EMA/694051/2019

# Xiapex

## 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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| PSUSA/871/201902 | Periodic Safety Update EU Single assessment - collagenase clostridium histolyticum (treatment of Dupuytren's contracture and treatment of Peyronie's disease) | 19/09/2019 | 28/11/2019 | | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/00000871/201902. |

[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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| II/0107 | Update of sections 4.4 and 5.1 of the SmPC to update the efficacy and safety information following the final results from study AUX-CC-810: Long-term Safety, Curvature Deformity, Characterization, and Immunogenicity over time in Subjects Previously Treated with AA4500 for Peyronie's Disease in Studies AUX-CC-802, AUX-CC-803, AUC-X-CC-804, and AUX-CC-806; listed as a category 3 study in the RMP. The RMP version 14.1 has also been approved. In addition, the Marketing authorisation holder took the opportunity to introduce minor editorial changes to SmPC and Package Leaflet.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 29/05/2019 | 28/11/2019 | SmPC and PL | A phase 4, non-treatment, long-term follow-up study (AUX-CC-810) was undertaken to evaluate the efficacy and safety up to 5 years after the first injection of Xiapex in the pivotal 12-month double-blind placebo controlled phase 3 studies or the 9 month open-label phase 3 studies. Through the 5 year follow up period, subjects demonstrated an improvement in penile curvature and in PDQ bother compared with the last observed value from the previous phase 3 studies. There were no changes in the international index of erectile function (IIEF) scores. No new safety signals were identified during the 5 year follow-up period. At five years after the initial injection of Xiapex the majority of subjects (>90%) were seropositive for anti-AUX-I and anti-AUX-II antibodies. In addition, seropositivity for neutralizing anti-AUX-I and anti-AUX-II antibodies was maintained. |
| II/0106 | C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 14/02/2019 | n/a | | |
| IB/0108 | B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product | 13/02/2019 | n/a | | |
| IB/0104 | B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) | 16/11/2018 | n/a | | |
| IA/0105 | 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 | 26/10/2018 | n/a | | |

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| | intermediate used in the manufacture of the AS or manufacturer of a novel excipient | | | | |
| PSUSA/871/201802 | Periodic Safety Update EU Single assessment - collagenase clostridium histolyticum (treatment of Dupuytren's contracture and treatment of Peyronie's disease) | 06/09/2018 | n/a | | PRAC Recommendation - maintenance |
| IAIN/0103 | B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site | 05/09/2018 | n/a | | |
| IB/0102 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 09/08/2018 | n/a | | |
| II/0099 | B.II.g.2 - Introduction of a post approval change management protocol related to the finished product | 26/07/2018 | n/a | | |
| IA/0101/G | This was an application for a group of variations.<br><br>B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test<br>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits | 18/06/2018 | n/a | | |
| IB/0098 | B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB | 15/05/2018 | n/a | | |

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| IB/0097 | B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation | 21/03/2018 | n/a | | |
| IB/0096 | 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 | 12/12/2017 | n/a | | |
| PSUSA/871/201702 | Periodic Safety Update EU Single assessment - collagenase clostridium histolyticum (treatment of Dupuytren's contracture and treatment of Peyronie's disease) | 12/10/2017 | 08/12/2017 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/871/201702. |
| IB/0095 | B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | 28/09/2017 | n/a | | |
| IA/0094 | 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 | 15/06/2017 | n/a | | |
| II/0089 | Submission of the final clinical study report for study B1531005, a non-interventional study to evaluate the outcomes (clinical treatment success measured by goniometry assessment, recurrence rate measured by goniometry assessment, subject and physician global assessment of treatment satisfaction, complications resulting from the | 09/06/2017 | n/a | | This non-interventional study B1531005 aimed at reflecting clinical practice and patient choices and satisfaction with 3 treatment options of Dupuytren's contracture: fasciectomy, fasciotomy, and Xiapex. Overall, clinical treatment success was reported in all treatment groups however it could only be assessed in limited numbers of joints and comparison of results between treatment groups was also limited. Taken |

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| | procedure based on the Adverse Event/Serious Adverse Event (AE/SAE)) of 3 various treatment options for Dupuytren's contracture, listed as a category 3 study in the RMP. The RMP (version 13.0) is updated accordingly.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | | | | together, efficacy results did not allow drawing any conclusions on efficacy. The safety profile in this study was consistent with the known safety profile of Xiapex. Overall, the results presented are consistent with the know efficacy and safety profile of Xiapex and did not warrant amendment to the product information. |
| IA/0092 | 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 | 26/04/2017 | n/a | | |
| PSUSA/871/201608 | Periodic Safety Update EU Single assessment - collagenase clostridium histolyticum (treatment of Dupuytren's contracture and treatment of Peyronie's disease) | 09/03/2017 | n/a | | PRAC Recommendation - maintenance |
| IB/0091/G | This was an application for a group of variations.<br><br>B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits<br>B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits<br>B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits | 22/02/2017 | n/a | | |

