# Modigraf

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/2839/ 202403 | Periodic Safety Update EU Single assessment - tacrolimus (systemic formulations) | 12/12/2024 | 12/02/2025 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2839/202403. |
| WS/2519/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No | 05/09/2024 | | SmPC and PL | Section 4.6 of the SmPC is updated with the results of study EUPAS37025. Based on limited data (289 prospectively-reported pregnancies with 1st trimester |

[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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| | 1234/2008.<br><br>A grouped application consisting of:<br><br>Type II (C.I.13): Submission of the final report from study F506-PV-0001 (EUPAS37025) listed as a category 3 study in the RMP for Advagraf and Modigraf. This is a non-interventional post-authorization safety study (NI-PASS) of outcomes associated with the use of tacrolimus around conception, or during pregnancy or lactation using data from Transplant Pregnancy Registry International (TPRI). The RMP version 5.2 has also been approved. In addition, section 4.6 of the SmPC has been updated to reflect the results of the study. The package leaflet is updated accordingly.<br><br>Type IB (C.I.11.z): To include the feasibility assessment of using alternative secondary-use data sources to replicate the Transplant Pregnancy Registry International (TPRI) study as a category 3 additional pharmacovigilance activity in the RMP, including the milestones for the progress report and the final report of the feasibility assessment, related to EMEA/H/C/000712/MEA/032 and EMEA/H/C/000954/MEA/024.<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.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing | | | | tacrolimus exposure), study results did not indicate an increased risk of major malformations. A higher prevalence of spontaneous abortion was observed among women treated with tacrolimus compared with alternative immunosuppressants. Among kidney transplant patients there was also a higher prevalence of pre-eclampsia in women treated with tacrolimus. However, overall, there were insufficient evidence to conclude on the risk of these outcomes. Among kidney and liver transplant patients exposed to tacrolimus, 45%-55% of their livebirths were premature, with 75%-85% having a normal birth weight for gestational age. Similar results were observed for other immunosuppressants, although conclusions were hindered by limited evidence. For more information, please refer to the Summary of Product Characteristics. |

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| | authorisation, including the RMP - Other variation | | | | |
| IAIN/0049/G | This was an application for a group of variations.<br><br>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site<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 | 06/08/2024 | n/a | | |
| N/0047 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 18/10/2023 | | PL | |
| WS/2402 | 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.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 26/04/2023 | n/a | | |
| IB/0044/G | This was an application for a group of variations.<br><br>B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation<br>B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits<br>B.II.c.2.b - Change in test procedure for an excipient - Deletion of a test procedure if an alternative test | 29/11/2022 | n/a | | |

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| | procedure is already authorised<br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure<br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | | | | |
| WS/2311/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF<br>B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF | 06/10/2022 | n/a | | |
| WS/2241/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of sections 4.4, 4.5 and 4.8 of the SmPC in order to add a warning on the adverse reaction Thrombotic microangiopathy (TMA) based on a cumulative review of fatal cases of TMA during treatment with tacrolimus, requested by the PRAC following the assessment of the PSUR (EMEA/H/C/00002839/202103). | 06/10/2022 | 19/06/2023 | SmPC and PL | Following a cumulative review and literature review of thrombotic microangiopathy (TMA) section 4.4 and 4.5 are updated to raise awareness about TMA and highlight that concomitant use of tacrolimus with mammalian target of rapamycin (mTOR) inhibitor may increase the risk of developing TMA. The frequency of TMA is also updated from rare to uncommon in section 4.8.<br>Information relating to the potential interaction between tacrolimus with caspofungin is included in section 4.5.<br>Based on post-marketing safety report and literature, section 5.2 is updated to add that tacrolimus is metabolized by the cytochrome P450-3A5 (CYP3A5). |

