CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 50-777

CHEMISTRY REVIEW(S)

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DIVISION OF DERMATOLOGIC AND DENTAL DRUG PR
HFD-540
Review of Chemistry, Manufacturing, and Co

REC
12/13/00
1:15PM

NDA #. 50-777 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 06-DEC-2000

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	08-SEP-1999	09-SEP-1999	20-SEP-1999
AMENDMENT/BL	31-JAN-2000	02-FEB-2000	11-FEB-2000
AMENDMENT/BC	17-MAR-2000	20-MAR-2000	23-MAR-2000
AMENDMENT/NC	02-OCT-2000	03-OCT-2000	12-OCT-2000

NAME & ADDRESS OF APPLICANT:

Fujisawa Healthcare, Inc.
Parkway North Center
3 Parkway North
Deerfield, IL 60015-2548

Donald E. Baker, J.D.
Sr. Director, Regulatory Affairs

DRUG PRODUCT NAME

Proprietary:	PROTOPIC®
Nonproprietary/USAN:	tacrolimus
Code Names/#'s:	FK-506, FR-900506
Chemical Type/	Macrolide
Therapeutic Class:	1 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Immunosuppressant for short and long-term treatment of the signs and symptoms of atopic dermatitis.

DOSAGE FORM: Ointment
STRENGTHS: 0.03% and 0.1% (w/w)
ROUTE OF ADMINISTRATION: Topical
DISPENSED: X Rx ____ OTC

APPEARS THIS WAY
ON ORIGINAL

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:

[3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.

Empirical Formula:	$C_{44}H_{69}NO_{12} \cdot H_2O$
Formula Weight:	822.05
CAS Number:	104987-11-3 (anhydrous)
	109581-93-3 (monohydrate)
Appearance:	White crystals or crystalline powder
Melting Point:	123.6°C - 131.9°C
Elemental Analysis:	Calculated %: C (64.29), H (8.71), N (1.70)
	Found %: C (64.20), H (8.86), N (1.72)

APPEARS THIS WAY
ON ORIGINAL

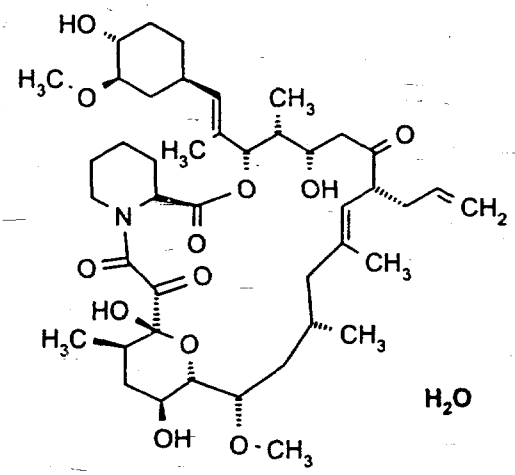
Solubility*:

Solvent	mg/mL	
Methanol	691	Very soluble
Chloroform	660	Very soluble
Acetone	548	Freely soluble
Dimethylformamide	511	Freely soluble
Acetonitrile	467	Freely soluble
Ethanol	341	Freely soluble
Ethyl Ether	49	Soluble
Water	<0.1	Practically Insoluble
Hexane	< 0.1	Practically Insoluble

*Source: data on file, Prograf® NDAs 50-708 for capsules and 50-709 for ampules, and supplements thereto.

Structural Formula:

APPEARS THIS WAY ON ORIGINAL



APPEARS THIS WAY ON ORIGINAL

SUPPORTING DOCUMENTS:

NDA 50-708, Progaf® Capsules, Fujisawa Healthcare, Inc.; approved April 1994.

NDA 50-709, Progaf® for Injection, Fujisawa Healthcare, Inc.; approved April 1997.

DMF — Type I, for the [redacted]

DMF — Type III, [redacted]

RELATED DOCUMENTS (if applicable):

INDs [redacted]

CONSULTS: N/A

REMARKS/COMMENTS:

Information supporting the acceptability of the drug substance has been provided in NDAs 50-708 and 50-709. No changes are pending which would have any bearing on the approvability of the ointment formulation. Future changes [redacted] are under discussion with FDA. FHI is not proposing [redacted] for tacrolimus ointment at this time. The data submitted in the NDA support the proposed 24 month expiration dating period. The protocol for the extension of shelf life is acceptable. Elements of the proposed drug product labeling are inconsistent with past practice in HFD-540. However, the proposed labeling is consistent with approved labeling for Prograf Capsules and Injection, NDAs 50-708 and 50-709. No changes to the labeling are expected at this time.