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| | B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | | | | |
| IB/0090 | B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB | 03/02/2017 | n/a | | |
| IB/0088 | B.II.z - Quality change - Finished product - Other variation | 20/12/2016 | n/a | | |
| IB/0086 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 22/11/2016 | n/a | | |
| IA/0084 | B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol | 11/11/2016 | n/a | | |
| IA/0083 | 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 | 04/11/2016 | n/a | | |
| IA/0085 | 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 | 26/10/2016 | n/a | | |
| IA/0082/G | This was an application for a group of variations. | 10/10/2016 | 20/03/2017 | Annex II | |

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| | 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.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) | | | | |
| PSUSA/871/201602 | Periodic Safety Update EU Single assessment - collagenase clostridium histolyticum (treatment of Dupuytren's contracture and treatment of Peyronie's disease) | 29/09/2016 | n/a | | PRAC Recommendation - maintenance |
| IA/0081 | B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | 14/09/2016 | n/a | | |
| IA/0080 | B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | 12/07/2016 | n/a | | |
| IB/0079 | B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | 21/06/2016 | n/a | | |

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| II/0074 | Update of sections 4.4 and 5.1 of the SmPC in order to reflect the results of a phase 3, open-label study of the safety and effectiveness of Xiapex in men with Peyronie's disease. The MAH took the opportunity of this variation to update annex III.A according to the last QRD template (version 10).<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 26/05/2016 | 20/03/2017 | SmPC and Labelling | |
| IAIN/0077 | C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring | 18/04/2016 | 20/03/2017 | SmPC and PL | |
| IB/0076 | B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | 21/03/2016 | n/a | | |
| PSUSA/871/201508 | Periodic Safety Update EU Single assessment - collagenase clostridium histolyticum (treatment of Dupuytren's contracture and treatment of Peyronie's disease) | 17/03/2016 | n/a | | PRAC Recommendation - maintenance |
| IB/0075 | 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 | 01/02/2016 | n/a | | |

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| IB/0072 | B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | 28/01/2016 | n/a | | |
| R/0061 | Renewal of the marketing authorisation. | 22/10/2015 | 18/01/2016 | SmPC, Annex II, Labelling and PL | Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Xiapex continues to be favourable.<br>The CHMP is of the opinion that an additional five-year renewal is required.<br>This is based on the following Pharmacovigilance grounds:<br>The most recently approved indication for Xiapex (treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity) differs significantly from the first granted indication (Dupuytren's contracture in adult patients with a palpable cord" and therefore different safety profile in the new target population may be expected. As there are several important potential risks and possible unknown issues related to safety and there the lack of exposure in the populations for the indication in Peyronie's disease, a further five-year renewal period is recommended for the product. |
| IA/0073 | 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) | 21/12/2015 | n/a | | |
| IA/0071 | A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the | 09/12/2015 | n/a | | |

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| | finished product, including quality control sites (excluding manufacturer for batch release) | | | | |
| PSUSA/871/201502 | Periodic Safety Update EU Single assessment - collagenase clostridium histolyticum (treatment of Dupuytren's contracture and treatment of Peyronie's disease) | 24/09/2015 | 23/11/2015 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/871/201502. |
| IB/0068 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 10/11/2015 | n/a | | |
| IB/0069 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 06/11/2015 | n/a | | |
| IA/0067 | B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits | 30/10/2015 | n/a | | |
| II/0059 | Update of sections 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC to include information on treatment of Dupuytren's contracture with 2 concurrent injections of Xiapex and to extend time interval for the finger extension procedure post injection. The Package Leaflet and RMP have been updated accordingly.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 21/10/2015 | 18/01/2016 | SmPC and PL | In this variation the MAH updated the Product information to indicate that injections in up to two cords or two affected joints in the same hand can be administered during a treatment visit. Each injection contains a 0.58 mg dose. If the disease has resulted in multiple contractures, additional cords may be treated at other treatment visits approximately 4 weeks apart. Furthermore, the time interval for a finger extension procedure has been prolonged to between 24 and 72 hours post injection. |

