



## Kivexa

### Procedural steps taken and scientific information after the authorisation

| Application number | Scope   | Opinion/ Notification <sup>1</sup> issued on | Commission Decision Issued <sup>2</sup> / amended on | Product Information affected <sup>3</sup> | Summary |
|--------------------|---|--|--|---|---------|
| WS/1334/G          | <p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters</p> | 15/02/2018                                   | n/a  |   |         |

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).



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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  |            |     |                        |   |
| WS/1156         | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.5 of the SmPC to add information regarding the interaction between lamivudine and sorbitol based on the results of Study 204857. The Package Leaflet has been updated accordingly.</p> <p>Further, a minor amendment has been implemented throughout the SmPC in order to update the clinical terminology of Pneumocystis carinii pneumonia to Pneumocystis jiroveci pneumonia. In addition, the MAH takes the opportunity to make minor editorial changes, to align the annexes with the QRD template version 10 and to update the contact details of the local representatives in the Package Leaflet.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 25/01/2018 |     | SmPC, Labelling and PL | <p>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.</p> <p>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 HIV-1 viral load when chronic co-administration cannot be avoided.</p> |
| PSUSA/11/201612 | Periodic Safety Update EU Single assessment - abacavir / lamivudine   | 01/09/2017 | n/a |                        | PRAC Recommendation - maintenance   |

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| IB/0071/G | <p>This was an application for a group of variations.</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> | 10/01/2017 | n/a        |          |  |
| WS/0956/G | <p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority</p> <p>C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing</p>   | 21/07/2016 | 06/07/2017 | Annex II |  |

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|           | authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required  |            |            |             |   |
| WS/0948   | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.4 and 4.5 of the SmPC to remove the current information regarding a potential interaction between abacavir and ribavirin. The Package Leaflet has been updated accordingly. In addition, updated RMPs were agreed during the procedure: Ziagen RMP version 13; Kivexa RMP version 5; Triumeq RMP version 10.</p> <p>C.1.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 21/07/2016 | 06/07/2017 | SmPC and PL | <p>PK study COL112055 did not show apparent impact of ABC on the intracellular concentrations of ribavirin triphosphate after 56 days of treatment (RBV alone: 15.93 pmol/106 cells; RBV+ABC: 15.87 pmol/106 cells). Although the variability of these measures is too high (80-100%) to achieve adequate statistical power (a difference between these 2 arms only &gt;40% can be excluded), the data are nonetheless reassuring, the intracellular values being quite similar in between arms.</p> <p>In addition, 3 retrospective studies performed in a large number of HCV/HIV coinfecting subjects do not support a potential impact of ABC on the sustained virologic response with Peg-IFN+ribavirin. Moreover, the potential interaction of ABC on RBV is currently not considered in the European guidelines for the treatment of HIV/HCV coinfecting subjects.</p> |
| IB/0068   | B.1.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate   | 20/04/2016 | n/a        |             |   |
| IG/0670/G | <p>This was an application for a group of variations.</p> <p>A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder</p>   | 13/04/2016 | n/a        |             |   |

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|         | <p>or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient</p> <p>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</p>   |            |            |                       |  |
| IG/0674 | <p>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</p>   | 13/04/2016 | n/a        |                       |  |
| WS/0845 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.2, 4.3, 4.4 and 5.2 of the SmPC in order to align the Hepatic Impairment wording for the 3 older abacavir-containing products (ZIAGEN™, KIVEXA™ and TRIZIVIR™) with the TRIUMEQ™ SmPC. The Package Leaflet is updated accordingly. In addition, the MAH has taken the opportunity to correct some minor administrative errors in the labelling for the 3 products.</p> <p>The requested worksharing procedure proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).</p> | 01/04/2016 | 29/06/2016 | SmPC, Annex II and PL |  |

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|           | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data  |            |            |             |   |
| WS/0769   | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</p> | 01/04/2016 | 29/06/2016 | SmPC and PL | <p>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.</p> |
| WS/0888/G | <p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation</p>   | 28/01/2016 | 29/06/2016 | SmPC and PL |   |

