CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 50-777

CORRESPONDENCE

(37)

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 Telefax (847) 317-7286

Fujisawa

NDA [illegible]

[illegible]

January 10, 2000

ARCHIVAL

Jonathan Wilkin, M. D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd. 2nd Fl., N-214
Rockville, Maryland 20850-3202

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 12 2000
MEGA DOC

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 11 2000
CDR

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

SUBMISSION OF 120-DAY SAFETY UPDATE

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc.'s (FHI) new drug application (NDA 50-777) submitted under Section 505(b) to the FDA on September 8. 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

We are herewith submitting the 120-day safety update for NDA 50-777.

An electronic archive copy and a paper desk copy have been included in this submission. The electronic archive copy of this NDA safety update is contained on one CDROM (approximately 12 megabytes). The electronic archive copy was checked with Norton Antivirus (version 4.04) and is virus-free. The electronic archive copy and the paper desk copy are identical.

Please feel free to contact me at **847/317-8872** or Robert M. Reed at **847/317-8985** if you have any questions or concerns.

Sincerely,

Robert M. Reed for

APPEARS THIS WAY
ON ORIGINAL

Donald E. Baker
Senior Director, Regulatory Affairs

Archive\Protopic\NDA 000107\word\120cover.pdf

ORIGINAL

ARCHIVAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

CENTER FOR DRUG EVALUATION AND RESEARCH JAN 12 2000

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Fujisawa Healthcare, Inc.	01/10/00
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number *(Include Area Code)***
(847) 317-8872	(847)317-7286

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
Parkway North Center
Three Parkway North
Deerfield, IL 60015-2548

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 50-777

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
tacrolimus ointment	PROTOPIC

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
Please refer to package insert

CODE NAME *(If any)* FK506, FK 506, FK-506, FR900506

DOSAGE FORM: Ointment	STRENGTHS: 0.03% and 0.1%	ROUTE OF ADMINISTRATION: Topical

(PROPOSED) INDICATION(S) FOR USE: Short and long term treatment of the signs and symptoms of atopic dermatitis.

APPLICATION INFORMATION

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D JAN 11 2000 CDR

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION Submission of Section 9 (120-Day Safety Update) to NDA 50-777

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 2 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications. INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

NDA 50-708
NDA 50-709

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
X	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Concurred for Dr. Baker	Donald E. Baker, JD Senior Director, Regulatory Affairs	1/10/00

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3 Parkway Center North Deerfield, IL 60015-2548	(847 317-8872

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

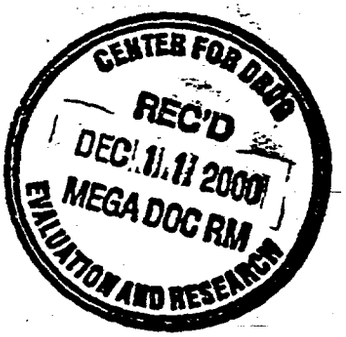
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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



December 8, 2000

ARCHIVAL

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug
Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

NDA ORIG AMENDMENT

BL

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Final Proposed Package Insert

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc., (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to the fax copy of the revised pages of the final proposed Package Insert for Protopic Ointment provided by Ms. Millie Wright on December 8, 2000.

We have reviewed the fax copy of the revised pages of the labeling and they are acceptable, subject to our understanding that the numbers in the Adverse Event Table (page 15) for "Eczema Herpeticum" will be rounded up or down, as agreed. In addition, please note that in the same table, the number under pruritus, adult vehicle will be rounded up to 37; the number under skin infection, pediatric vehicle will be rounded up to 14 and the number under fever, adult 0.03% tacrolimus ointment will be rounded up to 4.

For your reference, please find enclosed **(Attachment 1)** the revised pages provided by Ms. Wright on December 8, 2000.

Please note that an archival copy as well as one desk copy and one review copy of this submission are being provided (hard copy format).

