

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-110

PHARMACOLOGY REVIEW

PHARMACOLOGIST'S REVIEW

NDA 21-110

Date Submitted: 29 October 1999

Date Assigned: 2 November 1999

Date Completed: 25 August 2000

Related NDAs: 21-083

Related INDs: [REDACTED]

HFD-590

Sponsor: Wyeth-Ayerst

Drug: Rapamune™

(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-

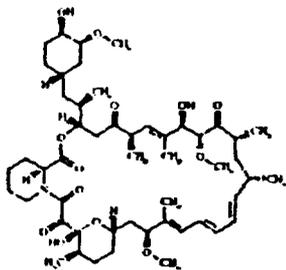
hexadecahydro-9,27-dihydroxy-3-[(1R)-2-

[(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]oxaazacyclohentricontine-1,5,11,28,29

(4H,6H,31H)-pentone.



Formulation: Each Rapamune tablet contains 1 mg sirolimus. The inactive ingredients are sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20000, glyceryl monooleate, [REDACTED] and carnuba wax.

INTRODUCTION

[REDACTED] is an immunosuppressant macrolide, structurally related to FK-506 (Tacrolimus™), which was developed for organ transplantation. [REDACTED] was isolated from *Streptomyces hygroscopicus*.

[REDACTED] appears to have a unique immunosuppressive biochemical mechanism of action, distinct from that of cyclosporin (CsA), tacrolimus (FK506), mycophenolate mofetil, or azathioprine. [REDACTED] inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism different from that of other immunosuppressants. In cells, [REDACTED] binds to the immunophilin, FK binding protein 12 (FKBP-12), producing an

immunosuppressive complex. Unlike cyclosporin and tacrolimus, the [redacted] complex appears to have no effect on calcineurin activity. This complex binds to and inhibits the activation of a kinase called the mammalian target of rapamycin (mTOR). Inhibition of mTOR by [redacted] suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G1 to the S phase of the cell cycle.

[redacted] prolongs allograft survival in animal models of transplantation, including rodents and primates, both for solid organ and for cellular allografts. Nephrotoxicity is a concern with many preceding immunosuppressants, particularly cyclosporin. [redacted] perhaps due to its differing mechanism of action, appears not to have the nephrotoxicity seen with cyclosporin. However, increased creatine levels in transplant patients receiving [redacted] in clinical trials have been observed, which may indicate nephrotoxicity. Combinations of [redacted] with other immunosuppressants remain problematic. Adverse effects seen with other immunosuppressive drugs, including elevation of glucose and hyperlipidemia, are of concern with [redacted] also.

Wyeth Ayerst produced a tablet form of Sirolimus in which drug substance is

[redacted]

[redacted] by Wyeth Ayerst Laboratories, Rouses Point, NY.

[Large redacted area]

PHARMACOLOGY STUDY

Evaluation of different oral formulations of sirolimus in rat heterotopic heart allograft model

TOXICOLOGY STUDY

Rapamune: twenty-eight day oral (gavage) toxicity study to qualify rapamune with elevated group II impurities in male rats

PHARMACOKINETIC STUDIES

[redacted] evaluation of oral formulations in cynomolgus monkeys

[redacted] the in vivo evaluation in cynomolgus monkeys of 1 mg rapamune tablets differing in dispersion particle size

PHARMACOLOGY STUDY REVIEW

Evaluation of different oral formulations of sirolimus in rat heterotopic heart allograft model.

Male Brown Norway rats (BN, RT1n) served as heart donors. Male Lewis rats (LEW, RT11) received the hearts (rat supplier, age, and size information not provided). The heart recipients received vehicle or [redacted] in one of three dosage forms: spray dried [redacted] powder, [redacted] dispersion, or phosal-based liquid formulation. Six recipient rats were assigned to each group. Each preparation was administered daily by oral gavage for 14 days at a dose of 1.5 mg/kg/day. Prolongation of graft survival and body weights were compared.

