# Evoltra

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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| N/0083 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 17/07/2024 | | PL | |
| S/0081 | 18th annual re-assessment | 27/06/2024 | n/a | | The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the |

[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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| S/0078 | Annual re-assessment. | 22/06/2023 | n/a | | |
| IA/0080/G | This was an application for a group of variations.<br><br>A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)<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 | 24/03/2023 | n/a | | |
| IAIN/0079 | A.1 - Administrative change - Change in the name and/or address of the MAH | 13/03/2023 | 16/02/2024 | SmPC, Labelling and PL | |
| II/0077 | Update of section 4.6 of the SmPC and the Package Leaflet in order to update information regarding breast-feeding based on a comprehensive safety review. In addition, the MAH took the opportunity to include editorial changes to align data in section 5.1 and to update the list of local representatives for Germany 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 | 09/03/2023 | 16/02/2024 | PL | Safety information have been implemented to require that breastfeeding should be discontinued prior to, during and within 2 weeks after completion of following treatment with Evoltra<br>For more information, please refer to the Summary of Product Characteristics. |

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| S/0076 | Annual re-assessment. | 21/07/2022 | n/a | | |
| II/0075 | Update of section 4.6 of the SmPC following a request during EMEA/H/C/PSUSA/00000805/202012 to revise Section 4.6 of the SmPC and corresponding sections in the PIL considering the recommendations of the Safety Working Party as reflected in the 'SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug' and available data. The proposed update of the product information should be based on a detailed scientific rationale from all available data. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.2<br><br>C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH | 13/01/2022 | 16/12/2022 | SmPC and PL | Due to the genotoxic risk of clofarabine, women of childbearing potential treated with clofarabine must use effective methods of contraception during treatment with clofarabine and for 6 months following completion of treatment.<br>Men should also use effective methods of contraception and be advised to not father a child while receiving clofarabine, and for 3 months following completion of treatment with clofarabine.<br>For more information, please refer to the Summary of Product Characteristics. |
| IB/0074 | B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation | 12/11/2021 | n/a | | |
| PSUSA/805/202012 | Periodic Safety Update EU Single assessment - clofarabine | 08/07/2021 | n/a | | PRAC Recommendation - maintenance |

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| S/0072 | Annual re-assessment. | 24/06/2021 | n/a | | |
| IA/0073 | A.7 - Administrative change - Deletion of manufacturing sites | 22/04/2021 | 12/11/2021 | Annex II and PL | |
| WS/1829 | This was an application for a variation 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 | 12/11/2020 | 12/11/2021 | SmPC, Annex II and PL | |
| PSUSA/805/201912 | Periodic Safety Update EU Single assessment - clofarabine | 23/07/2020 | 24/09/2020 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/805/201912. |
| II/0069 | C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing 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 | 03/09/2020 | n/a | | |
| S/0068 | Annual re-assessment. | 25/06/2020 | n/a | | |
| IAIN/0066 | B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site | 27/01/2020 | n/a | | |
| IA/0065 | A.7 - Administrative change - Deletion of manufacturing sites | 08/01/2020 | 24/09/2020 | Annex II and PL | |

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| IB/0064 | B.I.z - Quality change - Active substance - Other variation | 09/10/2019 | n/a | | |
| PSUSA/805/201812 | Periodic Safety Update EU Single assessment - clofarabine | 11/07/2019 | n/a | | PRAC Recommendation - maintenance |
| S/0063 | Annual re-assessment. | 27/06/2019 | n/a | | |
| IAIN/0061/G | This was an application for a group of variations.<br><br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place<br>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 | 12/03/2019 | 14/11/2019 | Annex II and PL | |
| IG/1003 | A.1 - Administrative change - Change in the name and/or address of the MAH | 20/12/2018 | 14/11/2019 | SmPC, Labelling and PL | |
| S/0059 | Annual re-assessment. | 18/10/2018 | 12/12/2018 | Annex II | |
| PSUSA/805/201712 | Periodic Safety Update EU Single assessment - clofarabine | 12/07/2018 | n/a | | PRAC Recommendation - maintenance |
| IB/0056 | C.I.11.z - Introduction of, or change(s) to, the | 05/12/2017 | n/a | | |