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| IB/0066 | B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | 20/10/2015 | n/a | | |
| IB/0064 | B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation | 22/09/2015 | n/a | | |
| IA/0065 | 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 | 03/09/2015 | n/a | | |
| IA/0062 | B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test | 23/07/2015 | n/a | | |
| IB/0057 | 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 | 08/06/2015 | n/a | | |
| IA/0058/G | This was an application for a group of variations.<br><br>A.7 - Administrative change - Deletion of manufacturing sites<br>A.7 - Administrative change - Deletion of manufacturing sites | 19/05/2015 | n/a | | |
| PSUSA/871/201402 | Periodic Safety Update EU Single assessment - collagenase clostridium histolyticum (treatment of | 26/02/2015 | 24/04/2015 | SmPC | Please refer to Xiapex PSUSA-871-201402 EPAR: Scientific conlusion and grounds recommending the variation to the |

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| | Dupuytren's contracture and treatment of Peyronie's disease) | | | | terms of the marketing authorisation |
| IB/0055 | B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product | 02/02/2015 | 24/04/2015 | Annex II | |
| II/0044 | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | 18/12/2014 | 30/01/2015 | SmPC and PL | |
| IB/0053 | B.I.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 | 13/01/2015 | n/a | | Please refer to Xiapex EMEA/H/C/002048 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation |
| IA/0054/G | This was an application for a group of variations.<br><br>B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits<br>B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits | 09/01/2015 | n/a | | |
| IA/0052 | B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits | 22/12/2014 | n/a | | |
| II/0049 | Update of the efficacy data in sections 4.4 and 5.1 of the SmPC based on clinical study AUX-CC-862, an | 18/12/2014 | 30/01/2015 | SmPC | |

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| | open-label study evaluating the safety and efficacy of retreatment with Xiapex in subjects who were participating in Study AUX-CC-860 and who had recurrence of contracture in a joint that was effectively treated with Xiapex in a Phase 3 Auxilium-sponsored study. This is linked to PAM number 16.<br>The Summary of Product Characteristics has been updated to include the retreatment data in Sections 4.4 (Immunogenicity) and 5.1 (Long-term efficacy and safety).<br>The requested variation proposed amendments to the Summary of Product Characteristics.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | |
| IA/0051 | A.7 - Administrative change - Deletion of manufacturing sites | 19/11/2014 | n/a | | |
| II/0046 | Change to in-process tests and limits applied during the manufacture of the AS<br><br>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | 26/09/2014 | n/a | | Change to in-process tests and limits applied during the manufacture of the AS |
| IB/0048 | B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol | 30/07/2014 | 30/01/2015 | SmPC | |

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| IA/0047 | 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 | 25/07/2014 | n/a | | |
| IA/0045/G | This was an application for a group of variations.<br><br>B.I.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<br>B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) | 10/07/2014 | n/a | | |
| IAIN/0043 | 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 | 26/06/2014 | 30/01/2015 | Annex II and PL | |
| II/0038 | Update of sections 4.4 and 5.1 of the SmPC in order to update the safety information on the long term safety and immunogenicity profile and the contraction recurrence profile of Xiapex based on the long term safety and efficacy study AUX-CC-860. A minor editorial change is introduced in the Package Leaflet. | 26/06/2014 | 30/01/2015 | SmPC and PL | A study was conducted, as requested by the CHMP, to evaluate the long-term safety profile of Xiapex. No new safety signals were identified among subjects who were followed for 5 years after their initial injection of Xiapex in a previous clinical study. The majority of adverse events reported during the long-term follow-up period were non-serious, mild or moderate in intensity, and were not related to the local administration of Xiapex. |

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| | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | The safety data provided with the 5 year final report of a long term follow up did not change the known safety profile of the medicinal product containing collagenase clostridium histolyticum. These data support the long term safety profile of Xiapex confirming that no new safety risks were identified during the 5 year follow-up period. No amendments with regard to the safety information of the product information were considered necessary with regards to Adverse Events.<br>The recurrence of contraction rate increased following 2, 3, 4 and 5 years of follow-up compared to 1 year, but overall the recurrence rates in Xiapex treated joints continue to be comparable to the rates observed in the literature for surgical intervention and appear still favourable compared to those reported for PNF (percutaneous needle fasciotomy). |
| II/0035 | Submission of a post-approval change management protocol.<br><br>B.I.e.2 - Introduction of a post approval change management protocol related to the AS | 26/06/2014 | n/a | | Submission of a post-approval change management protocol. |
| IB/0042 | B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB | 06/06/2014 | n/a | | |
| II/0036/G | This was an application for a group of variations.<br><br>To add new finished product QC testing sites.<br><br>B.II.b.2.b - Change to importer, batch release | 22/05/2014 | n/a | | |

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| | arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method<br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)<br>B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method | | | | |
| IB/0041 | B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation | 08/05/2014 | n/a | | |
| IAIN/0040 | 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 | 08/05/2014 | n/a | | |
| II/0029 | Change in active substance specification<br><br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | 25/04/2014 | n/a | | |
| IB/0039/G | This was an application for a group of variations.<br><br>B.I.b.2.e - Change in test procedure for AS or | 24/04/2014 | n/a | | |