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|             | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation  |            |            |                                  |   |
| IAIN/0063/G | <p>This was an application for a group of variations.</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form</p> <p>B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information</p> | 16/10/2015 | 29/06/2016 | SmPC, Annex II, Labelling and PL |   |
| WS/0755     | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>  | 17/09/2015 | 29/06/2016 | SmPC                             | This procedure update section 5.1 of the SmPC in order to include information regarding the absence of antagonist effects in vitro between the active substances and other retrovirals. |
| IB/0062/G   | This was an application for a group of variations.  | 24/08/2015 | n/a        |                                  |   |

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|         | <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p>  |            |            |             |  |
| WS/0733 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.1, 4.2, 4.3, 4.4 and 4.8 of the SmPC to revise the information on hypersensitivity reactions in line with a recent revision of the Triumeq SmPC. The Package Leaflet is updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 02/07/2015 | 29/06/2016 | SmPC and PL | In this worksharing variation, the information related to hypersensitivity reactions (HSR) to abacavir sulfate (ABC) has been revised to provide a more condensed and less redundant description of the HSR to abacavir. The most detailed description of the HSR have been kept in section 4.8 of the SmPC under the "description of the selected adverse reactions". |
| II/0057 | <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>   | 21/05/2015 | 22/06/2015 | SmPC and PL |  |
| IG/0552 | <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p>  | 08/05/2015 | n/a        |             |  |
| WS/0645 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p>   | 23/04/2015 | 22/06/2015 | SmPC and PL |  |



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|           | <p>Update of section 4.6 of the SmPC to include the WHO guidelines on breastfeeding. The Package Leaflet has been updated accordingly. In addition, the WSA has taken the opportunity to promote consistency across products by updating where relevant (i.e. for Trizivir, Combivir, Lamivudine/Zidovudine ViiV and Triumeq), the pharmacokinetic statements in section 4.6 of the SmPC to reflect the most recently approved wording for the components abacavir and lamivudine (Kivixa EMEA/H/C/581/R/0051 and Epiriv EMEA/H/C/107/I/0084).</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> |            |     |  |  |
| IB/0056/G | <p>This was an application for a group of variations.</p> <p>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation</p> <p>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation</p>   | 08/04/2015 | n/a |  |  |
| WS/0673/G | <p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.a.1.c - Change in the manufacturer of AS or of a</p>  | 26/03/2015 | n/a |  |  |

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|         | starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions<br>B.1.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method   |            |            |                                  |  |
| R/0051  | Renewal of the marketing authorisation.  | 25/09/2014 | 17/11/2014 | SmPC, Annex II, Labelling and PL |  |
| WS/0543 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>To add an alternative test method for the active substance.<br><br>B.1.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate | 25/09/2014 | n/a        |                                  |  |
| WS/0542 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Change of specification of abacavir sulphate to comply with the Ph.Eur..  | 25/09/2014 | n/a        |                                  |  |

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|           | B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS  |            |     |  |                                   |
| PSUV/0053 | Periodic Safety Update  | 11/09/2014 | n/a |  | PRAC Recommendation - maintenance |
| WS/0393/G | <p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.a.1.z - Change in the manufacturer of intermediate used in the manufacturing process of the active substance</p> <p>B.I.a.1.z - Change in the manufacturer of intermediates used in the manufacturing process of the active substance</p> <p>A.4 - Administrative change - Change in the name of a manufacturer of the intermediates used in the manufacture of the active substance</p> <p>A.7 - Administrative change - Deletion of multiple manufacturing sites</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> | 22/05/2014 | n/a |  |                                   |

