Protopic

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
PSUSA/2840/ 202303	Periodic Safety Update EU Single assessment - tacrolimus (topical formulations)	14/12/2023	09/02/2024	SmPC and PL	Please refer to Protopic-EMEA/H/C/PSUSA/00002840/202303 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
N/0091	Minor change in labelling or package leaflet not	23/11/2022	09/02/2024	PL	

[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).

	connected with the SPC (Art. 61.3 Notification)				
IB/0090/G	This was an application for a group of variations. 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	07/09/2022	n/a		
N/0089	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/01/2022	09/02/2024	PL	
PSUSA/2840/ 202103	Periodic Safety Update EU Single assessment - tacrolimus (topical formulations)	02/12/2021	n/a		PRAC Recommendation - maintenance
IAIN/0088	B.III.1.a.1 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from an already approved manufacturer	10/09/2021	n/a		
IB/0086	B.II.e.1.a.2 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Semi-solid and non-sterile liquid pharmaceutical forms	21/02/2021	n/a		
II/0083/G	This was an application for a group of variations. Update of sections 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC following results from two non-interventional	23/07/2020	24/06/2021	SmPC, Annex II and PL	The results from two long-term non-interventional post-authorisation safety studies were reviewed in this procedure: APPLES study (a prospective, non-interventional, prevalent user, single arm study based on

	post-authorisation safety studies: JOELLE study (Joint European Longitudinal Lymphoma and skin cancer Evaluation, category 3) and APPLES study (a prospective pediatric longitudinal evaluation to assess the long-term safety of tacrolimus ointment for the treatment of atopic dermatitis, category 3). The Package Leaflet is updated accordingly. The RMP is updated to version 16.0. In addition, the marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.1. 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				primary data collection evaluating the risk of malignancy in children aged less than 16 who had been using tacrolimus ointment for atopic dermatitis for at least 6 weeks) and JOELLE study (a large historical cohort study using 4 population-based databases to evaluate the risk of incident skin cancer [composite including melanoma and NMSC] and lymphoma [a composite including Hodgkin lymphoma, NHL and cutaneous T-cell lymphoma] among new adult and paediatric users of topical tacrolimus ointment compared to new and prevalent users of moderate to high potency topical steroids). Based on the review of the data provided a link between Protopic ointment treatment and development of malignancies has not been confirmed, but definitive conclusions cannot be drawn. It is therefore recommended to use tacrolimus ointment at the lowest strength and the lowest frequency for the shortest duration necessary as determined by the physician's evaluation of the clinical condition. Furthermore, it was agreed to not reflect the data in section 5.1 in line with the SmPC guideline, as it is considered that these studies have a number of important limitations. Limitations of the APPLES study include the potential for survivor bias, selection bias, and losses to follow-up, as well as comparison with an external comparator cohort with limited adjustment for confounding. Limitations of the JoELLE study include the potential for selection bias, protopathic bias, detection bias, confounding by indication, residual confounding, information bias, heterogeneity of findings across the study databases, and in children, limited power.
IB/0085	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	08/06/2020	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IB/0084/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 B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	06/02/2020	n/a		
PSUSA/2840/ 201903	Periodic Safety Update EU Single assessment - tacrolimus (topical formulations)	28/11/2019	n/a		PRAC Recommendation - maintenance
IB/0081	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/05/2019	n/a		
IB/0079/G	This was an application for a group of variations. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply	08/01/2019	n/a		

	with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS				
IB/0080/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.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	13/12/2018	n/a		
IB/0078	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	07/11/2018	n/a		
IB/0077	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/10/2018	n/a		
IB/0075	B.II.z - Quality change - Finished product - Other variation	30/06/2018	29/10/2018	SmPC, Labelling and PL	
IB/0074	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	15/05/2018	n/a		

II/0072/G	This was an application for a group of variations. B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF 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	22/03/2018	n/a		
IAIN/0073/G	This was an application for a group of variations. 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	16/03/2018	n/a		
IB/0070/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	28/11/2017	29/10/2018	SmPC, Annex II, Labelling and PL	

	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 B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing 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.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 B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.2.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number				
PSUSA/2840/ 201703	Periodic Safety Update EU Single assessment - tacrolimus (topical formulations)	26/10/2017	n/a		PRAC Recommendation - maintenance
IB/0069	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/09/2017	n/a		
PSUSA/2840/ 201603	Periodic Safety Update EU Single assessment - tacrolimus (topical formulations)	27/10/2016	n/a		PRAC Recommendation - maintenance

