Product Characteristics and Package Leaflet | | | | |
| I/0031 | 25_Change in test procedures of the medicinal product | 20/11/2002 | 25/11/2002 | | |
| I/0030 | 20_Extension of shelf-life as foreseen at time of authorisation | 09/10/2002 | 12/11/2002 | SmPC | |
| I/0028 | 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process | 05/09/2002 | 17/10/2002 | PL | |
| I/0029 | 08_Change in the qualitative composition of immediate packaging material | 05/09/2002 | 24/09/2002 | | |
| I/0027 | 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process | 05/09/2002 | 24/09/2002 | | |
| II/0025 | To update the Summary of Product Characteristics (SPC) section 5.1 (“Pharmacodynamic Properties”) relating to the use of lamivudine as part of HAART and relating to an update of virological information, following the CPMP assessment of the renewal dossier of the Epivir Marketing Authorisation. Furthermore, to update section 4.8 (“Undesirable Effects”) to reflect the frequencies of the adverse drug reactions in accordance with the SPC guideline. Also, to update section 4.4 (“ Special warnings and special precautions”) to reflect the class labelling statement for nucleoside analogues regarding lactic acidosis as revised by the CPMP. Finally, to update sections 4.2. | 30/05/2002 | 21/08/2002 | SmPC and PL | |

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| | ("Posology"), 4.4 ("Special warnings and special precautions") and 5.2 ("Pharmacokinetic properties") of the Epivir Oral solution to include a once a day dosing advice, following the CPMP assessment of the once a day dosing scheme. The relevant sections of the package leaflet have been amended accordingly. Furthermore, some minor changes have been incorporated in the SPC, and Package Leaflet in order to bring the text in line with the latest QRD/ EMEA templates. In addition, the list of the Local Representatives has been updated.<br><br>Update of Summary of Product Characteristics and Package Leaflet | | | | |
| I/0026 | 12a_Change in specification of starting material/intermediate used in manuf. of the active substance | 08/05/2002 | 15/05/2002 | | |
| X/0023 | X-3-iii_Addition of new strength | 26/07/2001 | 15/11/2001 | SmPC, Annex II, Labelling and PL | |
| R/0024 | Renewal of the marketing authorisation. | 26/07/2001 | 09/11/2001 | SmPC, Annex II, Labelling and PL | |
| II/0022 | The Marketing Authorisation Holder applied for an update of the Summary of Product Characteristics, (sections "Special warnings and special precautions for use", "Interactions" and "Undesirable effects", and as a consequence an update of the Package Leaflet). Furthermore, the MAH proposed some minor changes | 29/03/2001 | 11/07/2001 | SmPC, Labelling and PL | |

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| | in the SPC, Labelling and Package Leaflet in order to bring the text in line with the latest QRD/ EMEA templates.<br><br>Update of Summary of Product Characteristics, Labelling and Package Leaflet<br><br>Update of Summary of Product Characteristics and Package Leaflet | | | | |
| II/0021 | The Marketing Authorisation Holder applied for an update of the Summary of Product Characteristics (sections “Undesirable effects” and “Pharmacokinetics” and as a consequence an update of the Package Leaflet). Furthermore, the MAH proposed some minor changes in the SPC, Labelling and Package Leaflet in order to bring the text in line with the latest QRD/ EMEA templates.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 28/08/2000 | 22/01/2001 | SmPC, Labelling and PL | |
| I/0020 | 20_Extension of shelf-life as foreseen at time of authorisation | 14/04/2000 | 27/07/2000 | SmPC | |
| II/0018 | The Marketing Authorisation Holder applied to update the safety information in the Summary of Product Characteristics (SPC) and Package Leaflet with regard to “Special Warnings and Precautions for Use” (to include a warning statement on lactic acidosis), and “Undesirable effects” (introduction of the adverse event rhabdomyolysis) as requested by the CPMP | 23/06/1999 | 10/11/1999 | SmPC, Labelling and PL | |

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| | following the evaluation of the third periodic safety update report (PSUR) covering the period from 1 June 1997 to 30 November 1997. Furthermore, the Marketing Authorisation Holder proposed to amend the SPC, Labelling and Package Leaflet in line with the latest EMEA template and inserted the new ATC Code for lamivudine as published by the WHO in 1998 in the SPC.<br><br>Update of Summary of Product Characteristics and Package Leaflet | | | | |
| I/0019 | 12_Minor change of manufacturing process of the active substance<br>11b_Change in supplier of an intermediate compound used in manufacture of the active substance | 20/10/1999 | 25/10/1999 | | |
| I/0017 | 12_Minor change of manufacturing process of the active substance | 04/05/1999 | 18/05/1999 | | |
| II/0015 | The Marketing Authorisation Holder applied for an update of the Summary of Product Characteristics:<br>• To reflect current clinical practice<br>• To reflect current clinical experience and data generated in randomised clinical trials<br>• To reflect “full” approval status of Epivir<br>• To include alopecia and a revised statement on rebound hepatitis B in the “Undesirable effects” and “Special warning and precautions for use” sections respectively.<br><br>Update of Summary of Product Characteristics and | 25/03/1998 | 07/07/1998 | SmPC and PL | |

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| | Package Leaflet | | | | |
| II/0014 | Extension of Indication | 25/03/1998 | 07/07/1998 | SmPC and PL | |
| I/0016 | 20_Extension of shelf-life as foreseen at time of authorisation | 20/03/1998 | 07/07/1998 | SmPC | |
| S/0011 | Annual re-assessment. | 24/09/1997 | 07/01/1998 | SmPC, Annex II, Labelling and PL | |
| II/0013 | Update of the safety sections (4.4 and 4.8) of the Summary of Product Characteristics with regard to the occurrence of lactic acidosis.<br><br>Update of Summary of Product Characteristics | 24/09/1997 | 16/12/1997 | SmPC | |
| II/0012 | Change in formulation | 24/09/1997 | 16/12/1997 | SmPC, Labelling and PL | |
| II/0010 | Update of the Summary of Product Characteristics with regard to sections 4.1 “Therapeutic indications” (following the availability of clinical endpoint data from study NUCB 3007), 4.2 “Posology and method of administration” (statement on the hepatic impairment) and 4.8 “Undesirable effects’ (introduction of new adverse effects).<br><br>Update of Summary of Product Characteristics and Package Leaflet | 24/09/1997 | 16/12/1997 | SmPC and PL | |

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|---|---|---|---|---|---|
| I/0009 | 12a_Change in specification of starting material/intermediate used in manuf. of the active substance | 11/07/1997 | n/a | | |
| II/0005 | Update of the statement in the Summary of Product Characteristics related to the carcinogenicity and mutagenicity potential of Epivir following the finalisation of the studies.<br><br>Update of Summary of Product Characteristics | 19/02/1997 | 22/05/1997 | SmPC | |
| I/0008 | 11_Change in or addition of manufacturer(s) of active substance | 15/05/1997 | n/a | | |
| II/0004 | Change(s) to container | 22/01/1997 | 15/04/1997 | SmPC, Labelling and PL | |
| I/0007 | 11_Change in or addition of manufacturer(s) of active substance | 28/02/1997 | n/a | | |
| I/0006 | 11_Change in or addition of manufacturer(s) of active substance | 28/02/1997 | n/a | | |
| I/0003 | 01_Change following modification(s) of the manufacturing authorisation(s) | 02/12/1996 | 14/02/1997 | Annex II and PL | |
| I/0002 | 13_Batch size of active substance | 30/10/1996 | n/a | | |
| I/0001 | 11_Change in or addition of manufacturer(s) of active substance | 30/10/1996 | n/a | | |