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|  | <p>B.1.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>B.1.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>B.1.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</p> <p>B.1.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</p> <p>B.1.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</p> <p>B.1.b.1.b - Change in the specification limit of a reagent – Tightening of specification limits</p> <p>B.1.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation</p> <p>B.1.b.1.b - Change in the specification limits of a reagent - Tightening of specification limits</p> <p>B.1.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation</p> <p>B.1.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</p> <p>B.1.b.1.z - Change in the specification limits of a reagent - Other variation</p> <p>B.1.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</p> |  |  |  |  |
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| <p>overall quality of the AS</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification limit of a reagent - Other variation</p> <p>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</p> <p>B.I.b.1.z - Change in the specification limits of a reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification limit of a reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification limit of a reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of a reagent - Other variation</p> <p>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)</p> <p>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)</p> <p>B.I.b.1.b - Change in the specification parameters</p> |  |  |  |  |
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| <p>and/or limits of a starting material - Tightening of specification limits</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of a starting material – Other variation</p> <p>B.I.b.2.e - Change in test procedure for intermediate - Other changes to a test procedure (including replacement or addition) for the intermediate</p> <p>B.I.b.1.z - Change in the specification limit of an intermediate - Other variation</p> <p>B.I.b.1.z - Change in the specification limit of an intermediate - Other variation</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an intermediate - Tightening of specification limits</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an intermediate - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an intermediate - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an intermediate - Other variation</p> <p>B.I.b.1.z - Change in the specification limit of an intermediate - Other variation</p> <p>B.I.b.1.z - Change in the specification limit of an intermediate - Other variation</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a</p> |  |  |  |  |
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| <p>starting material/reagent/intermediate for AS - Other variation</p> <p>B.1.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p> <p>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</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>B.1.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>B.1.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>B.1.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>B.1.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</p> <p>B.1.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</p> <p>B.1.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</p> |  |  |  |  |
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|  | <p>size</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>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</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>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</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> |  |  |  |  |
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| <p>material/intermediate/reagent - Other variation<br/>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Other variation<br/>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting</p> <p>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</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Other variation<br/>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Other variation<br/>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Other variation<br/>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Other variation<br/>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Other variation<br/>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Other variation<br/>B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting</p> <p>material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)</p> |  |  |  |  |
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|  | <p>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)</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>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</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters</p> |  |  |  |  |
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|           | <p>and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p> |            |     |  |  |
| IG/0438   | C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location   | 16/05/2014 | n/a |  |  |
| IG/0410/G | <p>This was an application for a group of variations.</p> <p>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</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p>  | 28/03/2014 | n/a |  |  |

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|           | <p>B.1.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>B.1.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>B.1.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p>   |            |            |    |  |
| N/0046    | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)  | 12/12/2013 | 17/11/2014 | PL |  |
| IB/0043/G | <p>This was an application for a group of variations.</p> <p>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</p> <p>B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place</p> <p>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</p> | 23/08/2013 | n/a        |    |  |
| IB/0045   | B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation   | 28/06/2013 | n/a        |    |  |

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| IA/0044/G | <p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> <p>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</p> <p>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p> <p>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p> <p>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p> <p>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation</p> | 21/06/2013 | n/a        |             |  |
| WS/0361   | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.4 and 4.5 of the SmPC in order</p>  | 25/04/2013 | 27/05/2013 | SmPC and PL | The drug-drug interaction between lamivudine and cladribine (CdA) was assessed in a type II variation of Zeffix (EMEA/H/C/242/11/53) based on a publication by Chtioui et al (Concomitant treatment with lamivudine renders cladribine inactive by inhibition of its |

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|         | <p>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.</p> <p>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.</p> <p>C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH</p> |            |            |                                  | <p>phosphorylation. Br.J.Haematology. 2008; 144: 136-137). This article described a patient with chronic lymphoid leukaemia who was treated with CdA and Zeffix. No decrease of the peripheral blood lymphocyte count was observed after the first cycle of CdA. Zeffix was discontinued and the lymphocyte count decreased following the second and third cycles of CdA. The authors suspected a potential interaction based on intracellular phosphorylation when both medicines are administered 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.</p> |
| IG/0295 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation  | 29/04/2013 | n/a        |                                  |  |
| WS/0338 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>In addition, the list of local representatives was updated in the Package Leaflet.</p>   | 21/02/2013 | 26/03/2013 | SmPC, Annex II, Labelling and PL | <p>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</p>   |