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| | Update of section 4.5 of the SmPC in order to add the drug-drug interaction between tacrolimus and caspofungin based on post-marketing safety report and literature.<br>Update of section 5.2 of the SmPC in order to add that tacrolimus is metabolized by the cytochrome P450-3A5 (CYP3A5) based on post-marketing safety report and literature.<br>The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement some editorial changes.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data<br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data<br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | For more information, please refer to the Summary of Product Characteristics. |
| IAIN/0042 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 07/06/2022 | 19/06/2023 | SmPC and PL | To update sections 4.4 and 4.5 of the SmPC and section 2 of the PL, to implement the signal recommendation on 'drug interaction with cannabidiol leading to calcineurin inhibitors and mTOR inhibitors serum levels increased and toxicity' (EPITT 19614), adopted at the 7-10 March 2022 PRAC meeting. |
| IA/0041/G | This was an application for a group of variations.<br><br>A.5.b - Administrative change - Change in the name | 17/05/2022 | n/a | | |

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| | 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 | | | | |
| IA/0040 | 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 | 19/04/2022 | n/a | | |
| PSUSA/2839/202103 | Periodic Safety Update EU Single assessment - tacrolimus (systemic formulations) | 16/12/2021 | 16/02/2022 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2839/202103. |
| IAIN/0038 | A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release | 13/12/2021 | 16/02/2022 | Annex II and PL | |
| WS/1874/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation<br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 14/10/2021 | 16/02/2022 | SmPC and PL | |

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| WS/1805 | 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.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 | 11/02/2021 | n/a | | |
| WS/1703/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF<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 | 19/03/2020 | n/a | | |
| WS/1511/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of sections 4.5 and 4.8 of the SmPC to add | 19/09/2019 | 28/02/2020 | SmPC, Labelling and PL | Increased exposure to tacrolimus has been reported following concomitant use with the CYP3A4 inhibitor letermovir, a CMV anti-infective agent. Knowing that immunosuppressed patients may be at risk of CMV and the narrow therapeutic index for tacrolimus, the interaction with letermovir is added. |

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| | the drug-drug interaction with letermovir and to add the adverse reaction febrile neutropenia with frequency unknown, based on the cumulative review of the MAH safety database.<br>The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to implement the wording from the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' in the PI, to update the Maltese local representative in the PL and to implement minor editorial changes throughout the PI.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data<br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | The adverse reaction 'febrile neutropenia' is added at unknown frequency based on the possible contribution of tacrolimus to the development of febrile neutropenia in post-marketing cases. |
| IB/0033 | B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) | 20/08/2019 | n/a | | |
| IAIN/0032 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 12/03/2019 | 28/02/2020 | SmPC and PL | |
| PSUSA/2839/201803 | Periodic Safety Update EU Single assessment - tacrolimus (systemic formulations) | 13/12/2018 | 14/02/2019 | | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2839/201803. |
| IB/0029 | B.II.d.2.d - Change in test procedure for the finished | 10/07/2018 | n/a | | |

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| | product - Other changes to a test procedure (including replacement or addition) | | | | |
| IAIN/0028 | B.II.d.1.h - Change in the specification parameters and/or limits of the finished product - Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur. for the finished product | 04/06/2018 | n/a | | |
| WS/1295 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of section 4.8 of the SmPC in order to add new information on pain in extremity reported as part of calcineurin-inhibitor induced pain syndrome (CIPS). In addition, the Worksharing applicant (WSA) took the opportunity to introduce minor updates throughout the Product Information. The Package Leaflet was updated accordingly.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 17/05/2018 | 14/02/2019 | SmPC and PL | Pain in extremity has been described in a number of published case reports as part of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS). This typically presents as a bilateral and symmetrical, severe, ascending pain in the lower extremities and may be associated with supra-therapeutic levels of tacrolimus. The syndrome may respond to tacrolimus dose reduction. In some cases, it was necessary to switch to alternative immunosuppression. |
| IB/0027/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.c.2.c - Change in the specification parameters and/or limits of the immediate packaging of the AS - Deletion of a non-significant specification parameter | 11/05/2018 | n/a | | |

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| | (e.g. deletion of an obsolete parameter)<br>B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | | | | |
| N/0025 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 10/10/2017 | 14/02/2019 | Labelling and PL | |
| PSUSA/2839/ 201503 | Periodic Safety Update EU Single assessment - tacrolimus (systemic formulations) | 03/12/2015 | n/a | | PRAC Recommendation - maintenance |
| WS/0721 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update section 4.4 of the SPC with a more general description of pharmacokinetic interactions with herbal medicines and their potential clinical consequences and section 4.5 to add the specific interaction with Schisandra sphenanthera. Additionally, the applicant has taken the opportunity to update the MedDRA preferred terms in section 4.8 from MedDRA version 7.1 to MedDRA version 16.0. The Package Leaflet is updated accordingly.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 25/06/2015 | 21/06/2016 | SmPC and PL | The SmPCs for Advagraf, Modigraf and Prograf have been updated with a more general description of pharmacokinetic interactions with herbal medicines and their potential clinical consequences and in particular to add the specific interaction with Schisandra sphenanthera as consequence of an identified signal. The list of ADRs have been updated taking in consideration the MedDRA preferred terms based on MedDRA version 16.0. |