N/0067	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/10/2016	29/10/2018	Labelling	
II/0063	Submission of the final clinical study report of the non-interventional, registry PASS study JOELLE (JOint European Longitudinal Lymphoma and skin cancer Evaluation) final results. The RMP v.11 is updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/07/2016	n/a		
T/0064	Transfer of Marketing Authorisation	27/05/2016	16/06/2016	SmPC, Labelling and PL	
PSUSA/2840/ 201503	Periodic Safety Update EU Single assessment - tacrolimus (topical formulations)	22/10/2015	16/12/2015	SmPC and PL	Please refer to Protopic PSUSA/00002840/201503 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IB/0061	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	17/06/2015	16/12/2015	SmPC and PL	
IB/0060/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	07/01/2015	n/a		

	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				
PSUV/0057	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IB/0058	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/08/2014	n/a		
IB/0056	B.II.e.1.a.2 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Semi-solid and non-sterile liquid pharmaceutical forms	25/07/2014	n/a		
IAIN/0059	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	04/07/2014	n/a		
IB/0055	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	27/06/2014	n/a		
IAIN/0054	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/11/2013	18/12/2013	SmPC and PL	

IAIN/0053	A.1 - Administrative change - Change in the name and/or address of the MAH	31/01/2013	18/12/2013	SmPC, Labelling and PL	
N/0052	"Update of the local representatives contact details for Romania, Slovenia and the United Kingdom." Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/12/2012	18/12/2013	PL	
IB/0051/G	This was an application for a group of variations. 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 B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	12/12/2012	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	31/10/2012	n/a		

	starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
II/0049	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information following the review of the risk for cutaneous T-Cell Lymphoma within follow-up measures and the last RMP. The Package Leaflet was proposed to be updated in accordance. 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 and PL	Overall 24 events of CTCL/Mycosis fungoides/Sezary syndrome have been reported to date with Protopic, 5 in children and 19 in adults, for a total estimated exposure of 2.7 million patient years (as of 31 March 2012). It appears that the overall demographic characteristics were consistent with what is known on the epidemiology of CTCL from the general population. However it was agreed to specifically mention CTCL in the SmPC as some cases have been reported.
IB/0048	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	29/06/2012	30/08/2012	SmPC	
IA/0047/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)	16/08/2011	n/a		

	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)				
II/0046	Update of section 4.8 and consequently section 4.4 of the SmPC regarding the adverse events local skin infection, application site oedema, drug level increase, and folliculitis, further to a review of post-marketing safety data. The Package Leaflet has been amended accordingly. In addition the MAH took the opportunity to make an editorial amendment in section 4.2. The list of local representatives in the Package Leaflet has been updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/05/2011	23/06/2011	SmPC and PL	Following a review of post-marketing safety data the following adverse events were added to the SmPC section 4.8: - "local skin infection" under the System Organ Class (SOC) Infections and Infestations - "application site oedema" under the SOC General disorders and administration site conditions - "drug level increase" under the SOC Investigations. The term "folliculitis" was moved from SOC Skin and subcutaneous tissue disorders to the primary SOC Infections and infestations according to MedDRA version 13.1. As a consequence of this the text in SmPC section 4.4 describing that treatment of Protopic may be associated with an increased risk of infections and infestations has been updated by adding the term "folliculitis". The text in section 4.4 (Special warnings and precautions for use) which contains the warning to use Protopic ointment in patients with skin barrier defect has been rephrased and a sentence has been added related to the addition of the, above mentioned, drug level increase adverse event. To give clearer guidance how to use Protopic for short-term and intermittent long-term treatment in section 4.2 of the SmPC, the relevant sentence was moved under the sub-heading "Posology".