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|         | <p>Furthermore, the product information is being brought in line with the latest QRD template version 8.3.</p> <p>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p>  |            |            |          | <p>specific therapy and while Anti-Retroviral Therapy was continued. Most of cases had a relatively late onset following Anti-Retroviral Therapy initiation except cases of Guillain-Barré syndrome and adult onset Still's disease. The time to onset ranged from 2 weeks to 37 months. While it was recognised that the number of cases is small, the long and variable time to onset probably causes underreporting of such adverse reactions and therefore little is known on the exact pathogenesis and the risk factors. The CHMP agreed that information about autoimmune disorders occurring in the context of immune reconstitution should be reflected in the product information.</p>  |
| II/0039 | <p>To put in place a Risk Management Plan (RMP) following CHMP request during procedure PSU 042. Annex II has been modified accordingly, to include details of the additional risk minimisation activities. Furthermore, the MAH proposed this opportunity to bring Annex II in line with the latest QRD template version 8.3.</p> <p>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation</p> | 21/02/2013 | 26/03/2013 | Annex II | <p>Following assessment of Kivexa PSU 042 (MAH's 24th PSUR) the CHMP requested the MAH to produce a risk management plan (RMP) for Kivexa). The MAH submitted the present type II variation to fulfil this request and update Annex IIB to reflect that an RMP is now in place for Kivexa, with all of the requirements that this implies. This RMP version "00" of 31 May 2012 formalises existing pharmacovigilance activities and risk minimisation activities for Kivexa and appropriately reflects its safety profile. Upon CHMP request the educational program and patient Alert Card concerning the abacavir hypersensitivity reactions risk were detailed in the RMP and in the Annex IIC, in accordance with the EMA guideline on good pharmacovigilance practice and the current templates. Also upon request a summary of all the of the risk minimisation activities proposed, routine and additional was included in the RMP.</p> |

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| WS/0163 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>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</p> | 21/06/2012 | 21/06/2012 | Annex II              | Update of the Detailed Description of the Pharmacovigilance System (DDPS) to ViiV Healthcare Ltd version 4 dated May 2012.  |
| IA/0036 | B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size   | 19/12/2011 | n/a        |                       |   |
| II/0035 | Update of sections 4.4 and 4.5 of the SmPC to alert on the possible reduction of SVR in ABC/RBV co-treated patients as requested by the CHMP (Ziagen RMP084). The PL has been amended accordingly. The MAH took the opportunity to reorganize the existing information on Liver Disease in section 4.4 and to correct a typo error in the title "Antihistamines (Histamine H1 receptor antagonists)"  | 22/09/2011 | 24/10/2011 | SmPC, Annex II and PL | Section 4.4 of the SmPC has been updated with a warning that caution should be exercised when ABC and RBV are co-administered. Conflicting clinical findings are reported in the literature with some data suggesting that HIV/HCV co-infected patients receiving abacavir-containing ART may be at risk of a lower response rate to pegylated interferon/ribavirin therapy. A possible intracellular mechanism has been postulated that ABC and RBV (two |



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|           | <p>in the table in section 4.5. Minor changes have been made in the English and Romanian PL to improve readability. Annex II was amended to reflect the three yearly PSUR cycle, as requested following PSU042.</p> <p>C.1.3.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</p>  |            |            |             | <p>guanosine analogues) may be competing for the enzymes of a shared phosphorylation pathway. This could lead to a reduction in intracellular phosphorylated metabolites of ribavirin and, as a potential consequence, a reduced chance of sustained virological response (SVR) for Hepatitis C (HCV) in HCV co-infected patients treated with pegylated interferon plus RBV. SmPC section 4.5 has also been updated accordingly.</p> |
| II/0032/G | <p>This was an application for a group of variations.</p> <p>Update of sections 4.4, 4.5 and 4.6 of the SmPC in fulfilment of commitments related to all antiretroviral agents containing lamivudine based on clinical experience gained on the use of lamivudine during pregnancy and on new information available on interactions. The PL was updated accordingly. In addition, further to Kivexa R/23 (FUM 038), section 4.5 has been revised and the format of the pharmacokinetic interaction data updated in line with the latest HIV guideline. The MAH took this opportunity to bring the SmPC in line with the latest QRD template and to update the address list in the PL.</p> <p>C.1.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article</p> | 17/03/2011 | 06/05/2011 | SmPC and PL |   |

