Advagraf

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
N/0072	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/10/2023		PL	
IA/0070	A.7 - Administrative change - Deletion of manufacturing sites	28/06/2023	n/a		

[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).

WS/2402	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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		
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. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF 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. 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	06/10/2022	31/05/2023	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. Information relating to the potential interaction between tacrolimus with caspofungin is included in section 4.5. Based on post-marketing safety report and literature, section 5.2 is updated to add that tacrolimus is metabolized

	(EMEA/H/C/00002839/202103). 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. 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. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement some editorial changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				by the cytochrome P450-3A5 (CYP3A5). For more information, please refer to the Summary of Product Characteristics.
IAIN/0067	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/06/2022	31/05/2023	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/0066/G	This was an application for a group of variations.	23/05/2022	n/a		

	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 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/2839/202103	Periodic Safety Update EU Single assessment - tacrolimus (systemic formulations)	16/12/2021	17/02/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2839/202103.
IB/0064/G	This was an application for a group of variations. B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits	14/12/2021	n/a		
IB/0063	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	12/11/2021	n/a		

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. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/10/2021	17/02/2022	SmPC and PL	
IB/0062	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	08/09/2021	n/a		
IA/0060/G	This was an application for a group of variations. B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or	24/06/2021	n/a		

	deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer				
WS/1805	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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		
IA/0059	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	19/10/2020	n/a		
IAIN/0056	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	08/04/2020	22/03/2021	Annex II and PL	
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. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an	19/03/2020	n/a		

	ASMF 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				
II/0054	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/10/2019	28/02/2020	SmPC	The SmPC section 4.2 has been updated as follows: Different oral formulations of tacrolimus should not be substituted without clinical supervision. Inadvertent, unintentional or unsupervised switching between different oral formulations of tacrolimus with different release characteristics is unsafe.
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. Update of sections 4.5 and 4.8 of the SmPC to add 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. 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.	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. 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.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0053	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	18/02/2019		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2839/201803.
IB/0050	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	13/07/2018	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. 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. C.I.4 - Change(s) in the SPC, Labelling or PL due to	17/05/2018	18/02/2019	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.

	new quality, preclinical, clinical or pharmacovigilance data				
IB/0049/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation 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 (e.g. deletion of an obsolete parameter) 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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	11/05/2018	n/a		
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/10/2017	18/02/2019	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. Update section 4.4 of the SPC with a more general description of pharmacokinetic interactions with	25/06/2015	16/06/2016	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

	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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				been updated taking in consideration the MedDRA preferred terms based on MedDRA version 16.0.
IB/0044	B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products	17/02/2015	n/a		
IB/0043/G	This was an application for a group of variations. 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 A.7 - Administrative change - Deletion of manufacturing sites B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	09/01/2015	n/a		

IB/0042/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.f - Change to in-process tests or limits applied during the manufacture of the finished product - Addition or replacement of an in-process test as a result of a safety or quality issue	11/06/2014	n/a		
IA/0041	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	09/01/2014	n/a		
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. 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	24/10/2013	15/10/2014	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. 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

	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). Furthermore, the PI is being brought in line with the latest QRD template Versions 8.3 and 9 C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				the warning about these possible events in patients using Tacrolimus has been further implemented in the Product Information.
IAIN/0039	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/08/2013	n/a		
IA/0040	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	29/07/2013	n/a		
IAIN/0038/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance	14/05/2013	n/a		

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IB/0033	B.II.b.5.f - Change to in-process tests or limits applied during the manufacture of the finished product - Addition or replacement of an in-process test as a result of a safety or quality issue	25/03/2013	n/a		
IAIN/0036	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	06/03/2013	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. 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. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	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. These drugs include in particular protease inhibitors for HIV and HCV and amiodarone.
IAIN/0035/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the	08/02/2013	n/a		

	contact details of the QPPV 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				
IAIN/0034	A.1 - Administrative change - Change in the name and/or address of the MAH	11/01/2013	18/02/2013	SmPC, Labelling and PL	
IB/0030	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	15/11/2012	n/a		
IG/0223/G	This was an application for a group of variations. 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 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 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	31/10/2012	n/a		

