I BACKGROUND INFORMATION ON THE PROCEDURE

1. Submission of the dossier

The company Wyeth Europe Ltd submitted on 23 December 1998 an application for Marketing Authorisation to the European Agency for the Evaluation of Medicinal Products (EMEA) for Rapamune, through the centralised procedure. After agreement by the CPMP on 27 May 1998 this medicinal product has been referred to Part B of the Annex to Council Regulation No (EEC) 2309/93 of 22 July 1993.

The Rapporteur and Co-Rapporteur appointed by the CPMP and the evaluation teams were:

Initial assessment

Rapporteur:	Prof. B. Odlind (until December 1999) Dr. P. Nilsson (from December 1999)	Co-Rapporteur:	Prof. S. Garattini
Evaluators:	Dr. S.-E. Hillver Dr. S. Hovmark Dr. I. Anundi Dr. M. Gårdmark Dr. P. Nilsson	Evaluators:	Dr. C. Caramella Dr. M. Terreni Dr. I. Bartosek Dr. S. Caccia Dr. J. Golay Dr. N. Perico Dr. G. Remuzzi

Appeal

Rapporteur:	Dr. D. Brasseur	Co-Rapporteur:	Prof. R. Bass
Evaluators:	Prof. D. Abramowicz Dr. M. Zeicher		Dr. R. Lehnert Dr. U. Fürstenau

Licensing status:

At the time of the initial submission Rapamune had not been given a Marketing Authorisation anywhere.

2. Steps taken for the assessment of the product

- The procedure started on 29 January 1999.
- The Rapporteur's assessment report was circulated to all CPMP Members on 9 April 1999. The Co-Rapporteur's first assessment report was circulated to all CPMP Members on 12 April 1999.
- On 27 April 1999 the applicant informed Rapporteur and Co-Rapporteur about an error in the efficacy data analyses. During the meeting on 18-20 May 1999 the CPMP decided to stop the clock of the procedure in order to allow the applicant to submit an amended Efficacy Summary.
- The corrected Efficacy Summary was submitted on 7 June 1999. The Rapporteur's revised assessment report was circulated to all CPMP Members on 17 June 1999. The Addendum to the Co-Rapporteur's first assessment report was circulated to all CPMP Members on 22 June 1999.
- During the meeting on 27-29 July 1999 the CPMP agreed on the consolidated list of questions to be sent to the applicant. The final consolidated list of questions was sent to the applicant on 30 July 1999.
- The Applicant submitted the responses to the consolidated list of questions on 21 January 2000.
- The summary report of the inspection carried out at the manufacturing site on 8-9 December 2000 was issued on 20 March 2000.
- The Rapporteur circulated the response assessment report on the applicant’s responses to the list of questions to all CPMP Members on 22 March 2000. A revised overall conclusion and assessment report on Part II was circulated to all CPMP Members on 4 April 2000.
- During the meeting on 11-12 April 2000 the CPMP agreed on the list of outstanding issues to be sent to the applicant. This list was sent to the applicant on 13 April 2000.

- The applicant submitted written responses to the consolidated list of outstanding issues on 14 June 2000.
- The Rapporteur circulated the response assessment report on the Applicant's responses to the list of outstanding issues to all CPMP Members on 11 July 2000.
- During the CPMP meeting on 25 July 2000, outstanding issues were addressed by the applicant during an oral explanation before the CPMP.
- During the meeting on 25-27 July 2000 the CPMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Rapamune on 27 July 2000.

3. Steps taken for the appeal procedure

- A valid intent for appeal against the CPMP Opinion on Rapamune was submitted by the applicant, Wyeth Europa Ltd, on 17 August 2000.
- Grounds for appeal were submitted by the applicant on 13 September 2000.
- During its meeting on 19-21 September 2000, the CPMP appointed Dr. D. Brasseur as Rapporteur and Prof. R. Bass as Co-Rapporteur for the appeal procedure.
- The Rapporteur's assessment report was circulated to all CPMP members on 26 October 2000 (Annex 1) and the Co-Rapporteur's assessment report was circulated to all CPMP members on 31 October 2000 (Annex 2).
- An expert panel meeting was held on 13 November 2000. The report of the expert panel meeting was circulated to all CPMP members on 14 November 2000 (Annex 3).
- During the meeting on 14-16 November 2000, the CPMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Rapamune.
- The CPMP Opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 13 March 2001.

II GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

1. Manufacturing Authorisation Holder and inspection status

Manufacturers of the active substance for Oral Solution

Mercian Corporation
Iwata Plant
1808 Nakaizumi
Iwata-shi
Shizuoka
Japan

Wyeth-Ayerst Laboratories
Maple Street
Rouses Point
NY, 12979
USA

Manufacturers of the finished product

Wyeth-Ayerst Laboratories
Maple Street
Rouses Point
NY, 12979
USA

PACO Pharmaceutical Services, Inc.
1200 Paco Way
Lakewood, NJ 08701
USA

Wyeth Medica Ireland
Little Connell
Newbridge, Co. Kildare
Ireland

Manufacturers of the active substance for Tablets

Mercian Corporation
Iwata Plant
1808 Nakaizumi
Iwata-shi
Shizuoka
Japan

Wyeth-Ayerst Laboratories
Maple Street
Rouses Point
NY, 12979
USA

Manufacturers of the finished product

(Manufacture of sirolimus NanoSytems Dispersion only:)
NanoSystems, Division of Elan
Pharmaceutical Technologies
3000 Horizon Drive
King of Prussia
PA 19406
USA

At:Pharmaceutical Manufacturing Research
Services Inc. (PMRS)
423 Sargon Way
Horsham
PA 19044
USA

(Manufacture of the coated tablets:)
Wyeth-Ayerst Laboratories
Maple Street
Rouses Point
NY, 12979
USA

(Site for printing and testing of the coated tablets and alternate site for manufacture of the compressed inert tablet core:)
Wyeth Pharmaceutical Company
Highway no.3, Km 142.1
Barrios Pozo Hondos and Jobos
Guayama
Puerto Rico 00784

Manufacturer responsible for batch release

Wyeth Laboratories
New Lane
Havant
Hants PO9 2NG
United Kingdom

Manufacturer responsible for batch release

Wyeth Laboratories
New Lane
Havant
Hants PO9 2NG
United Kingdom

Manufacturing Authorisation issued on 28 January 1999 by the Irish Medicines Board.

2. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (refer to section 4.2 of the Summary of Product Characteristics for further information).