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| IB/0022/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<br>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation | 07/01/2015 | n/a | | |
| R/0019 | Renewal of the marketing authorisation. | 18/12/2013 | 17/02/2014 | SmPC 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 Modigraf continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Modigraf continues to be favourable in the prophylaxis of transplant rejection in adult and paediatric, kidney, liver or heart allograft recipients and in the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult and paediatric patients. |
| IA/0021/G | This was an application for a group of variations.<br><br>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process<br>B.II.b.4.a - Change in the batch size (including batch | 31/10/2013 | n/a | | |

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| | size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size | | | | |
| WS/0382/G | This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of section 4.4 of the SmPC for both Advagraf and Modigraf, to introduce special warnings and precautions for use regarding gastrointestinal (GI) perforation, QT prolongation and torsade de pointes (TdP). As consequence of the addition of QT prolongation/TdP in section 4.4 an update for recommendation to monitor QT prolongation with ECG is introduced in section 4.5 of the SmPC. The Package Leaflet is adequately amended in the corresponding sections. The MAH takes the occasion to do some minor editorial corrections in the SmPC and to update the list of local representatives for Advagraf (Latvia, Estonia, Lithuania, Italy, Romania, Slovenia, Sweden and introduction of Croatia) and for Modigraf (Lithuania, Latvia, Estonia, Cyprus and introduction of Croatia).<br>Furthermore, the PI is being brought in line with the latest QRD template Versions 8.3 and 9<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<br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre- | 24/10/2013 | 17/02/2014 | SmPC, Annex II and PL | Analysis of the MAH's global safety database indicates cases of GI perforation which have been described in patients using tacrolimus. Most of the cases have been described having confounding factors indicating that the contribution of tacrolimus, even though not to be excluded, is not completely clear. As a conservative approach the Product Information document has been updated to include warnings about this possible event.<br>Analysis of the MAH's Safety Database, literature and external database (FDA and WHO) retrieved cases of QT prolongation and Torsade de Pointes in patients using tacrolimus. Even though only suspected correlation of these events has been possible in connection with tacrolimus, patients using the drug are usually under concomitant treatments or at risk of conditions triggering the QT prolongation and the possible torsade de pointes. Therefore the warning about these possible events in patients using Tacrolimus has been further implemented in the Product Information. |

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| | clinical, clinical or pharmacovigilance data | | | | |
| IAIN/0020 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 01/08/2013 | n/a | | |
| IAIN/0018/G | This was an application for a group of variations.<br><br>C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV<br>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV<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 | 07/05/2013 | n/a | | |
| IAIN/0016 | C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV | 08/03/2013 | n/a | | |
| WS/0305 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of SmPC sections 4.4., 4.5 and PL section 2 regarding interactions with protease inhibitors and amiodarone. The MAH also took the opportunity to perform minor editorial corrections in the SmPC and amend the list of local representatives in the PL. | 17/01/2013 | 18/02/2013 | SmPC and PL | A cumulative search of the literature and of the company global safety data for tacrolimus has shown that concomitant use of tacrolimus with protein inhibitors or amiodarone results in an increase of its levels. The mechanism related to this interaction is mainly reported to be due to an inhibition of CYP3A4 enzyme which is involved in the metabolism of tacrolimus and is inhibited by either the protease inhibitors or amiodarone. Therefore, the current warning related to the use of tacrolimus together with drugs capable of reducing CYP3A4 activity is amended. |