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| | obligations and conditions of a marketing authorisation, including the RMP - Other variation | | | | |
| IB/0057 | C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation | 14/11/2017 | 18/10/2018 | SmPC, Labelling and PL | |
| S/0055 | Annual re-assessment. | 09/11/2017 | n/a | | |
| PSUSA/805/201612 | Periodic Safety Update EU Single assessment - clofarabine | 06/07/2017 | n/a | | PRAC Recommendation - maintenance |
| IA/0052/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<br>A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)<br>A.7 - Administrative change - Deletion of manufacturing sites | 18/11/2016 | n/a | | |

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| S/0050 | Annual re-assessment. | 13/10/2016 | n/a | | |
| PSUSA/805/201512 | Periodic Safety Update EU Single assessment - clofarabine | 21/07/2016 | 15/09/2016 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/805/201512. |
| IA/0051/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.7 - Administrative change - Deletion of manufacturing sites | 03/08/2016 | n/a | | |
| R/0047 | Renewal of the marketing authorisation. | 19/11/2015 | 14/01/2016 | 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 Evoltra continues to be favourable. |
| S/0048 | 9th Annual Re-assessment. | 19/11/2015 | n/a | | The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Evoltra should be maintained. |
| PSUSA/805/201412 | Periodic Safety Update EU Single assessment - clofarabine | 23/07/2015 | 18/09/2015 | SmPC and PL | Please refer to Evoltra PSUSA-00000805-201412 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation |

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| S/0045 | 8th Annual Re-assessment. | 22/01/2015 | 16/03/2015 | Annex II | The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Evoltra should be maintained. |
| PSUV/0044 | Periodic Safety Update | 25/09/2014 | 19/11/2014 | SmPC | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0044. |
| II/0042 | Update of sections 4.4 and 4.8 of the SmPC to include warnings regarding reported cases of haemorrhage including fatal cases further to the PRAC/CHMP request following the assessment of PSUR 8. The PL has been updated accordingly.<br><br>C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation | 25/04/2014 | 10/10/2014 | SmPC and PL | The search of the MAH safety database retrieved a total of 146 cases with adverse drug reactions of Haemorrhage related to the use of clofarabine. There were 90 cases that were considered fatal. Patients fully recovered or recovered with sequelae in 36 cases, did not recover in 15 cases and no information is available in 5 cases. Haemorrhagic ADRs of mouth haemorrhage, gingival bleeding, hematemesis and haematuria were already listed in section 4.8 of the clofarabine SmPC. Haemorrhagic ADRs from SOC Respiratory disorders and Nervous system disorders, which are potentially more severe than those previously listed in the SmPC and which can lead to fatal outcome, have now been included in the PI. |
| IG/0418 | 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 | 11/04/2014 | n/a | | |
| S/0041 | 6th and 7th Annual Re-assessments. | 20/03/2014 | n/a | | The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the |

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| N/0040 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 15/01/2014 | 10/10/2014 | PL | |
| II/0039 | Update of sections 4.4 and 4.8 of the SmPC to include warnings regarding reported cases of caecitis, Stevens-Johnson syndrome and toxic epidermal necrolysis as requested by the CHMP further to the assessment of PSUR 8. The warning has also been strengthened regarding enterocolitis and veno-occlusive disease. Additional information regarding selected adverse drug reactions has also been included in section 4.8 of the SmPC. The Package leaflet has been updated accordingly.<br>In addition, the MAH took the opportunity of this procedure to correct Annex II and to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9.0.<br>Finally the MAH introduced some editorial changes and corrections to the PI.<br><br>C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation | 24/10/2013 | 10/10/2014 | SmPC, Annex II, Labelling and PL | Further to the CHMP review of the 8th PSUR, the MAH was requested to include warnings regarding reported cases of caecitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The MAH was also requested to strengthen the warning regarding enterocolitis and veno-occlusive disease (VOD). The section 4.8 was also updated to include further information on prolonged cytopenias and bone marrow failure, infections and infestations, VOD, capillary leak syndrome, gastrointestinal disorders and SJS and TEN. |
| IA/0038 | A.7 - Administrative change - Deletion of manufacturing sites | 03/06/2013 | n/a | | |
| IG/0283 | C.I.z - Changes (Safety/Efficacy) of Human and | 22/03/2013 | n/a | | |

