CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-110

CHEMISTRY REVIEW(S)

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS—HFD-590

Review of Chemistry, Manufacturing and Controls Section

NDA #: 21-110
CHEMISTRY REVIEW #: 1 **REVIEW COMPLETED:** August 18, 2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA	October 29, 1999	October 29, 1999	November 4, 1999
BC	December 3, 1999	December 6, 1999	December 7, 1999
BC (stability update)	March 30, 2000	March 31, 2000	April 6, 2000
BC	June 5, 2000	June 6, 2000	June 6, 2000
BL	July 6, 2000	July 7, 2000	July 7, 2000
NC	July 24, 2000	July 25, 2000	July 26, 2000
BZ	August 15, 2000	August 16, 2000	August 16, 2000
BL	August 16, 2000	August 16, 2000	August 16, 2000
BL	August 17, 2000	-	-
BC	August 17, 2000	-	-
BL	August 18, 2000	-	-

NAME/ADDRESS OF APPLICANT: Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

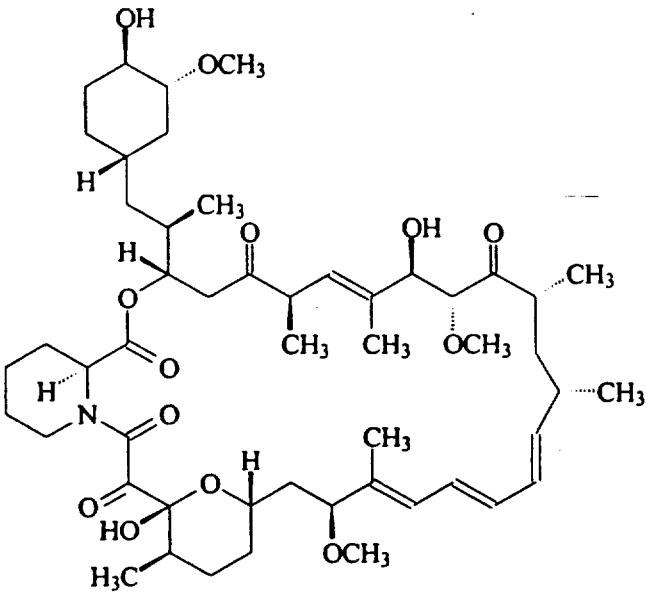
DRUG PRODUCT NAME:

- Proprietary: Rapamune Tablets
- Nonproprietary: sirolimus tablets
- Other: rapamycin
- Code Name: AY-22989; WY-090217

CHEM. TYPE/THER. CLASS: 3S
DRUG CLASS: 5010400
PHARMACOLOGICAL CATEGORY: Immunosuppressant
INDICATION: The prophylaxis of organ rejection in patients receiving renal transplants
DOSAGE FORM/STRENGTH: Tablets, 1 mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: X Rx __ OTC
SPECIAL PRODUCTS: __ Yes X No

CHEMICAL NAME/STRUCTURAL FORMULA:
(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone

CAS Registry: 53123-88-9
Molecular Formula: $C_{51}H_{79}NO_{13}$
Molecular Weight: 914.19



Isomer B shown

SUPPORTING DOCUMENTS:

[redacted]

NDA 21-083 Rapamune Oral Solution, approved September 15, 1999

Drug Master Files (v. 4, p. 13)

DMF	Document Holder	Reason for Reference (Location in DMF)	Status	LoA Date
[redacted]			Reviewed 8/11/00 Adequate	3/23/99
			Type I	-
			12/15/98, p. 4001, updated 5/30/00; composition acceptable	12/15/98
			Vol. 1, pp. 5-9, updated 10/13/98; Reviewed 5/7/99 (adequate)	1/4/99
			Vol. 3 Reviewed 8/9/99 (adequate)	1/5/99
				12/30/98
			Vol. 1, pp. A1 – O19, updated 11/18/98; last reviewed 7/21/00 (adequate)	1/5/99
			Vol. 1, updated 7/31/98 Reviewed 8/2/99 (acceptable)	1/5/99
			pp. 5.01-5.04, 8.01-8.32, 9.01-9.09, last update 8/7/98; last reviewed 3/24/00 (adequate)	8/7/98
			Vol. 1, p. 2.929, submitted 4/4/98	9/25/98

	Supplement 9/1/95, updated 7/7/98 Last reviewed 8/12/99 (adequate)	1/5/99
	Submitted 6/25/97; last reviewed 5/3/00 (adequate)	1/5/99
	Submitted 10/5/93, pp. G-11-a-1, 2, 3, & 4; last reviewed 3/2/00 (adequate)	1/4/99
	Last submitted 8/24/98; last reviewed 9/9/99 (adequate)	1/4/99
	Sections 6 and 8, amended 1/1/99; last reviewed 7/26/00 (adequate)	1/28/99
	Type I	-
	Type I	-

RELATED DOCUMENTS:

CONSULT REVIEWS:

OPDRA Review of Labeling, August 4, 2000 (Consult #00-0184)

REMARKS/COMMENTS:

This New Drug Application provides for a tablet dosage form of the immunosuppressant Rapamune® (sirolimus). Rapamune® Oral Solution was approved on September 15, 1999, for use in the prevention of organ rejection in patients receiving renal transplants. Rapamune is recommended for use in a regimen with cyclosporine and corticosteroids, and is administered once daily. The typical dose is 2 mg/day.