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| | C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | | These drugs include in particular protease inhibitors for HIV and HCV and amiodarone. |
| IAIN/0015/G | This was an application for a group of variations.<br><br>C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV<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 | 08/02/2013 | n/a | | |
| IAIN/0014 | A.1 - Administrative change - Change in the name and/or address of the MAH | 11/01/2013 | 18/02/2013 | SmPC, Labelling and PL | |
| IG/0223/G | This was an application for a group of variations.<br><br>B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer<br>B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer<br>B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The | 31/10/2012 | n/a | | |

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| | proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer | | | | |
| IA/0013 | C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH | 15/10/2012 | n/a | | |
| II/0010/G | This was an application for a group of variations.<br><br>• Update of section 4.6 of the SmPC in order to update the safety information regarding the occurrence of cases of spontaneous abortion.<br>• Update of section 4.8 of the SmPC in order to update the safety information with agranulocytosis and haemolytic anaemia as new adverse reactions.<br>The Package Leaflet is updated accordingly.<br>In addition, the PI is being brought in line with the latest QRD template version and minor redactional changes have been implemented. Furthermore, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.<br>The requested group of variations proposed amendments to the Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.<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 | 19/07/2012 | 30/08/2012 | SmPC, Annex II, Labelling and PL | Based on a cumulative overview of pregnancy-related events, information on reported cases of spontaneous abortions was included in section 4.6 of the SmPC, in order to appropriately reflect the post-marketing experience with systemic tacrolimus in exposed pregnancies. Pregnancy-related cases remain under close monitoring and will be reported and discussed in the PSURs.<br>Review of the available data in the safety database of the MAH concluded that cases of agranulocytosis and haemolytic anaemia have been reported in association with use of tacrolimus. Regarding agranulocytosis, 36 cases were identified as of October 2010, of which four and 17 were classified as 'Index' and 'Informative', respectively. The reported index and informative cases suggest a causative relationship between administration of systemic tacrolimus and agranulocytosis. Regarding haemolytic anaemia, 67 cases were identified as of October 2010, of which one and 21 cases were classified as 'Index' and 'Informative', respectively. Based on these cases a possible causative relationship between administration of systemic tacrolimus and haemolytic anaemia is suggested. The two identified adverse reactions were included in the SmPC and |

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| | C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | | the PIL and the benefit-risk balance of the product remains positive. |
| IAIN/0009/G | This was an application for a group of variations.<br><br>C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV<br>C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database<br>C.I.9.e - Changes to an existing pharmacovigilance 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 | 30/01/2012 | n/a | | |
| IA/0008/G | This was an application for a group of variations.<br><br>B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer<br>B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a | 13/01/2012 | n/a | | |

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| | Member State | | | | |
| WS/0131 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>Update of section 4.4 and 4.8 of the SmPC regarding Pure Red Cell Aplasia (PRCA). The PIL is updated accordingly. Furthermore, the MAH took the opportunity to update the list of local representatives in section 6 of the PIL.<br>This application was submitted for a group of variations consisting of a Type II variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | 21/07/2011 | 24/08/2011 | SmPC and PL | The MAH provided the Signal Evaluation Report for Pure Red Cell Aplasia for Prograf (systemic tacrolimus). While the number of cases are limited, and many of the 27 reported "informative cases" of PRCA are confounded by factors such as co-administration of other medication, evidence of parvovirus B19 infection or the presence or history of thymoma/myasthenia gravis, the available data strongly suggests a causative association between exposure to tacrolimus and the development of PRCA. Therefore, a warning statement has been included in the SmPC of all three systemic tacrolimus products (Advagraf, Modigraf, Prograf) and the PRCA has been added as an adverse reaction in the section "Undesirable effects". |
| IA/0006/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS<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) | 24/08/2011 | n/a | | |

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| IA/0005/G | This was an application for a group of variations.<br><br>C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV<br>C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV<br>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV<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 | 07/04/2011 | n/a | Annex II | |
| IB/0004 | B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF | 17/12/2010 | n/a | | |
| IA/0003/G | This was an application for a group of variations.<br><br>C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV<br>C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV<br>C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV<br>C.I.9.d - Changes to an existing pharmacovigilance | 23/08/2010 | n/a | Annex II | |

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|---|---|---|---|---|---|
| | system as described in the DDPS - Change in the safety database<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 | | | | |
| N/0002 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 09/12/2009 | n/a | PL | |
| IA/0001 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site | 24/09/2009 | n/a | | |