IA/0032	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		
IB/0028	B.II.e.4.z - Change in shape or dimensions of the container or closure (immediate packaging) - Other variation	24/08/2012	29/10/2012	Labelling	
R/0023	Renewal of the marketing authorisation.	16/02/2012	13/04/2012	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit-risk balance, the CHMP was of the opinion that the quality, safety and efficacy of Advagraf continued to be adequately and sufficiently demonstrated and considered that the benefit-risk profile of Advagraf continued to be favourable. The CHMP recommended the renewal of the Marketing Authorisation with unlimited validity. Product Information was updated according to the latest version of the QRD template.
IAIN/0026/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons	03/02/2012	n/a		

	or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD 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/0025/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer 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 Member State 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 Member State	13/01/2012	n/a		
II/0022	Update of Summary of Product Characteristics and Package Leaflet. Update of section 4.8 of the SmPC regarding agranulocytosis and haemolytic anaemia. The PIL is updated accordingly.	20/10/2011	22/11/2011	SmPC and PL	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

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				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 case 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 the PIL and the benefit-risk balance of the product remains positive.
II/0020	Update of section 4.6 of the SmPC regarding the occurrence of spontaneous abortion in patients using tacrolimus, as requested by CHMP. The PIL is not affected by this variation. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/09/2011	27/10/2011	SmPC	Based on a cumulative overview of pregnancy-related events, the MAH was requested to submit a variation to include spontaneous abortions in section 4.6 of the SmPC 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.
WS/0131	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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.	21/07/2011	05/09/2011	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.

	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. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				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/0021/G	This was an application for a group of variations. 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 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)	19/08/2011	n/a		
IB/0019	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size	23/06/2011	n/a		
IA/0018/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the	07/04/2011	n/a	Annex II	

	contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV 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				
IB/0017	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	17/02/2011	n/a		
IA/0016/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	20/09/2010	20/09/2010	SmPC, Labelling and PL	

	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				

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IA/0015/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database 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	23/08/2010	n/a	Annex II	
N/0014	The Marketing Authorisation Holder (MAH) took this opportunity to update the contact details for the local representatives in Bulgaria, Romania, Estonia, Lithuania, Latvia and Malta. Furthermore the MAH corrected the labeling in Danish to reflect the correct dosing "once daily".	29/01/2010	n/a	Labelling and PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
IA/0013	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	04/08/2009	n/a		
X/0004	Annex I_2.(c) Change or addition of a new strength/potency	19/02/2009	27/04/2009	SmPC, Labelling and PL	
II/0009	Update of sections 4.2, 4.4 and 4.8 of the SPC to include warnings on medication errors between Advagraf and Prograf, as requested by the CHMP in November 2008. Section 3 of the PL was updated accordingly. An updated version of the RMP has been submitted to address this issue. Consequently, the Annex II was updated to include the statement on RMP reflecting the updated version. The MAH also took the opportunity to update the contact details of some local representatives in the PL. Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	25/03/2009	SmPC, Annex II and PL	Up to 14 November 2008, 50 cases of medication errors have been reported involving confusion between Advagraf (prolonged release formulation of tacrolimus to be taken once daily) and Prograf (immediate release formulation of tacrolimus to be taken twice daily). Thirty-seven (37) of these cases were reported in the UK and 37 were dispensing errors. In 22 cases, the patient did not take the wrong medicinal product or did not follow the wrong regimen. Of the 28/50 patients who were administered the incorrect formulation or dosage regimen, 9 experienced at least one adverse event (14 adverse events were reported in total). Of these, 4 were serious adverse events, including graft rejection or reduced graft function. Therefore warnings have been included in the product information to prevent inadvertent, unintentional or unsupervised switching of immediate- or prolonged release formulations of tacrolimus.
II/0008	Update of section 5.1 of the SPC to include the results from phase III clinical studies performed with Advagraf, as requested by the CHMP in July 2008.	22/01/2009	25/02/2009	SmPC	The efficacy and safety of Advagraf and Prograf, both in combination with corticosteroids, was compared in 471 de novo liver transplant recipients. The event rate of biopsy