II/0043/G	This was an application for a group of variations. Update of sections 4.4, 4.5 and 5.1 of the Summary of Product Characteristics (SmPC) with information related to the impact of the use of tacrolimus ointment on the immunocompetence in paediatric patients. The Package Leaflet (PL) was amended accordingly. Furthermore, the ATC code stated in the SmPC has been changed in line with recent WHO amendments, and the SmPC and the PL have been revised to reflect the Guideline on the Summary of Product Characteristics and the QRD template. List of local representatives in the PL has been updated. Results of package leaflet user testing are included in the dossier. This was an application for a group of variations. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/01/2011	21/02/2011	SmPC and PL	Results from a seven-month, double blind, randomised parallel group study in 2-11 years old paediatric patients with moderate to severe atopic dermatitis (study FG-506-06-27) demonstrated that after 5 weeks the response rate [95% CI], defined as the percentage of patients with a serum bactericidal antibody (SBA) titre ? 8, was similarly high in the groups of hydrocortisone ointment 99% [97.3, 100], tacrolimus ointment 98% [94.8, 100] and control 98% [93.3, 100]. The results of study FG-506-06-27 show that primary response to vaccination study is not affected by use of Protopic, induction of a T-cell dependent response and immunological memory is present and there is no evidence of systemic immunosuppression in the presence of efficacy and safety findings which are consistent with the results of previous studies. There is no new clinical data with impact on the benefit/risk assessment of the product.
IB/0045	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	11/02/2011	n/a		
IB/0044/G	This was an application for a group of variations. B.II.e.1.a.2 - Change in immediate packaging of the finished product - Qualitative and quantitative	14/09/2010	n/a		

	composition - Semi-solid and non-sterile liquid pharmaceutical forms B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.2.d - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition or replacement of a specification parameter as a result of a safety or quality issue				
IA/0042/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	19/03/2010	n/a		
IA/0041	IA_09_Deletion of manufacturing site	11/09/2009	n/a		
T/0040	Transfer of Marketing Authorisation Holder	13/03/2009	07/04/2009	SmPC, Labelling and	

	Transfer of Marketing Authorisation			PL	
II/0034	Extension of Indication to include 'maintenance treatment' further to completion of one study in adult patients (FG-506-06-40) and one in paediatric patients (FG-506-06-41). Sections 4.2, 4.4, 4.8 and 5.1 of the SPC and Sections 1, 2, 3 and 4 of the PL have been revised accordingly. In addition, Annex II has been updated to include the reference to version 4 of the EU RMP (dated 21 January 2009). Extension of Indication	22/01/2009	26/02/2009	SmPC, Annex II and PL	Please refer to the Scientific Discussion: Protopic H-374-II-34-AR
IB/0039	IB_17_a_Change in re-test period of the active substance	20/02/2009	n/a		
IB/0038	IB_10_Minor change in the manufacturing process of the active substance	20/02/2009	n/a		
IB/0037	IB_10_Minor change in the manufacturing process of the active substance	20/02/2009	n/a		
IB/0035	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release IB_07_b_02_Replacement/add. of manufacturing site: Primary packaging site - Semi-solid ph. forms	02/07/2008	n/a		
IA/0033	IA_09_Deletion of manufacturing site	16/08/2007	n/a		
IA/0032	IA_05_Change in the name and/or address of a manufacturer of the finished product	16/08/2007	n/a		

II/0031	Update of section 5.2 of the SPC to include information on tacrolimus blood concentrations in infants from age of 5 months and to specify the approved strengths of tacrolimus ointment used in the pharmacokinetic studies in adults and children following the assessment of a post approval commitment. Amendment of section 5.3 to correct a mistake in the route of administration used in a reproduction toxicity study. The Package Leaflet has been updated to include the details of local representatives for Bulgaria and Romania and to amend the details for some other Member States. Update of Summary of Product Characteristics and Package Leaflet	22/03/2007	03/05/2007	SmPC and PL	Further to the CHMP assessment of the pharmacokinetic study FG-506-06-32 which characterised the PK profile of 0.03 % tacrolimus in paediatric patients aged 3-24 months, the MAH amended Section 5.2 of the SPC to reflect the information on the absorption in infants from age of 5 months, as requested by the CHMP. The MAH has also amended Section 5.3 to correct a mistake with respect to the route of administration in the male reproductive toxicity study. The Package leaflet has been amended to include the two new Member States, Bulgaria and Romania, to the list of local representatives. The contact details for some local representatives have also been updated.
R/0030	Renewal of the marketing authorisation.	21/09/2006	20/11/2006	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 this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of Protopic continues to be favourable. The CHMP was also of the opinion that the renewal can be granted with unlimited validity. The renewal required amendments to the terms of the Community Marketing Authorisation. The following annexes have been amended: Annexes I, II,