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| | Veterinary Medicinal Products - Other variation | | | | |
| N/0036 | Update of the list of local representatives.<br><br>Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 05/07/2012 | 10/10/2014 | PL | |
| N/0035 | Update in the local representative for Spain in the package leaflet.<br><br>Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 25/04/2012 | 10/10/2014 | PL | |
| S/0033 | 5th Annual Re-assessment | 16/02/2012 | 13/04/2012 | Annex II | The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable. |
| IB/0034/G | This was an application for a group of variations.<br><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.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 | 15/02/2012 | n/a | | |

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| II/0031 | To update sections 4.2, 4.4 and 5.2 to include a dosing recommendation for paediatric patients with moderate renal impairment further to the request of the CHMP following the assessment of the responses to Specific Obligation 12 (SO2 012.7). Based on the population pharmacokinetic and safety analyses of paediatric and adult data, the MAH proposes to reduce the dose of Evoltra by 50% for patients with moderate renal impairment. No dose modification is proposed for patients with mild renal impairment. The MAH took the opportunity of this variation to introduce minor editorial changes and to update the list of local representatives in the PL.<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 | 20/10/2011 | 21/11/2011 | SmPC and PL | In order to provide a dose recommendation in patients with renal impairment, the MAH conducted a population PK analysis of clofarabine concentrations in adult and paediatric patients from 6 studies together with a safety analysis in patients with renal impairment following CHMP request. . Pharmacokinetic data indicate that clofarabine may accumulate in patients with decreased creatinine clearance. As a result of these analyses, it was concluded that paediatric patients with moderate renal impairment (creatinine clearance 30-<60ml/min) require a 50% dose reduction. For the time being no dose adjustment is recommended in mild renally impaired paediatric patients. The safety profile of clofarabine has not been established in patients with severe renal impairment or patients receiving renal replacement therapy. |
| IA/0032/G | This was an application for a group of variations.<br><br>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<br>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 | 09/09/2011 | n/a | | |

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| R/0027 | Renewal of the marketing authorisation. | 20/01/2011 | 24/03/2011 | 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 Evoltra continues to be favourable.<br>The CHMP is however of the opinion that one additional five-year renewal on the basis of pharmacovigilance grounds is required. The grounds for one additional renewal are as follows:<br>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 Evoltra (clofarabine) remains positive, but considers that its safety profile is to be closely monitored for the following reasons:<br>- Data from the voluntary European Registry Programme for prescribers of clofarabine, which is a specific obligation of the marketing authorisation, is needed to further characterise the risk/benefit profile of clofarabine during routine clinical use for the treatment of ALL in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens.<br>- The MAH should continue to submit a yearly PSURs and reassessments. |
| IA/0030/G | This was an application for a group of variations.<br><br>A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) | 17/02/2011 | n/a | | |

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| | A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)<br>A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) | | | | |
| IA/0028 | A.7 - Administrative change - Deletion of manufacturing sites | 26/10/2010 | n/a | | |
| IA/0026 | A.7 - Administrative change - Deletion of manufacturing sites | 01/10/2010 | n/a | | |
| IA/0024 | B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place | 24/09/2010 | n/a | | |
| II/0019 | Quality changes | 22/04/2010 | 27/04/2010 | | |
| II/0018 | Quality changes | 22/04/2010 | 27/04/2010 | | |
| IA/0020 | B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information | 26/03/2010 | n/a | | |
| II/0016 | Update of sections 4.4, 4.5 and 4.8 of the Summary of Product Characteristics (SPC) to include | 17/12/2009 | 19/03/2010 | SmPC, Labelling and | Following the review of cases of renal events reported with Evoltra, it was concluded that some factors other than |