CONCLUSIONS & RECOMMENDATIONS: **APPROVAL**

The application is approvable for manufacturing and controls under section 505 of the FD&C Act. All manufacturing facilities are currently in acceptable GMP compliance as of 23-MAY-2000 (see item G., Establishment Inspections).

J. S. Hathaway, Ph.D.,
Review Chemist

cc: Orig. NDA 50-777
HFD-540/DivFile
HFD-540/Chem/JSHathaway/12-06-2000
HFD-540/MedOffr/RLabib
HFD-540/PharmTox/BHill
HFD-540/DivDir/JWilkin
HFD-830/DivDir/CWChen
HFD-540/ProjMgr/MAWright
HFD-540/ChemTeamLdr/WHDeCamp

R/D Init by: WHDeCamp

filename: C:\My Documents\MSWordDocs\NDAS\OrigNDAs\Nda50777\N50777rev.000.doc

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 30 PAGE (S)

/s/

Steve Hathaway
12/6/00 03:45:15 PM
CHEMIST
The recommendation for this NDA is APPROVAL.

Wilson H. DeCamp
12/6/00 04:06:42 PM
CHEMIST
Concur with review recommendation.

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 50777/000
Stamp: 09-SEP-1999
Regulatory Due: 09-OCT-2000
Applicant: FUJISAWA HLTHCARE
3 PKY NORTH
DEERFIELD, IL 600152548
Priority: 3S
Org Code: 540

Action Goal:
District Goal: 10-MAY-2000
Brand Name: PROTOPIC(TACROLIMUS) 0.03%/0.1% OINTMEN
Estab. Name:
Generic Name: TACROLIMUS OINTMENT
Dosage Form: (OINTMENT)
Strength: 0.03%, 0.1%

Application Comment: NEW DOSAGE FORM, INTENDED FOR SHORT- AND LONG-TERM TREATMENT OF ATOPIC DERMATITIS. (on 06-OCT-1999 by J. HATHAWAY (HFD-540) 301-827-2069)

FDA Contacts: M. WRIGHT (HFD-540) 301-827-2084 , Project Manager
J. HATHAWAY (HFD-540) 301-827-2069 , Review Chemist
W. DECAMP II (HFD-540) 301-827-2041 , Team Leader

Overall Recommendation: ACCEPTABLE on 23-MAY-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:

DMF No:
AADA:
Responsibilities:
Profile: OIN
OAI Status: NONE
Estab. Comment: FUJISAWA FACILITY IN GRAND ISLAND, NY, (on 19-OCT-1999 by J. HATHAWAY (HFD-540) 301-827-2069)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-OCT-1999				HATHAWAYS
SUBMITTED TO DO	20-OCT-1999	GMP			FERGUSONS
ASSIGNED INSPECTION	20-OCT-1999	PS			JPODSADO
INSPECTION PERFORMED	23-MAY-2000		19-MAY-2000		JPODSADO
CORRECTION: THE ESTABLISHMENT IS FUJISAWA HEALTHCARE INC.					
DO RECOMMENDATION	23-MAY-2000			ACCEPTABLE INSPECTION	JPODSADO
THIS RECOMMENDATION IS BASED ON AN INSPECTION (5/8-19/2000). CORRECTION: THE ESTABLISHMENT IS FUJISAWA HEALTHCARE INC.					
OC RECOMMENDATION	23-MAY-2000			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: 9612809
FUJISAWA PHARMACEUTICAL CO LTD
2-178 KOJIN-CHO
TOYAMA CITY, , JA
DMF No:
AADA: 050708
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CFN
OAI Status: NONE
Estab. Comment: THIS FACILITY MANUFACTURES BULK DRUG SUBSTANCE MANUFACTURING INFORMATION FOR DRUG SUBSTANCE IS CROSS-REFERENCED FROM APPROVED NDA 50-708 AND APPROVED SUPPLEMENTS FOR PROGRAF (TACROLIMUS) CAPSULES. (on 06-OCT-1999 by J. HATHAWAY (HFD-540) 301-827-2069)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator

SUBMITTED TO OC	19-OCT-1999	HATHAWAYS	
OC RECOMMENDATION	20-OCT-1999	ACCEPTABLE BASED ON PROFILE	FERGUSONS

APPEARS THIS WAY
ON ORIGINAL