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|         | <p>45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH</p> <p>C.1.3.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</p>  |            |            |                        |   |
| II/0034 | <p>Update of Summary of Product Characteristics, Labelling and Package Leaflet</p> <p>Update of Section 5.1 of the SmPC in line with the Annex B template of the guideline on the clinical development of medicinal products for the treatment of HIV infection, as requested by the CHMP. The MAH took the opportunity to introduce minor changes to the SmPC, labelling and patient leaflet.</p> <p>C.1.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data</p> | 17/02/2011 | 18/03/2011 | SmPC, Labelling and PL | <p>Section 5.1 has been restructured with data obtained from literature review and reports previously submitted by the MAH, in line with the HIV guideline EMEA/CPMP/EWP/633/02. The revision concerned the data on in vitro antiviral activity against HIV-1, including non-B subtypes, and HIV-2 for the individual drug components abacavir and lamivudine and/or in combination; data on the impact of selection for additional resistance mutations upon the susceptibility to abacavir or lamivudine in-vitro and in vivo and for therapy-naive versus experienced patients. Furthermore the clinical experience data was organised under separate headings for treatment naive patients and treatment-experienced patients. In addition the results of treatment-naive studies CNA30021, EPZ104057 (HEAT), CNA109586 (ASSERT) are now presented in the proposed tabulated format. The tables for CNA30021, EPZ104057 (HEAT) and CNA109586 (ASSERT) have been updated with additional sub-group analyses for baseline ribonucleic acid (RNA) for each of the studies and also for baseline CD4 categories for the CNA30021 study. Data from studies CAL30001 and ESS30008 has been revised to expand on the statistical test results of the</p> |

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|         |  |            |            |                        | analyses. Two tables were introduced from CAL30001 and CNA30021 studies on the Proportion of Patients with <50 cps/mL at Week 48 by Genotypic Sensitivity Score in OBT and Number of Baseline Mutations.   |
| IA/0033 | B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing  | 07/10/2010 | n/a        | Annex II and PL        |  |
| N/0031  | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)   | 30/07/2010 | n/a        | PL                     |  |
| II/0025 | Update of section 5.1 of the SmPC based on data from long-term studies evaluating the relative efficacy of different combination regimens in fulfilment of follow-up measures (FUMs) 029.3, 029.4 and 029.5.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 24/06/2010 | 28/07/2010 | SmPC and PL            | Major changes affected section 5.1 of the SmPC due to the introduction of new data from three comparative clinical trials (HEAT, ACTG5052 and ASSERT). These data are partially conflicting; however they clearly show the emergence of a signal towards a higher risk of virological failure for Kivexa versus other backbones. A warning statement has therefore been introduced in section 4.4 which also redirects the reader to section 5.1. A cross-reference was added for the same reason in section 4.1. In the PL the contact details for the Spanish local representative were amended. |
| T/0030  | Transfer of Marketing Authorisation  | 29/03/2010 | 26/05/2010 | SmPC, Labelling and PL |  |
| IB/0027 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer   | 28/01/2010 | n/a        |                        |  |
| IB/0026 | To introduce a minor change in the manufacturing process of a starting material  | 25/01/2010 | n/a        |                        |  |

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|         | IB_10_Minor change in the manufacturing process of the active substance   |            |            |                                  |   |
| IA/0028 | 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 | 12/01/2010 | n/a        |                                  |   |
| R/0023  | Renewal of the marketing authorisation.   | 24/09/2009 | 11/12/2009 | SmPC, Annex II, Labelling and PL | <p>Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Kivexa (3TC-ABC fixed dose combination) remains positive. However specific safety issues related to pharmacovigilance remain, which warrant a close monitoring.</p> <p>The main safety issue of Kivexa is hypersensitivity reaction (HSR) associated with ABC, which can be severe and life threatening and is a matter of concern. Studies showed an association between patients carrying HLA B5701 allele and occurrence of HSR. Based on this information the screening for carriage of the HLA-B*5701 allele should be performed before initiating treatment with Kivexa and Kivexa should not be used in patients known to carry HLA B5701 allele.</p> <p>Two further issues are of potential concern involving the use of Kivexa.</p> <p>First, results from a clinical trial show that Kivexa has been associated with a statistically significantly shorter time to virologic failure versus the group receiving emtricitabine-tenofovir. Further clinical trial results have supported this signal and the MAH has submitted a variation to reflect this</p> |