					IIIA and IIIB.
IA/0029	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	24/02/2006	n/a		
IA/0028	IA_05_Change in the name and/or address of a manufacturer of the finished product	19/10/2005	n/a	Annex II and PL	
IA/0027	IA_01_Change in the name and/or address of the marketing authorisation holder IA_05_Change in the name and/or address of a manufacturer of the finished product	09/09/2005	n/a	SmPC, Labelling and PL	
IA/0026	IA_05_Change in the name and/or address of a manufacturer of the finished product	19/07/2005	n/a		
II/0025	The Marketing Authorisation Holder applied for an update of section 4.8 (Undesirable effects) of the Summary of Product Characteristics and section 4 of the Package Leaflet to include information on rosacea following the assessment of the 5th PSUR. Update of Summary of Product Characteristics and Package Leaflet	21/04/2005	10/06/2005	SmPC and PL	Based on the assessment of the 5th Periodic Safety Update Report the Marketing Authorisation Holder applied to update section 4.8 of the Summary of Product Characteristics to state that the adverse reaction, rosacea, has been reported after marketing. This information has also been included in section 4 of the Package Leaflet.
IB/0024	IB_10_Minor change in the manufacturing process of the active substance	10/03/2005	n/a		
IA/0023	IA_13_a_Change in test proc. for active substance - minor change	10/02/2005	n/a		

IA/0022	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	29/11/2004	n/a		
N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/11/2004	n/a	Labelling and PL	
II/0019	Update of Summary of Product Characteristics and Package Leaflet	26/02/2004	19/05/2004	SmPC and PL	This variation concerns an update of section 4.2 of the Summary of Product Characteristics to amend the wording of the current prescription restriction from "Protopic should only be prescribed by dermatologists and physicians with extensive experience in the treatment of atopic dermatitis with immunomodulating therapy" to "Protopic should be prescribed by physicians with experience in the treatment of atopic dermatitis". The list of local representatives has also been updated to include the local representatives in the Accession Countries in the package leaflet.
II/0011	Update of Summary of Product Characteristics	17/12/2003	04/03/2004	SmPC	This variation concerns an update of section 5.1 (Pharmacodynamic properties) of the Summary of Product Characteristics to include the results of three active comparator clinical studies.
II/0010	Update of Summary of Product Characteristics	17/12/2003	04/03/2004	SmPC	This variation concerns an update of section 4.4 (Special warnings and special precautions for use) of the Summary of Product Characteristics following long-term experience for up to 4 years with consequential changes to section 5.1 (Pharmacodynamic properties) of the Summary of Product Characteristics.
II/0009	Update of Summary of Product Characteristics and Package Leaflet	17/12/2003	04/03/2004	SmPC and PL	The Marketing Authorisation Holder applied for an update of section 4.2 (Posology) of the SPC and of section 3 (How to use Protopic) of the Package Leaflet in order to delete the 3-week restriction on treatment duration for 0.1%

					tacrolimus twice daily treatment.
II/0014	Update of Summary of Product Characteristics	21/01/2004	02/03/2004	SmPC	This variation concerns an update of section 5.2 (Pharmacokinetic properties) of the Summary of Product Characteristics to include further information on the distribution of tacrolimus ointment following topical application.
II/0018	Update of or change(s) to the pharmaceutical documentation	26/02/2004	01/03/2004		The MAH applied for changes to the manufacturing method of the active substance.
II/0012	Update of Summary of Product Characteristics and Package Leaflet	22/10/2003	27/01/2004	SmPC and PL	The MAH applied for changes to the Summary of Product Characteristics and the Package Leaflet following the switch from COSTART terminology to MedDRA. New terms included represented the higher specificity of the MedDRA terminology and the changes reflected the change in terminology rather than a change in the safety profile.
IA/0017	IA_06_a_Change in ATC code: Medicinal products for human use	04/12/2003	n/a	SmPC	
IA/0016	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	26/11/2003	n/a		
IA/0015	IA_13_a_Change in test proc. for active substance - minor change	26/11/2003	n/a		
I/0013	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	22/09/2003	22/09/2003		
I/0008	20_Extension of shelf-life as foreseen at time of authorisation	01/08/2003	22/09/2003	SmPC	

I/0007	30_Change in pack size for a medicinal product	20/02/2003	10/04/2003	SmPC, Labelling and PL	
I/0006	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	06/11/2002	12/11/2002		
I/0005	03_Change in the name and/or address of the marketing authorisation holder	03/10/2002	08/11/2002	SmPC, Labelling and PL	
I/0004	25_Change in test procedures of the medicinal product	03/10/2002	07/10/2002		
I/0003	24_Change in test procedure of active substance	03/10/2002	07/10/2002		
I/0002	12_Minor change of manufacturing process of the active substance	03/10/2002	07/10/2002		
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/09/2002	09/10/2002	PL	