STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 1 October 2004, please refer to module 8b.

- The Marketing Authorisation Holder submitted on 24 April 2001 an application for an application for a Notification of a Type I variation (to introduce a smaller pack size of 50ml bottle), pursuant to Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The Head of Sector Quality of Medicines signed a positive notification 1 June 2001.

- The Marketing Authorisation Holder submitted on, 14 June 2001 an application for an application for a Notification of a Type I variation (an additional site for secondary packaging and batch release), pursuant to Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The Head of Sector Quality of Medicines signed a positive notification on 20 July 2001.

- The Marketing Authorisation Holder submitted on 04 April 2001 an Annex II application for Marketing Authorisation Pursuant to Article 2(1) of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. A positive opinion was adopted by the CPMP on 15 November 2001 and the European Commission granted a Commission Decision on 12 April 2002.

- The Marketing Authorisation Holder submitted on 05 September 2001 an application for a Type II variation, pursuant to Article 6 of Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. It concerned an update of the Product literature (SPC section 4.5, 4.8 & 4.9) in line with the safety information provided. A positive opinion was adopted by the CPMP on 15 November 2001 and the European Commission granted a Commission Decision on 12 April 2002.

Subsequent post Marketing Authorisation applications agreed upon are summarised in the table below:

Scope	Application number	Type of modification[1]	Notification/ Opinion issued on[2]	Commission Decision Issued/amended on
The MAH submitted to the EMEA on 3 May 2002 an Annex II application.	X/005	X	19.09.02	10.01.03
Change in specification of starting material/intermediate used in manuf. of the active substance	I/006	I	23.08.02	16.09.02
Minor change of manufacturing process of the active substance	I/007	I	23.08.02	16.09.02
Minor change of manufacturing process of the active substance	I/008	I	23.08.02	16.09.02

[1] In accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended: **I** refers to a minor variation (Type I variation); **II** refers to a major variation (Type II variation); **I/II** refers to a minor variation following the procedure set out in Article 6, 7 and 8 of the Regulation; **X** refers to an Annex II application.
T refers to a transfer of a Marketing Authorisation in accordance with Commission Regulation (EC) No 2141/96 of 7 November 1996.
N refers to a notification in accordance with Article 10(3) of Council Directive 92/27/EEC of 31 March 1992.

[2] For Notifications and Type I variations, the date of entry into force of the change is the EMEA Notification date. The Commission Decision will be amended accordingly.

Minor change of manufacturing process of the active substance	I/009	I	23.08.02	16.09.02
Extension of shelf-life as foreseen at time of authorisation	I/010	I	23.08.02	08.10.02
Update of the SPC section 4.4 (Special warnings and special precautions for use), section 4.8 (Undesirable effects) and the Package Leaflet. The changes reflect the recommendations of the fifth PSUR and amendments to the Company's reference safety information (Core Data Sheet) for Rapamune.	II/0011	II	19.11.02	28.01.03
Change in the name of a manufacturer of the medicinal product	I/0012	I	13.09.02	20.09.02
Update of the SPC section 4.4 (Special warnings and special precautions for use), section 4.8 (Undesirable effects) and an update of the PL. The proposed changes reflect the recommendations made following the sixth PSUR and amendments to the reference safety information (Core Data Sheet) for Rapamune.	II/0014	II	22.05.03	01.09.03
Change in storage conditions	I/0015	I	14.05.03	14.05.03
Extension of the shelf life of Rapamune 2 mg coated tablets from 18 months to 23 months.	I/0016	I	04.07.03	04.07.03
To introduce an improved strength of Streptomyces hygroscopicus used to produce sirolimus in order to produce a higher yield with a more robust fermentation process. The fermentation and purification processes have been modified and an additional impurity specification added to the active substance specifications.	I/0017	I	23.10.03	
Change in the name of the manufacturer of the medicinal product from Wyeth-Ayerst Pharmaceuticals Inc. to Wyeth Pharmaceuticals Inc.	I/0018	I	01.10.03	01.10.03
Update of section 4.5 and to intoduce consequential changes in section 4.2 and section 4.4 of the (SPC). The proposed changes reflect amendments with regard to co-administration of strong inhibitors/inducers of CYP3A4 and sirolimus. Also amendments to section 4.5 concerning drug interaction with cyclosporin, erythromycin and verapamil reflecting the amendment to the Company reference safety information. The addition of drug interaction with voriconazole follows the recommendation of the 6th PSUR, also submitted to meet the post-approval commitment resulting from previous type II variation II/14. Relevant changes are equally proposed for the Package Leaflet (PL).	II/0019	II	20.11.03	29.01.04
The MAH applied for an alternative manufacturing site (sealing of placebo tablet cores, inert fill coating, active fill coating, colouring and polishing) for Rapamune 1 mg coated tablets: Wyeth Pharmaceutical Company - Highway no. 3, Km 142.1 - Barrios Pozo Hondos and Jobos - Guayama - Puerto Rico 00784.	IB/0020	IB	30.01.04	-
Change in test procedure of finished product - minor change to approved test procedure	IA/0022	IA	07.04.04	-

Change in test procedure of finished product - minor change to approved test procedure	IA/0023	IA	07.04.04	-
Update the SPC in section 4.8 “Undesirable effects” with safety information concerning data from renal transplant patients at high immunological risk in an ongoing clinical study investigating conversion from calcineurin inhibitors to sirolimus based therapy. The MAH also proposes to add a warning in the SPC in section 4.4 “Special warnings and special precautions for use” concerning the sucrose excipient in Rapamune 1 mg and 2 mg tablets and a corresponding change is proposed to the PL. The MAH also proposes to amend the labelling text for Rapamune 1 mg and 2 mg tablet to use the short standard term “tablets” on the blister.	II/0024	II	23.06.04	02.09.04
Update of the PL in order to include the additional local representatives of the MAH for all 10 new European Member States and to revise the format of the list in line with the latest EMEA/ QRD template.	N/0025	N	20.05.04	-
Change in BR/QC testing - repl./add. of batch control/testing site	IA/0026	IA	20.09.04	-
Change in test procedure of finished product - minor change to approved test procedure	IA/0027	IA	20.09.04	-