The tablet dosage form should provide greater convenience for transplant patients when compared to the oral solution. Dosing of the oral solution requires the use of disposable plastic syringe to withdraw product from the bottle or the use of scissors to open the foil pouch. The oral solution must be diluted in water or orange juice immediately prior to administration. Refrigerated storage is recommended for the oral solution. The tablet may be stored at room temperature and administration does not require further manipulation. Increased convenience for patients may improve compliance.

DRUG SUBSTANCE

[redacted]

The chemistry, manufacturing and controls (CMC) for the drug substance are documented in NDA 21-083.

[redacted]

DRUG PRODUCT

A variety of oral formulations were evaluated. Poor water solubility and instability in aqueous media precluded the use of an aqueous formulation. A solid oral dosage form is the subject of this NDA. An oral solution composed primarily of phospholipids and the organic solvent propylene glycol was approved September 15, 1999 (see NDA 21-083, Chemistry Review #1).

[redacted]

While an oval shaped tablet was developed for investigational use, a triangular shaped tablet was selected for commercialization. The change in shape was made to facilitate identification, and to prevent confusion with other oval tablets on the market. The oval tablet core used in clinical development was the same core that is used in the manufacture of Premarin tablets. The triangular tablet core has the same composition as the oval core used for the manufacture of the clinical supplies. The oval tablet used in pharmacokinetic and clinical studies is linked to the commercial triangular tablet by comparison of dissolution profiles and calculation of similarity factors, and by comparison of tablet surface areas.

ESTABLISHMENT EVALUATION

As of July 7, 2000, the facilities involved in the manufacture and testing of the drug product intermediate and finished tablet had acceptable cGMP status [redacted] Minor deficiencies were noted in the inspection of the operations at [redacted] but the company has adequately addressed the issues.

METHODS VALIDATION

The analytical methods for the control of the drug product appear to be suitable for the intended uses. The submitted validation data appears to be adequate. Since the drug is not an NME, only one FDA laboratory (Philadelphia) was asked to confirm the suitability of the methods. FDA lab work is not completed at this time. The NDA Action Letter should include a request for the continued cooperation of the applicant should any questions arise or if modifications to the methods are deemed necessary.

LABELING

Comments regarding the package insert, bottle label, blister card and blister carton were conveyed to the applicant. Comments resulting from an OPDRA consult review of the labeling were also conveyed to the applicant. Minor revisions have been made to the 'Description' and 'How Supplied' sections of the package insert. Minor changes have also been made to the container and carton labeling. The 'Description' and 'How Supplied' sections of the package insert are acceptable as presented in the August 16, 2000 draft. The August 17, 2000 versions of the 100-count bottle label (5th proof) and the blister carton (4th proof) are acceptable. The July 18, 2000 version of the blister label (1st proof) is also acceptable. These sections of the final printed labeling should be identical to the referenced draft labeling.

ENVIRONMENTAL ASSESSMENT

The Expected Introduction Concentration (EIC) is below [redacted] A categorical exclusion from the environmental assessment requirements is claimed in accordance with the revised regulations published in the July 29, 1997, Federal Register (21 CFR 25.31(b)). The applicant knows of no extraordinary circumstances associated with the proposed action. The categorical exclusion is acceptable.

CONCLUSIONS & RECOMMENDATIONS:

The chemistry, manufacturing and controls (CMC) for sirolimus drug substance and sirolimus tablets have been adequately established and are satisfactorily documented in the NDA. The applicant has addressed the deficiencies in the original submission. The GMP and product specific inspections of the manufacturing facilities were satisfactory. The NDA, as amended, for sirolimus tablets is in conformance with section 505(b) of the Food, Drug and Cosmetic Act in relation to the CMC and is approvable from the chemist's perspective. The product is to carry an 18-month expiration date until data to support its extension are provided.

/S/

Mark R. Seggel, Review Chemist

Concurrence:
HFD-590/NSchmuff /S/ 9/27/2000

cc:
Orig. NDA
HFD-590/Div. File
HFD-590/NSchmuff
HFD-830/CChen
HFD-590/MSeggel
HFD-590/MBacho
HFD-590/SKunder
HFD-590/RTiernan
HFD-590/KKumi