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|         |  |            |            |             | <p>information on the product information.</p> <p>Secondly, a signal has been raised towards an association between ABC and risk of myocardial infarction. A causal relationship between myocardial infarction and ABC could neither be confirmed nor refuted, however as a precautionary measure, a warning was included in the SPC to reflect this information.</p> <p>Based on these issues, the CHMP is of the opinion that one additional five-year renewal on the basis of pharmacovigilance grounds is required. The MAH should continue to submit yearly PSURs and other safety information, until otherwise specified by the CHMP.</p>   |
| II/0024 | <p>Update of section 4.1 "Therapeutic indications", section 4.4 "Special warnings and precaution for use" and section 4.8 "Undesirable Effects" of the SPC to improve clarity for prescribers on HLA-B*5701 screening and the clinical management of abacavir (ABC) hypersensitivity reaction (HSR), as requested in the CHMP's assessment of the abacavir PSUR covering the period 01 January 2008 to 31 December 2008. The information on the HSR incidence was revised. Section 2 "Before you take Kivexa" of the PL was updated accordingly.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p> | 22/10/2009 | 25/11/2009 | SmPC and PL | <p>There has been one report of a case of hypersensitivity reaction (HSR) against the active substance abacavir at re-initiation of treatment in a patient who previously had well tolerated this medicinal product. However afterwards, this patient was tested positive for the gene HLA-B*5701, which is associated with a higher HSR risk. There have also been case reports of HSR in patients who already had shown HSR symptoms before, but were tested HLA-B*5701 negative. Based on these facts, it was regarded as necessary to amend the recommendation for HLA-B*5701 testing before re-initiation of abacavir treatment and to highlight that HSR can also occur in HLA-B*5701 negative patients in the Product Information. Regarding the latter issue, also the information on HSR incidence was updated and is now reflecting the still significant HSR incidence obtained for HLA-B*5701 negative patients in recent studies which differentiated between HLA-B*5701 negative and positive patients.</p> |

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| II/0021 | <p>Update of Summary of Product Characteristics, Labelling and Package Leaflet</p> <p>To update section 4.4 of the SPC and section 2 of the Package Leaflet for Kivexa Tablets to include information regarding abacavir use and the potential increased risk of myocardial infarction. Annex IIIA was updated with information in Braille.</p> <p>Furthermore, the contact details for Denmark, Latvia and Slovakia were updated in the PL.</p> <p>Update of Summary of Product Characteristics, Labelling and Package Leaflet</p> | 23/04/2009 | 08/06/2009 | SmPC, Labelling and PL | <p>In April 2008 EMEA issued a press release on an association between the use of abacavir and the risk of myocardial infarction shown in an observational study (DAD study). Since then additional data derived from observational studies and clinical trials have become available on this issue including FHDH study.</p> <p>Observational studies have shown an association between myocardial infarction and the use of abacavir. The patients studied have generally received antiretroviral treatment prior inclusion in the study (experienced patients). There were limited numbers of myocardial infarction in data from clinical trials and a small increase in risk could not be excluded.</p> <p>The data available so far present some inconsistencies and can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction.</p> <p>To date, there is no established biological mechanism to explain a potential increase in risk.</p> <p>The CHMP concluded that on the basis of the data available no recommendation could be made for changing the therapeutic management of patients. When prescribing Kivexa action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).</p> |
| IA/0022 | IA_06_a_Change in ATC code: Medicinal products for human use  | 14/08/2008 | n/a        | SmPC                   |  |
| II/0018 | Update of Summary of Product Characteristics and Package Leaflet  | 24/01/2008 | 29/02/2008 | SmPC and PL            | Hypersensitivity reaction (HSR) is a potential life-threatening adverse reaction which occurs in approximately 5% of patients taking abacavir (ABC).   |