Allograft survival for various [redacted] formulations

Group	Median allograft survival (days±sd)
Control	6.3±0.5
Spray dried [redacted]	30.5±3.7
NanoSystem [redacted] formulation	30.5±2.4
Liquid oral [redacted]	28.7±2.6

There was no significant difference of allograft survival time between any of the rat allograft recipient groups receiving different [redacted] formulations. There was no significant difference in weight gain between any of the rat allograft recipient groups receiving different [redacted] formulations.

TOXICOLOGY STUDY REVIEW

Rapamune: twenty-eight day oral (gavage) toxicity study to qualify rapamune with elevated group II impurities in male rats, conducted by Wyeth Ayerst Drug Safety, Chazy, NY; study GRT-35078; 23 April 1999; GLP

Male CD VAF rats (Charles River Canada, 7 weeks old, 221-263 grams) were randomized into groups (10/dose) receiving either control (vehicle) or rapamune, 5 mg/kg/day (HED=0.83 mg/kg/day) with Group II (G2) impurities of either [redacted] (within specifications), [redacted] daily by oral gavage for 28 days. The G2 concentration was determined to be [redacted] in the high G2 preparation. During the study, rats were monitored for mortality (2x daily), body weight (weekly), food consumption (weekly), or clinical observations (daily) or received ophthalmoscopic examinations (week -2, 3), and hematology and clinical chemistry procedures (weeks 1,4). During the study, lameness occurred in the [redacted] G2 treated groups. All rats survived until sacrifice. At sacrifice, organs and tissues were collected for histopathologic examination (see table in appendix). Group mean body weights were decreased in all rapamune-treated groups relative to controls at week 1 [redacted] and week 4 [redacted]. Food consumption was slightly decreased in rapamune-treated groups relative to controls at week 1, but G2 content did not significantly affect food consumption between treated groups. Cataracts were found in all treated groups. Organ weights of treated rats were decreased relative to

control organ weights for the heart, pituitary, testes, and brain. These organ weight decreases appear related to body weight decreases. Hematology findings in treated groups included hyperglycemia, decreased total leukocytes, lymphocytes, and platelets, and increased neutrophils, prothrombin time, and activated partial thromboplastin time, all of which were unaffected by G2 content. In treated groups, histopathologic findings across all G2 concentrations included alveolar macrophages, myocardial degeneration, islet cell vacuolation of the pancreas, atrophy of the thymus, atrophy of the cervical and mesenteric lymph nodes, tubular degeneration of the testes, and bone fracture. Histopathologic findings coincided with organ weight changes for the heart and testes. A single rat treated with [redacted] G2 had a focal, discrete glioma in the cerebral cortex. In the previous two year carcinogenicity study, a single undifferentiated glioma was observed in a rat receiving 0.2 mg/kg [redacted]. The Charles River historical incidence for malignant gliomas ranges from 3.3 to 4.0% in males. Otherwise, the toxicities seen in this study are consistent with those previously seen at this dose and duration of exposure.

A NOAEL was not observed in this study. Concentrations of G2 impurities (up to [redacted]) did not appear to affect the toxicity of [redacted] in this 28-day rat study. Inclusion of female rats in this study would provide additional toxicity information for the G2 impurities.

PHARMACOKINETIC STUDY REVIEWS

[redacted] evaluation of oral formulations in cynomolgus monkeys, conducted by Wyeth Ayerst Research, Pearl River, NY, report GTR-35082, protocol no. 96045, 29 Jan 1999, not conducted under GLP

Male cynomolgus monkeys (age, source information not provided) were given single doses of a panel of rapamune formulations in a crossover design study. Following intravenous dosing, blood was sampled at 0, 5, 10 and 30 minutes and 1, 2, 4, 8, 12, 16, and 24 hours. Following oral dosing by nasogastric gavage, blood was sampled at 0, 0.25, 0.5, 1, 2, 4, 8, 12, 16 and 24 hours. Samples were analyzed on [redacted]. The following formulations were evaluated:

Formulation IV113: [redacted]

Formulation PO78: [redacted]

Formulation PO147: [redacted]

Oral Dose = 1x5 mg tablet [redacted]

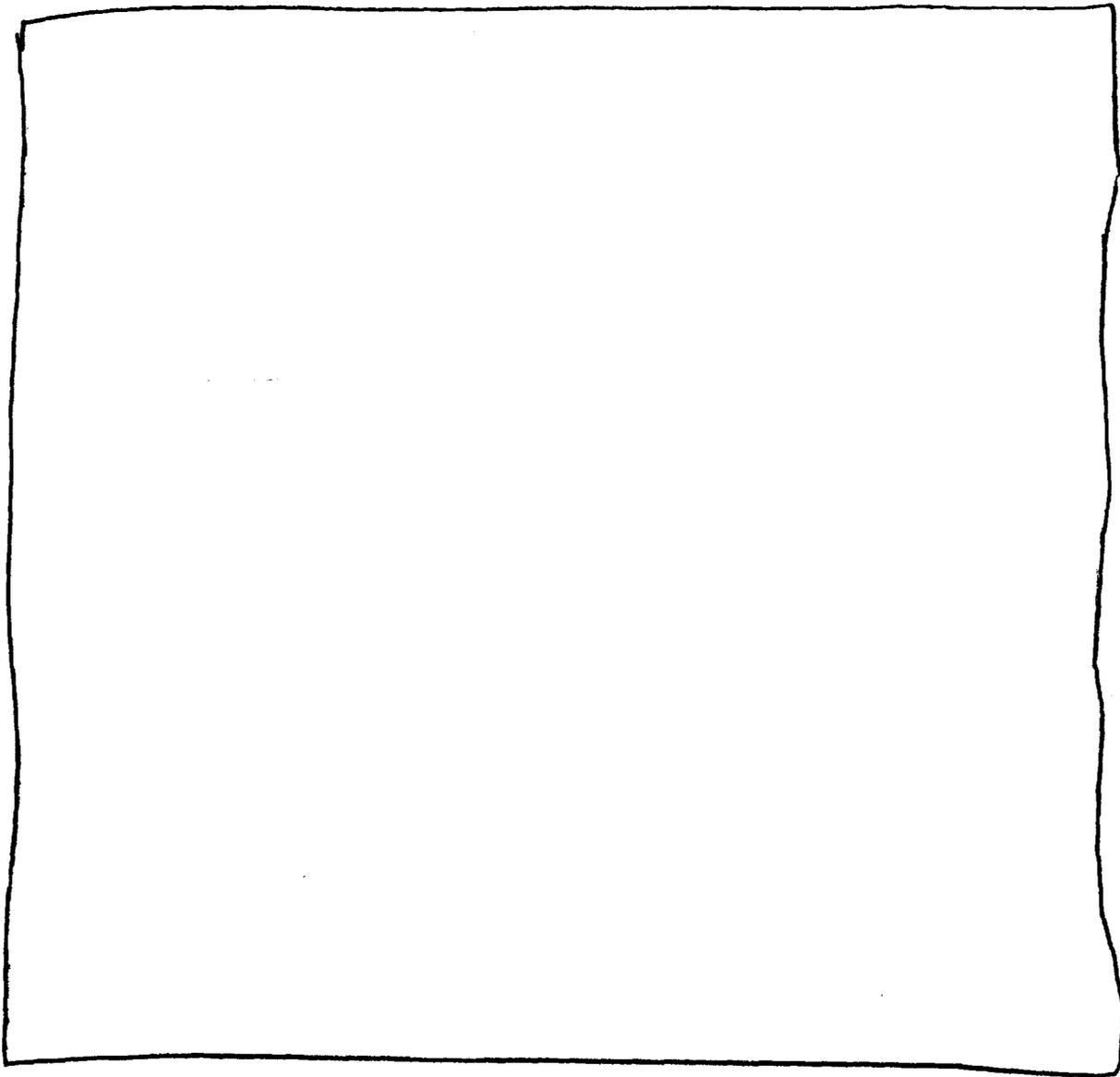
Formulation PO148: [redacted]

[redacted]

[redacted] Oral Dose=1x5 mg tablet [redacted]

[redacted]

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.