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| | recommendations drawing attention to supportive care measures of adequate hydration, treatment of sepsis and hypotension, prophylactic treatment to mitigate risk of tumour lysis syndrome, and avoidance of nephrotoxic medications and drugs eliminated by renal secretion further to the CHMP request following the assessment of the 4th PSUR. Sections 4.4 and 4.8 of the SPC were also updated to include information regarding enterocolitis, neutropaenic colitis and Clostridium difficile colitis further to the CHMP request following the assessment of the 5th PSUR. The MAH also aligned the safety information with the Company Core Data Sheet (CCDS) to include information in sections 4.4 and 4.8 of the SPC, regarding suppression of bone marrow and associated haematological abnormalities and supportive care measures for correction of an anti-emetic effect of Evoltra (clofarabine). The MAH also took the opportunity to present post-marketing reports currently included in section 4.8 of the SPC (Stevens-Johnson syndrome, toxic epidermal necrolysis and pancreatitis) in tabular format with a frequency unknown in accordance with the SPC guideline recommendations. In addition, the list of local representatives in the package leaflet was updated. Furthermore, editorial and linguistic changes have been introduced in the SPC, labelling and Package leaflet.<br><br>Update of Summary of Product Characteristics | | | PL | Evoltra (clofarabine) could have contributed to the occurrence of these events. During the assessment of the 4th PSUR, the CHMP recommended the inclusion in the SPC of recommendations drawing attention to supportive care measures of adequate hydration, treatment of sepsis (and hypotension, common in the setting of sepsis), prophylactic treatment to mitigate the risk of tumour lysis syndrome, together with the avoidance of nephrotoxic medications and drugs eliminated by renal tubular secretion. Therefore, sections 4.4, 4.5 and 4.8 of the SPC have been updated.<br><br>A cumulative safety review of neutropenic colitis identifying 17 cases was included in the 5th PSUR. Further to the CHMP request following the assessment of the 5th PSUR, the MAH introduced information on colitis, Clostridium difficile colitis and related complications (e.g., ulceration, perforation) in sections 4.4 and 4.8 of the SPC.<br><br>The MAH also proposed to align the SPC with the Company Core Data Sheet (CCDS) including suppression of bone marrow and related haematological abnormalities, and supportive care measures to correct an anti-emetic effect of clofarabine. In addition, the MAH proposed to replace existing descriptive text concerning Stevens - Johnson syndrome, toxic epidermal necrolysis and pancreatitis with presenting these events in a tabular format in Section 4.8. |

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| S/0015 | 3rd Annual reassessment.<br>The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendment of Annexes I and III of the Commission Decision is necessary and that the marketing authorisation remains under exceptional circumstances.<br>Annex II.C has been amended according to the conclusions reached during the CHMP discussion. | 17/12/2009 | 15/03/2010 | Annex II | |
| IB/0014 | IB_33_Minor change in the manufacture of the finished product | 07/09/2009 | n/a | | |
| IA/0013 | IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing | 26/06/2009 | n/a | Annex II and PL | |
| IB/0011 | IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size | 19/05/2009 | 19/05/2009 | SmPC, Labelling and PL | |
| IA/0012 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site | 19/05/2009 | n/a | | |
| II/0009 | Update of Summary of Product Characteristics and Package Leaflet<br><br>Update of Summary of Product Characteristics and Package Leaflet | 19/03/2009 | 29/04/2009 | SmPC and PL | This type II variation concerns updates of sections 4.4, 4.8 and minor updates of section 5.1 of the SPC in line with the data from the final follow-up that have now become available from studies CLO212 and CLO222.<br>The clinical trial patient numbers so far stated in section |