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|         | <p>To update sections 4.1 and 4.4 of the SPC to inform prescribers that before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed. Abacavir should not be used in patients known to carry the HLA-B*5701 allele. This update on genetic risk factors associated to abacavir hypersensitivity was supported by two recently completed clinical studies. Section 2 of the PL was updated accordingly.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p> |            |            |                              | <p>Retrospective studies reported a highly significant association between HLA-B*5701 allele carriage and ABC HSR. The MAH has conducted two new phase IV studies to assess the association of HLA-B*5701 and the occurrence of ABC HSR as well as the clinical utility of a pharmacogenetic pre-screening strategy prior to initiating therapy with ABC.</p> <p>Results from a prospective study demonstrate that patients with the HLA-B*5701 allele are at a significantly higher risk of developing an HSR than patients without the HLA-B*5701 allele (i.e. 48 to 61% of patients with the HLA-B*5701 allele will develop and HSR versus 0 to 4% in patients without the HLA-B*5701 allele). Therefore, HLA-B*5701 testing should be performed before any initiation of abacavir treatment. Moreover, CHMP recommended that patients carrying the HLA-B*5701 allele should not be considered for the treatment with abacavir.</p> <p>Furthermore, results show that skin patch testing fails to detect ABC HSR in a subset of patients and therefore should not be used in clinical practice for the purpose of HSR diagnosis.</p> |
| II/0020 | Change(s) to the manufacturing process for the active substance  | 24/01/2008 | 29/01/2008 |                              |   |
| IB/0017 | IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size   | 16/11/2007 | 16/11/2007 | SmPC,<br>Labelling and<br>PL |   |
| IB/0019 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer   | 08/11/2007 | n/a        |                              |   |

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| II/0016 | <p>To update section 5.1 of the SPC concerning the emergence of M184V mutation following CHMP request dated 18 October 2006.</p> <p>Update of Summary of Product Characteristics</p>   | 19/07/2007 | 27/08/2007 | SmPC | <p>The MAH submitted this type II variation II/16 to update 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 Eпивir (lamivudine), which is another NRTIs indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection.</p>   |
| II/0015 | <p>To update section 5.2 of the SPC to include the results from a study evaluating abacavir intracellular pharmacokinetics in HIV infected patients in relation to FUM 17.1.</p> <p>Update of Summary of Product Characteristics</p>   | 19/07/2007 | 27/08/2007 | SmPC | <p>The MAH provided the results of studies to support the once daily regimen for abacavir and lamivudine. For abacavir it was demonstrated that the pharmacokinetic parameters of CBV-TP (carbovir thiphosphate, active metabolite of abacavir) were higher with the abacavir once daily regimen than with the abacavir twice daily regimen. Regarding lamivudine it was found that intracellular lamivudine-TP pharmacokinetic parameters were similar or lower for the lamivudine 300 mg once daily regimen compared to the lamivudine 150 mg twice daily regimen.</p>                   |
| II/0013 | <p>To update section 5.1 of the SPC with information on resistance to abacavir, based on an analysis of resistance data derived from pertinent clinical trials. The MAH took the opportunity of this change to update the ATC code for Kivexa.</p> <p>Update of Summary of Product Characteristics</p> | 22/02/2007 | 30/05/2007 | SmPC | <p>Based on results from the available relevant studies, the SPC has been updated with information on the resistance pattern of abacavir, in particular on the mutation pejorative to the virological response of abacavir, since this information could be clinically helpful. The information is now presented for in vitro resistance and for in vivo resistance in therapy naive patients as well as therapy experienced patients. Concerning in vivo resistance in therapy naive patients, isolates from most patients experiencing virological failure with a regimen containing</p> |



