# Nulojix

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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| IA/0087 | 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 | 10/02/2023 | | Annex II | |

[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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| PSUSA/311/202206 | Periodic Safety Update EU Single assessment - belatacept | 09/02/2023 | n/a | | PRAC Recommendation - maintenance |
| IB/0086 | B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation | 13/01/2023 | n/a | | |
| IB/0085 | 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 | 21/12/2022 | n/a | | |
| II/0082/G | This was an application for a group of variations.<br><br>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process<br>B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product | 15/12/2022 | 23/01/2023 | Annex II | |
| IB/0084 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 28/11/2022 | n/a | | |
| IA/0081 | 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 | 25/07/2022 | n/a | | |

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| | intermediate used in the manufacture of the AS or manufacturer of a novel excipient | | | | |
| II/0079/G | This was an application for a group of variations.<br><br>B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol<br>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation<br>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 07/04/2022 | n/a | | |
| IAIN/0080 | A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release | 14/02/2022 | 23/01/2023 | Annex II and PL | |
| IB/0078 | 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 | 22/12/2021 | n/a | | |
| IA/0077 | B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier | 14/12/2021 | n/a | | |

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| II/0065/G | This was an application for a group of variations.<br><br>Update of the SmPC section 4.2, 5.2 and 6.6 to reflect new maintenance dose and revised PK data following the change in manufacturing process. Labelling and Package leaflet are updated accordingly. Furthermore, the MAH introduced minor editorial changes throughout the PI.<br><br>B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol<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.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised | 11/11/2021 | 13/12/2021 | SmPC, Labelling and PL | Please refer to Scientific Discussion Nulojix EMEA/H/C/002098/II/0065/G |
| II/0076 | B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS | 28/10/2021 | n/a | | |

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| IA/0075 | B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | 24/06/2021 | n/a | | |
| II/0070 | Extension of indication to include the use of belatacept in conversion from a calcineurin inhibitor - based regimen to a belatacept-based regimen post transplantation; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 18.0 of the RMP has also been updated. Furthermore, the product information is brought in line with the latest QRD template version 10.1 and requirement on sodium excipients is added. Editorial changes have been made in the labelling.<br><br>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | 22/04/2021 | 01/06/2021 | SmPC, Annex II, Labelling and PL | Please refer to Scientific Discussion "Nulojix EMEA/H/C/002098/II/0070". |
| II/0071 | B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS | 11/02/2021 | n/a | | |
| IB/0073/G | This was an application for a group of variations.<br><br>B.I.a.4.z - Change to in-process tests or limits | 22/12/2020 | n/a | | |

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| | applied during the manufacture of the AS - Other variation<br>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | | | | |
| IB/0074 | B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits | 18/12/2020 | n/a | | |
| II/0072/G | This was an application for a group of variations.<br><br>B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes<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.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.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 | 10/12/2020 | 30/04/2021 | SmPC, Annex II and PL | |

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| | 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.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products<br>A.7 - Administrative change - Deletion of manufacturing sites | | | | |
| II/0069 | B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS | 24/09/2020 | n/a | | |
| IB/0067 | B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | 28/05/2020 | n/a | | |
| IAIN/0066 | A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release | 11/05/2020 | 30/04/2021 | Annex II and PL | |
| PSUSA/311/201906 | Periodic Safety Update EU Single assessment - belatacept | 30/01/2020 | 03/04/2020 | Annex II, Labelling and PL | Please refer to EMEA/H/C/PSUSA/00000311/201906 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation. |
| II/0063/G | This was an application for a group of variations. | 12/03/2020 | n/a | | Results from both studies showed that cases of PTLD occurred infrequently. In study IM103075, 9/1,631 |