[redacted] the in vivo evaluation in cynomolgus monkeys of 1 mg rapamune tablets differing in dispersion particle size, conducted by Wyeth Ayerst Research, Pearl River, NY, report GTR-37178, protocol no. 946.98004, 13 September 1999, not conducted under GLP

Six mature male cynomolgus monkeys (age, source information not provided) received single doses of 3x1 mg tablets during two periods for a total of two treatments in a complete randomized crossover design study. Monkeys were fasted prior to treatment. Blood was sampled at 0, 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours following treatment for analysis by [redacted]. The two dosage forms evaluated consisted of tablets composed of either mean particle sizes of 290 nm (lot 1998B0254) or 200 nm (lot R979079).

Pharmacokinetic parameters for two dosage dispersion formulations

	290 nm	200nm
AUC (ng•hr/ml)	631	591
Cmax (ng/ml)	53.7	45.7
Tmax (hr)	6.00	6.67

These two different particle size formulations appear approximately equivalent in pharmacokinetic parameters in the cynomolgus monkey.

CONCLUSIONS

This submission is acceptable with respect to pharmacology/toxicology. The sponsor has attempted to qualify Group II degradation products in a 28-day rat study at concentrations up to [redacted]. Despite the fact that ICH guidances on impurities in drug substance do not apply to fermentation products and therefore do not include [redacted] these impurities remain an area of concern due to their lack of characterization and the potential for decreased efficacy of the parent drug due to decreased content and/or antagonism by the impurities. Subsequent elevated concentration of the Group II impurities may necessitate their evaluation in longer duration toxicity studies and genetic and reproductive toxicity studies. The issue of contaminants [redacted] [redacted] in the manufacturing process was discussed internally and found not to merit further studies.

/S/

✓ S.C. Kunder, Ph.D.
Reviewing Pharmacologist

concurrences:

HFD-590/ADir/RAIbrecht **/S/ 8/31/00**
HFD-590/SPharm/KHastings **8/30/00**
Steven C. Kunder/Pharm/

disk:

HFD-590/KHastings

cc:

HFD-590 (original)
HFD-590 Division file
HFD-340
HFD-590/MBacho
HFD-590/RTieman

HFD-590/Mseggel
HFD-590/SBala
HFD-345

Histopathology Inventory for Toxicology Studies

Study /Species	rat
Adrenals	X
Aorta	X
Bone Marrow smear	X
Bone (femur)	X
Brain	X
Cecum	X
Cervix	
Colon	X
Duodenum	X
Epididymis	X
Esophagus	X
Eye	X
Fallopian tube	
Gall bladder	
Gross lesions	X
Harderian gland	
Heart	X
Hypophysis	
Ileum	X
Injection site	
Jejunum	X
Kidneys	X
Lachrymal gland	
Larynx	
Liver	X
Lungs	X
Lymph nodes, cervical	X
Lymph nodes mandibular	
Lymph nodes, mesenteric	X
Mammary Gland	X
Nasal cavity	
Optic nerves	
Ovaries	
Pancreas	X
Parathyroid	X
Peripheral nerve	
Pharynx	
Pituitary	X
Prostate	X
Rectum	
Salivary gland	X
Sciatic nerve	X
Seminal vesicles	X
Skeletal muscle	X
Skin	X
Spinal cord	X
Spleen	X
Sternum	
Stomach	X
Testes	X
Thymus	X
Thyroid	X
Tongue	X
Trachea	X
Urinary bladder	X

Uterus	
Vagina	
Zymbal gland	

X=histopathology examination

**APPEARS THIS WAY
ON ORIGINAL**

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