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|         |  |            |            |             | abacavir in pivotal clinical trials showed either no NRTI-related changes from baseline or only M184V or M184I selection. Concerning in vivo resistance in therapy experienced patients, a clinically significant reduction of susceptibility to abacavir has been demonstrated in clinical isolates of patients with uncontrolled viral replication, who have been pre-treated with and are resistant to other nucleoside inhibitors. Phenotypic resistance to abacavir requires M184V with at least one other abacavir-selected mutation, or M184V with multiple thymidine analogue mutations. The currently recommended resistance algorithms can help in the appropriate use of abacavir.  |
| IA/0014 | 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/0012 | <p>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.</p> <p>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.</p> <p>The contact details for the local representatives in Portugal have been updated.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p> | 14/12/2006 | 17/01/2007 | SmPC and PL | <p>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.</p> |

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| II/0009 | To update section 4.4 of the SPC and section 2 of the PL with new information relating to genetic and clinical risk factors for the abacavir hypersensitivity reaction. The MAH also took the opportunity to update the product information according to the QRD template version 7.1.<br><br>Update of Summary of Product Characteristics, Labelling and Package Leaflet | 18/10/2006 | 28/11/2006 | SmPC, Annex II, Labelling and PL | A review of genetic risk factors for the hypersensitivity to abacavir has shown that Caucasian patients with the HLA-B*5701 allele are more likely to develop a hypersensitivity reaction to abacavir. Analyses of clinical risk factors for the hypersensitivity to abacavir have identified the risk for Black patients to be approximately half the risk for other racial groups combined. However, since approximately 5% of patients receiving abacavir develop a hypersensitivity reaction, the risk for Black patients is of the same magnitude as for other racial groups and the same close monitoring should apply to patients of all racial groups. |
| IB/0010 | IB_17_a_Change in re-test period of the active substance  | 10/08/2006 | n/a        |                                  |  |
| IA/0011 | IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold  | 26/07/2006 | n/a        |                                  |  |
| II/0008 | Change(s) to the manufacturing process for the active substance   | 01/06/2006 | 07/06/2006 |                                  |  |
| IB/0005 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer  | 06/01/2006 | n/a        |                                  |  |
| IB/0006 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer  | 05/01/2006 | n/a        |                                  |  |
| IB/0004 | IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer  | 22/12/2005 | n/a        |                                  |  |
| IA/0007 | IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold  | 08/12/2005 | n/a        |                                  |  |

|         |   |            |            |             |   |
|---------|---|------------|------------|-------------|---|
| II/0003 | <p>To update section 5.3 "Preclinical safety data" of the Summary of Product Characteristics (SPC) to include data from the oral rat micronucleus study report as requested by CHMP in April 2005.</p> <p>Update of Summary of Product Characteristics</p>  | 15/09/2005 | 07/11/2005 | SmPC        | <p>To update section 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics (SPC) to introduce the 48 week results of the study ESS30008 as requested by CHMP in April 2005.</p> <p>Also the Marketing Authorisation Holder took the opportunity to update the address of the Polish and Swedish representatives in the Package Leaflet</p> |
| II/0002 | <p>To update section 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics (SPC) to introduce the 48 week results of the study ESS30008 as requested by CHMP in April 2005.</p> <p>Also the Marketing Authorisation Holder took the opportunity to update the address of the Polish and Swedish representatives in the Package Leaflet.</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p>                              | 15/09/2005 | 07/11/2005 | SmPC and PL | <p>To update section 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics (SPC) to introduce the 48 week results of the study ESS30008 as requested by CHMP in April 2005.</p> <p>Also the Marketing Authorisation Holder took the opportunity to update the address of the Polish and Swedish representatives in the Package Leaflet</p> |
| II/0001 | <p>To update section 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics (SPC) to introduce the 48 week results of the study CAL30001 as requested by CHMP in March 2005.</p> <p>In addition, the Marketing Authorisation Holder took the opportunity of this variation to update the address of the local representative in Slovenia in the Package Leaflet (PL).</p> <p>Update of Summary of Product Characteristics and Package Leaflet</p> | 27/07/2005 | 08/09/2005 | SmPC and PL |   |