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| | Submission of the final report from studies IM103075 and IM103076 listed as category 3 studies in the RMP. Study IM103075 is a prospective cohort study to assess the association between belatacept use and risk of post-transplant lymphoproliferative disorder (PTLD) in renal transplant recipients in the US. Study IM103076 is a prospective patient registry study to estimate the incidence rates of confirmed PTLD, central nervous system (CNS) PTLD and progressive multifocal leukoencephalopathy (PML) in adult renal transplant recipients treated with belatacept in the US. The RMP version 17.2 has also been updated to reflect the completion of both studies and to make some administrative updates.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority<br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | | | | (0.55%) of the Epstein-Barr virus (EBV) positive subjects in the belatacept group developed post-transplant lymphoproliferative disorder (PTLD). In study IM103076, of the 942 subjects, 933 were EBV-seropositive, and there were 4 cases of PTLD, of which one case with central nervous system (CNS)-PTLD. The incidence rates of PTLD and CNS-PTLD remained low. There were no reports of progressive multifocal leukoencephalopathy (PML).<br>Both studies were non-interventional cohort studies. The use of observational studies to assess the drug utilisation patterns of marketed therapeutic products is challenging for many reasons, including any potential biases due to the non-randomised or allocation of treatment in routine the clinical practice setting, and limitations related to the quality and completeness of the information available for patient demographics and the outcomes of interest.<br>Given the limited number of patients who have received belatacept to date, and the nature of the information available from the United Network for Organ Sharing (UNOS) database, it is concluded that these 2 studies have fulfilled their intended purpose. UNOS captures all transplants performed in the United States since 01-Oct-1987. The MAH will continue to monitor these safety concerns via routine pharmacovigilance activities. The RMP version 17.2 is also approved to remove all currently listed safety concerns from the summary of safety concerns, except for the missing information 'pregnancy and lactation'. |
| IB/0062 | B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | 13/12/2019 | n/a | | |

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| IB/0064 | B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | 11/12/2019 | n/a | | |
| N/0060 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 29/08/2019 | 03/04/2020 | PL | |
| II/0059/G | This was an application for a group of variations.<br><br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method<br>B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method | 20/06/2019 | n/a | | |
| IAIN/0058 | B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking | 29/03/2019 | n/a | | |
| IA/0057 | B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | 27/03/2019 | n/a | | |

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| IB/0055 | B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation | 13/03/2019 | n/a | | |
| II/0051 | B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and any of the test methods is a biol/immunol/immunochemical method | 28/02/2019 | 02/04/2019 | Annex II and PL | |
| II/0052/G | This was an application for a group of variations.<br><br>B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol<br>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation | 21/02/2019 | n/a | | |
| IG/1059 | A.1 - Administrative change - Change in the name and/or address of the MAH | 15/02/2019 | 02/04/2019 | SmPC, Labelling and PL | |
| II/0050/G | This was an application for a group of variations.<br><br>Submission of the final report from studies (IM103074 and IM103077) listed as category 3 studies in the RMP. Study IM103074 is an observational study designed to assess the pattern of use of belatacept in US transplant recipients in routine clinical practice. Study IM103077 is an | 14/02/2019 | n/a | | IM103074 and IM103077 are two real world pattern of use studies designed to describe the prevalence of Epstein-Barr virus (EBV) seropositive and EBV-seronegative in the US (IM103074 using UNOS database) and in Europe (IM103077 using CTS database). By the end of study IM103077 in 2018, the cumulative prevalence of EBV seropositivity was 82% in all belatacept-treated patients and 96.6% in those with known serostatus in IM103077. By |

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| | observational study designed to assess the patterns of use of belatacept in renal transplantation using the collaborative transplant study.<br>An updated RMP (version 16.1) is submitted in order to reflect the results of the above studies. In addition, the MAH took the opportunity to update the RMP in line with the new RMP template (GVP Module V rev.2), to reflect minor editorial changes and to reflect the earlier completion dates for two remaining studies (IM103075 and IM103076) listed as category 3 studies in the RMP.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority<br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | | | | the end of Study IM103074, the cumulative prevalence of EBV-seropositivity was 93.8% in all belatacept-treated patients and 94.8% in those with known serostatus. During the 7 years after the approval of belatacept, the prevalence of EBV seropositivity in belatacept-treated patients had remained high. The review of the studies results does not warrant an update to the product information. |
| II/0054/G | This was an application for a group of variations.<br><br>B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)<br>B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of | 17/01/2019 | n/a | | |