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| | starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate<br>B.I.b.z - Change in control of the AS - Other variation | | | | |
| PSUV/0031 | Periodic Safety Update | 10/04/2014 | n/a | | PRAC Recommendation - maintenance |
| T/0037 | Transfer of Marketing Authorisation from Auxilium UK Limited to Swedish Orphan Biovitrum AB (publ)<br><br>Transfer of Marketing Authorisation | 24/02/2014 | 03/04/2014 | SmPC, Labelling and PL | |
| IB/0034 | B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation | 11/02/2014 | n/a | | |
| II/0028 | Change in active substance shelf life<br><br>B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation | 23/01/2014 | n/a | | |
| IAIN/0033 | 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 | 10/01/2014 | 03/04/2014 | Annex II and PL | |
| IA/0032 | A.7 - Administrative change - Deletion of manufacturing sites | 16/12/2013 | n/a | | |

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| IAIN/0030 | C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring | 12/12/2013 | 03/04/2014 | SmPC and PL | |
| N/0027 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 31/10/2013 | 03/04/2014 | PL | |
| IAIN/0026 | B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site | 30/09/2013 | n/a | | |
| IAIN/0025 | 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 | 26/09/2013 | n/a | | |
| IAIN/0023 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 01/07/2013 | n/a | | |
| IAIN/0022 | A.1 - Administrative change - Change in the name and/or address of the MAH | 11/06/2013 | 03/04/2014 | SmPC, Labelling and PL | |
| T/0021 | Transfer of Marketing Authorisation | 12/03/2013 | 09/04/2013 | SmPC, Labelling and PL | |
| IB/0020 | B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation | 21/02/2013 | n/a | | |
| IB/0019 | B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation | 21/02/2013 | n/a | | |

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| II/0016 | Update of section 4.8 of the SmPC in order to include the adverse reaction 'lymphangitis' following assessment of the last PSUR and the CHMP's request. The Package Leaflet was proposed to be updated accordingly.<br>Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8.2.<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 | 17/01/2013 | 09/04/2013 | SmPC, Annex II and PL | The MAH cumulatively reviewed the evidence of the association between collagenase clostridium histolyticum treatment and lymphangitis. In clinical studies, the safety population included 1082 subjects who had received at least 1 dose of collagenase Clostridium histolyticum. Lymphangitis had been reported in 11 (1.0%) of these subjects. In postmarketing reports through the current PSUR reporting period, 6 cases of lymphangitis have been reported. Based on clinical studies with collagenase clostridium histolyticum the frequency of lymphangitis has shown to be about 1%. A causal relationship between the medicinal product and this adverse event is at least a reasonable possibility. Consequently the addition of lymphangitis as an adverse reaction to the product information with the frequency uncommon is endorsed. |
| II/0015 | To replace the current qualitative SDS-PAGE Silver Stain HCP assay used to test collagenase clostridium histolyticum drug substance with a quantitative ELISA-based assay for Host Cell Protein (HCP).<br><br>B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS | 17/01/2013 | n/a | | |
| IB/0018 | B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits | 04/01/2013 | n/a | | |

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| IG/0235/G | This was an application for a group of variations.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation<br>C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV | 06/12/2012 | n/a | | C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF). |
| IB/0014/G | This was an application for a group of variations.<br><br>B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits<br>B.I.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 | 30/10/2012 | n/a | | |
| II/0009 | B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range | 20/09/2012 | n/a | | |
| II/0008 | to revise the current release and stability specifications for the active substance, Collagenase clostridium Histolyticum.<br><br>This variation is submitted to fulfil FUM007 - it presents a reassessment of the AS specifications based on data from a total of 15 commercial batches.<br>The applciant takes the opportunity to implement | 20/09/2012 | n/a | | |

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| | editorial changes.<br><br>B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS | | | | |
| IB/0011 | 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 | 15/08/2012 | n/a | | |
| IA/0013 | B.I.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 | 08/08/2012 | n/a | | |
| IA/0012 | A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS | 27/07/2012 | n/a | | |
| IA/0010 | B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits | 24/07/2012 | n/a | | |
| IG/0169/G | This was an application for a group of variations.<br><br>C.I.9.e - Changes to an existing pharmacovigilance | 08/06/2012 | n/a | | |

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| | system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD<br>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system | | | | |
| IA/0005 | B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | 30/04/2012 | n/a | | |
| IA/0003 | 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) | 01/03/2012 | n/a | | |
| IA/0002 | 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) | 01/02/2012 | n/a | | |
| IB/0001 | B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation | 31/01/2012 | n/a | | |