	Update of Summary of Product Characteristics				confirmed acute rejection within the first 24 weeks after transplantation was 32.6% in the Advagraf group and 29.3% in the Prograf group. The 12 month patient survival rates were 89.2% for Advagraf and 90.8% for Prograf. In the Advagraf arm 25 patients died (14 female, 11 male) and in the Prograf arm 24 patients died (5 female, 19 male). The 12-month graft survival was 85.3% for Advagraf and 85.6% for Prograf. In a second clinical trial comparing the efficacy and safety of Advagraf and Prograf, both in combination with mycophenolate mofetil and corticosteroids in 667 de novo kidney transplant recipients, the event rate for biopsy-confirmed acute rejection within the first 24 weeks after transplantation was 18.6% in the Advagraf group and 14.9% in the Prograf group. The 12 month patient survival rates were 96.9% for Advagraf and 97.5% for Prograf. In the Advagraf arm 10 patients died (3 female, 7 male) and in the Prograf arm 8 patients died (3 female, 5 male). The 12-month graft survival was 91.5% for Advagraf and 92.8% for Prograf. For the sake of completeness, data from a third clinical trial in renal transplantation submitted and evaluated for the initial approval of Advagraf have also now been included in section 5.1.
IB/0012	IB_17_a_Change in re-test period of the active substance	18/02/2009	n/a		
IB/0011	IB_10_Minor change in the manufacturing process of the active substance	18/02/2009	n/a		

IB/0010	IB_10_Minor change in the manufacturing process of the active substance	18/02/2009	n/a		
II/0007	Update of sections 4.4 and 4.8 of the SPC and section 4 of the PL to implement the warning on BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML) requested by the CHMP in July 2008. Update of Summary of Product Characteristics and Package Leaflet	25/09/2008	28/10/2008	SmPC and PL	Cases of BK virus associated nephropathy (BKVN) and cases of JC virus associated progressive multifocal leukoencephalopathy (PML) have been reported in patients treated with immunosuppressants, including Advagraf. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions. Thus physicians should consider BKVN and PML in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.
II/0005	Update of section 4.4 of the SPC to include information on posterior reversible encephalopathy syndrome (PRES) as requested by the CHMP following assessment of the first PSUR (covering the period 01.04.07 - 30.09.07). The MAH took the opportunity of this variation to update section 9 of the Labelling in line with the EMEA/QRD template (version 7.2) and to correct minor spelling mistakes in the SPC and PL. In addition, the contact details of some local representatives have been updated in the PL. The MAH also took the opportunity of this variation to make linguistic corrections to the SPC, Annex II, Labelling and PL, as relevant, for Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden.	25/09/2008	28/10/2008	SmPC, Annex II, Labelling and PL	A cumulative review of the MAH's safety database up to 28 May 2008 identified 32 cases of posterior reversible encephalopathy syndrome (PRES). In the majority of the 32 cases the patients recovered after discontinuation of tacrolimus. Given that PRES can be definitely diagnosed with neuro-imaging techniques, is reversible if treated, and potentially fatal if not, a warning has been included in the SPC to make physicians aware of this condition.

	Update of Summary of Product Characteristics, Labelling and Package Leaflet				
IA/0006	IA_39_Change/addition of imprints, bossing or other markings	22/08/2008	n/a	SmPC and PL	
T/0003	Transfer of Marketing Authorisation	20/12/2007	25/01/2008	SmPC, Labelling and PL	
IB/0002	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/07/2007	30/07/2007	SmPC, Labelling and PL	
IB/0001	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/07/2007	30/07/2007	SmPC, Labelling and PL	