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| | the AS and/or the FP | | | | |
| II/0053 | B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS | 17/01/2019 | n/a | | |
| IB/0049 | B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation | 21/08/2018 | n/a | | |
| II/0047/G | This was an application for a group of variations.<br><br>Submission of the final reports from studies IM103061 and IM103089, listed as a category 3 studies in the RMP. IM103061 is an epidemiological study on pregnancy outcome among belatacept users in the US. IM103089 evaluates data retrospectively to assess the association between belatacept and the risk of PTDL in renal transplant recipients in Europe. An updated RMP, reflecting completion of the two above studies is approved as part of this variation (Version 15.1).<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority<br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 12/04/2018 | n/a | | |

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| IB/0048 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 20/10/2017 | n/a | | |
| II/0045 | Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and update the safety information on the risk of venous thrombosis of the renal allograft when anti-thymocyte globulin (ATG) and belatacept are coadministered (at the same or nearly the same time) in patients with other predisposing risk factors for thrombosis. The update is based on a review of the potential increased risk for allograft thrombosis with belatacept given in close temporal relation to Thymoglobulin, as requested during assessment of PSUR 8 (PSUSA/00000311/201606).In addition, the MAH took the opportunity to update section 6.6 "Special precautions for disposal and other handling" of the SmPC and the "Information for healthcare professionals (HCPs)" in the Package Leaflet (PL) with additional safety instructions for the co-administration of belatacept. The submission of this variation application fulfils LEG 021 for Nulojix. Consistently with the above, RMP version 14.2 has also been submitted, including addition of the potential risk of venous thrombosis of the allograft when ATG and belatacept are coadministered in patients with other predisposing risk factors for thrombosis and a number of administrative changes.<br><br>C.I.3.b - Change(s) in the SPC, Labelling or PL | 01/09/2017 | 05/02/2018 | SmPC and PL | Following a request from the PRAC as part of PSUSA/00000311/201606, the MAH conducted a review of the potential increased risk for allograft thrombosis with belatacept given in close temporal relation to Thymoglobulin. In clinical trials, an increased incidence of graft thrombosis was observed in the post-transplant period in recipients of extended criteria donor allografts. In postmarketing experience in patients with other predisposing risk factors for thrombosis of the renal allograft, renal allograft thrombosis has occurred when the initial dose of anti-thymocyte globulin, as immunosuppressive induction, was coadministered at the same or nearly the same time with the first dose of belatacept. Finally, additional safety instructions for the co-administration of belatacept have been included in section 6.6 "Information for healthcare professionals (HCPs)" of the Summary of Product Characteristics and in the Package Leaflet (PL) to explain that Nulojix should not be infused concomitantly in the same intravenous line with other agents as no physical or biochemical compatibility studies have been conducted to evaluate the its coadministration with other agents. |

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| | 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 | | | | |
| IB/0046 | B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation | 01/08/2017 | n/a | | |
| IB/0044 | 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 | 07/04/2017 | n/a | | |
| PSUSA/311/201606 | Periodic Safety Update EU Single assessment - belatacept | 26/01/2017 | 24/03/2017 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/311/201606. |
| II/0038 | Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information following the completion of an additional open-label 4-year (totally each of the studies lasted for 7 years) follow up from the two Phase 3 pivotal studies (IM103027 and IM103008) in de novo renal transplant recipients to retrieve long-term safety and efficacy data. The Risk Management Plan (Version 12) is updated accordingly.<br>In addition, the marketing authorisation holder took the opportunity to introduce editorial changes in the Package Leaflet.<br>The requested variation proposed amendments to | 23/02/2017 | 05/02/2018 | SmPC | This variation has led to updates of sections 4.8 and 5.1 of the SmPC proposed in order to update the safety and efficacy information following the completion of a 4-year open label follow-up from the two Phase 3 pivotal studies (IM103027 and IM103008) in de novo renal transplant recipients. Overall, each of the studies lasted for 7 year including the completed 3 years of treatment during the pivotal studies and the 4-year long-term open label extension period. Section 4.8 has been updated with the overall observed adverse events. Table 3 Malignancies and post-transplant lymphoproliferative disease as well as safety information regarding infections and autoimmunity have been updated with specific information on events |