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| | | | | | 4.8 of the SPC (n=132), which included patients who received any dose of clofarabine, have been changed to the number of patients who received only the marketed dose of clofarabine (n=115). With reference to the indication, this is considered a more relevant approach. Hence, figures and percentages in section 4.8 of the SPC have been revised accordingly.<br>Section 4.4 of the SPC now highlights that in the event that a patient experiences a haematologic toxicity of Grade 4 neutropenia (ANC <0.5 x 109/L) lasting ?4 weeks, then the dose should be reduced by 25% for the next cycle.<br>The Package Leaflet has been updated accordingly. |
| II/0008 | Update of Summary of Product Characteristics<br><br>Update of Summary of Product Characteristics | 19/03/2009 | 29/04/2009 | SmPC | This type II variation concerns an update of the SPC, upon request by the CHMP following the assessment of the 3rd PSUR, to add information regarding veno-occlusive disease (VOD) in sections 4.4 and 4.8, statements on the occurrence of pancreatitis, Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in section 4.8, and further information regarding tumour lysis syndrome (TLS), Systemic Inflammatory Response Syndrome (SIRS) and capillary leak syndrome (CLS) in section 4.4.<br><br>Patients should receive IV fluids throughout the 5 day clofarabine administration period. The use of prophylactic steroids (e.g., 100 mg/m2 hydrocortisone on Days 1 through 3) may be of benefit in preventing signs or symptoms of SIRS or capillary leak.<br><br>Patients who have previously received a hematopoietic stem cell transplant (HSCT) may be at higher risk for hepatotoxicity suggestive of veno-occlusive disease (VOD) |

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| | | | | | following treatment with clofarabine (40 mg/m2) when used in combination with etoposide (100 mg/m2) and cyclophosphamide (440 mg/m2). Severe hepatotoxic events have been reported in an ongoing Phase 1/2 combination study of clofarabine in paediatric patients with relapsed or refractory acute leukaemia. Two paediatric reports (1,7%) of veno-occlusive disease (VOD) were considered related to study drug.<br><br>Uncommon occurrences of Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients treated with clofarabine.<br>Occurrences of pancreatitis and/or elevations in serum amylase and lipase have been reported during clofarabine treatment. |
| S/0007 | Annual re-assessment. | 18/12/2008 | 20/02/2009 | Annex II | 2nd Annual reassessment:<br>The CHMP having reviewed the evidence of compliance with specific obligations submitted by the MAH and having reassessed the benefit/risk profile, concluded that the overall benefit/risk balance for Evoltra remains unchanged in the authorised indication and the Marketing Authorisation should remain under exceptional circumstances. |
| IB/0010 | IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening | 22/12/2008 | n/a | | |
| N/0006 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 26/08/2008 | n/a | PL | |
| T/0005 | Transfer of Marketing Authorisation | 18/04/2008 | 04/06/2008 | SmPC, Labelling and | The MAH applied for the transfer of the Marketing Authorisation of Evoltra from Bioenvision Ltd to Genzyme |

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| S/0004 | Annual re-assessment. | 15/11/2007 | 17/01/2008 | Annex II | 1st Annual reassessment:<br>The CHMP having reviewed the evidence of compliance with specific obligations submitted by the MAH and having reassessed the benefit/risk profile, concluded that the overall benefit/risk balance for Evoltra remains unchanged in the authorised indication and the Marketing Authorisation should remain under exceptional circumstances. |
| II/0003 | Quality changes | 19/07/2007 | 29/08/2007 | Annex II and PL | New manufacturer of the finished product Pharmachemie B.V. (PCH), The Netherlands. |
| II/0002 | Quality changes | 19/07/2007 | 24/07/2007 | | New site of manufacture of the active substance (Ferro Phahnstiel Laboratories, (FPL)). |