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| | the Summary of Product Characteristics and to the Risk Management Plan (RMP).<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | occurred for each of these undesirable effects. Section 5.1 has also been updated with efficacy information on the extension of these studies. No new safety findings were detected and the benefit risk profile of Nulojix remains unchanged. The Risk Management Plan (Version 12) is updated accordingly. |
| IB/0043 | B.IV.z - Quality change - Change in Medical Devices - Other variation | 22/02/2017 | n/a | | |
| IB/0042/G | This was an application for a group of variations.<br><br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>B.I.a.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.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 | 21/12/2016 | n/a | | |
| II/0034/G | This was an application for a group of variations.<br><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 | 17/11/2016 | n/a | | |

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| | an obsolete parameter)<br>B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)<br>B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological 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<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 | | | | |
| IB/0041/G | This was an application for a group of variations.<br><br>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation<br>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation<br>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation | 10/10/2016 | n/a | | |

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| | B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation | | | | |
| IB/0037/G | This was an application for a group of variations.<br><br>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation<br>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | 12/08/2016 | n/a | | |
| IB/0036/G | This was an application for a group of variations.<br><br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 02/08/2016 | n/a | | |
| IA/0039/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>B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier | 21/07/2016 | n/a | | |

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| IB/0035 | B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process | 24/05/2016 | n/a | | |
| N/0033 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 12/05/2016 | 24/03/2017 | PL | |
| R/0031 | Renewal of the marketing authorisation. | 17/12/2015 | 18/02/2016 | SmPC, Annex II, Labelling and PL | |
| IA/0032 | 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) | 27/01/2016 | n/a | | |
| PSUSA/311/201506 | Periodic Safety Update EU Single assessment - belatacept | 14/01/2016 | n/a | | PRAC Recommendation - maintenance |
| II/0028/G | This was an application for a group of variations.<br><br>B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product<br>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<br>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor | 24/09/2015 | n/a | | |

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| | changes to an approved test procedure<br>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 | | | | |
| IB/0029 | B.I.z - Quality change - Active substance - Other variation | 20/08/2015 | n/a | | |
| PSUSA/311/201412 | Periodic Safety Update EU Single assessment - belatacept | 09/07/2015 | n/a | | PRAC Recommendation - maintenance |
| IB/0027 | B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process | 01/07/2015 | n/a | | |
| IB/0025 | B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | 30/01/2015 | n/a | | |
| PSUV/0023 | Periodic Safety Update | 09/01/2015 | n/a | | PRAC Recommendation - maintenance |
| II/0022 | Update of section 4.5 of the SmPC based on the results of a Phase 1, open-label, single-sequence study which assessed the effect of belatacept on the pharmacokinetics of caffeine, losartan, omeprazole, dextromethorphan and midazolam as substrates of cytochrome P450.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to | 18/12/2014 | 18/02/2016 | SmPC | The interaction results from the submitted study (a Phase 1, open-label, single-sequence study in healthy volunteers) may not be used to draw the conclusion on whether an interaction risk exists for belatacept, and should not be cited in the SmPC. However, the conclusion may still be drawn, that based on the mechanism of action of belatacept, it appears that belatacept does not have any relevant direct effects on cytokine levels in liver transplant |

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| | new quality, preclinical, clinical or pharmacovigilance data | | | | recipients or in healthy volunteers.<br>The following text was therefore approved to be included in the SmPC, section 4.5:<br>"Belatacept is a fusion protein that is not expected to be metabolised by the cytochrome P450 enzymes (CYPs) and UDP glucuronosyltransferases (UGTs). No formal interaction studies have been performed with belatacept. Belatacept appears not to have any relevant direct effects on cytokine levels in liver transplant recipients or in healthy volunteers. Belatacept is therefore not expected to affect cytochrome P450 enzymes via effects on cytokines."<br>The results of the currently submitted study did not affect the benefit/risk balance for belatacept. |
| IB/0024 | B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation | 16/12/2014 | n/a | | |
| II/0020 | Change in a specification limit of the finished product<br><br>B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range | 24/07/2014 | n/a | | Change in a specification limit of the finished product |
| PSUV/0021 | Periodic Safety Update | 10/07/2014 | n/a | | PRAC Recommendation - maintenance |
| PSUV/0017 | Periodic Safety Update | 09/01/2014 | n/a | | PRAC Recommendation - maintenance |
| IAIN/0019 | 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 | 17/12/2013 | 16/12/2014 | SmPC and PL | |

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| IA/0016 | B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | 08/05/2013 | n/a | | |
| II/0008 | to replace the Isoelectric focusing (IEF) method by an imaged capillary electrophoresis IEF (iCIEF) used to monitor charge variant groups in belatacept drug substance and drug product. The specifications are updated accordingly.<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 | 25/04/2013 | n/a | | |
| IA/0015 | B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits | 11/04/2013 | n/a | | |
| II/0012 | Update of sections 4.2 and 4.4 of the SmPC in order to add a warning that corticosteroid tapering in patients taking belatacept should be implemented cautiously, particularly in patients at high immunologic risk, such as those with 4 to 6 human leukocyte antigen (HLA) mismatches. The package leaflet has been updated accordingly. Section 5.1 of the SmPC has been updated to reflect the corticosteroid doses used during the first 6 months post-transplant in Phase III studies. | 21/02/2013 | 09/04/2013 | SmPC, Annex II, Labelling and PL | The analysis conducted by the MAH upon the signal observed in postmarketing setting experience showed that the use of belatacept in conjunction with basiliximab induction, mycophenolate mofetil and corticosteroid taper to 5 mg/day by Week 6 post-transplant was associated with an increased rate of acute rejection, particularly Grade III rejection. These Grade III rejections occurred in patients with 4 to 6 human leukocyte antigen (HLA) mismatches. Corticosteroid tapering in patients taking belatacept should be implemented cautiously, particularly in patients at high |

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| | Furthermore, the PI is being brought in line with the latest QRD template version.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | | immunologic risk, such as those with 4 to 6 human leukocyte antigen (HLA) mismatches.<br>The dose of corticosteroids used in two Phase III studies was tapered during the first 6 months following transplantation. In study 1 in recipients of standard criteria donor organs, the median corticosteroid doses administered with the belatacept recommended regimen up to months 1, 3, and 6 were 20 mg, 12 mg and 10 mg, respectively. In Study 2 in recipients of extended criteria donor organs, the median corticosteroid doses administered with the belatacept recommended regimen up to months 1, 3, and 6 were 21 mg, 13 mg, and 10 mg, respectively.<br>A Direct Healthcare Professional Communication (DHPC) has been agreed upon to communicate on the increased rate of acute graft rejection reported with Nulojix (belatacept) when corticosteroids have been rapidly tapered in patients at high immunologic risk for acute rejection. Additionally, the letter communicates that corticosteroid tapering should be implemented cautiously, particularly in patients with 4-6 human leukocyte antigen (HLA) mismatches. |
| IG/0254 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 17/12/2012 | n/a | | |
| IB/0010 | 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 | 19/11/2012 | n/a | | |

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| II/0006/G | This was an application for a group of variations.<br><br>To apply changes in test procedure, surface plasmon resonance-based binding assay, for the active substance and the finished product.<br>Specifications for this test procedure are tightened.<br><br>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits<br>B.I.b.2.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 | 20/09/2012 | 23/10/2012 | Annex II | |
| IB/0009 | B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products | 07/09/2012 | n/a | | |
| IB/0007 | B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits | 10/05/2012 | n/a | | |
| IB/0003 | B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | 02/03/2012 | 23/10/2012 | Annex II | |
| II/0004 | C.I.z - Changes (Safety/Efficacy) of Human and | 19/01/2012 | 14/02/2012 | Annex II | |

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| | Veterinary Medicinal Products - Other variation | | | | |
| IB/0005/G | This was an application for a group of variations.<br><br>B.IV.z - Quality change - Change in Medical Devices - Other variation<br>B.IV.z - Quality change - Change in Medical Devices - Other variation | 26/01/2012 | n/a | | |
| IB/0001 | 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) | 09/09/2011 | n/a | SmPC and Labelling | |
| IB/0002 | B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data | 08/09/2011 | n/a | | |