Should you have any questions regarding this submission, please do not hesitate to contact the undersigned at (847) 317-8872 or Jerry D. Johnson, Ph.D. at (847) 317-8898.

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

DEB:kjg
attachment

cc: Ms. Millie Wright, Project Manager (desk copy)

APPEARS THIS WAY
ON ORIGINAL

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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

December 7, 2000

ARCHIVAL

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

NDA [illegible]AMENDMENT
BL

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Final Proposed Labeling
Package Insert, Patient Package Insert and Container Labels

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc., (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to a FDA Fax Memo dated December 7, 2000 from Ms. Millie Wright containing the Package Insert (PI), Patient Package Insert (PPI) and Container Labels.

We have reviewed the fax copy of the labeling and labels and they are acceptable, subject to the corrections noted. For your reference, please find enclosed **(Attachment 1)** the labeling provided by Ms. Wright in the December 7, 2000 Fax Memorandum.

Please note that during our review of the fax copy of the Package Insert, we identified the following minor errors:

1. On **Page 4, Line 140,** — was changed to —
2. On **Page 4, Line 141,** — was changed to —
3. On **Page 4, Line 144,** —was changed to —
4. On **Page 12, Line 366,** a period following Ointment has been added and the word '

5. On **Page 12, Line 375,** (0.04X-0.12X MRHD based on BSA) was moved to the end of the sentence. We believe that it should correctly follow the doses of 0.32 and 1.0 mg/kg on lines 372, 373

Please note that an archival copy as well as one desk copy and one review copy of this submission are being provided (hard copy format).

Should you have any questions regarding this submission, please do not hesitate to contact the undersigned at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898.**

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

DEB:kjg
attachment

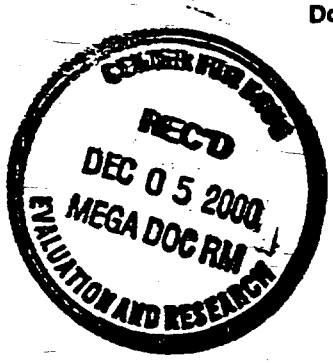
cc: Ms. Millie Wright, Project Manager (desk copy)

APPEARS THIS WAY
ON ORIGINAL

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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



ARCHIVAL

December 4, 2000

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

NDA [illegible] MENT

BL

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Response to FDA Proposed Draft Package Insert (PI) and Draft Patient Package Insert (PPI)

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc., (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to a telephone request from Ms. Millie Wright, on Monday, December 4, 2000, for a diskette containing the revised draft proposed Package Insert (PI) and Patient Package Insert (PPI) which was submitted to the Division via facsimile on Saturday, December 2, 2000.

Since our fax was submitted on Saturday, we have conducted a careful QA check of the revised Package Insert. As a result, please note that the version of the revised draft PI provided on the electronic disk, differs slightly from the version submitted to the Division via facsimile on Saturday, December 2, 2000, with respect to the following:

1. On **Page 9, Line 243**, the word "of" was inadvertently deleted. However, it should not have been deleted.

2. On **Page 16** of the Table following **Line 482**, the second line of the Table title has been revised to delete the word ——— following 12-week and the word "Incidence" was added following after the word "Adjusted."

3. On **Page 17** in the Table, a "dagger" symbol (†) was added to the Table entry following the word Acne.

4. On **Page 18, Line 513**, the statement, "exacerbation of untreated area" was added.

Please note that an archival copy (hard copy format) as well as one desk copy and one review copy of this submission are being provided. The electronic files are provided in the desk copy and were checked with Norton Antivirus (version 7.0) and found to be virus free.

We apologize for any inconvenience these changes may have caused and, we look forward to the next round of labeling negotiations tentatively scheduled for late Wednesday afternoon, December 6, 2000.

Should you have any questions regarding this submission, please do not hesitate to contact the undersigned at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898**.

Sincerely,

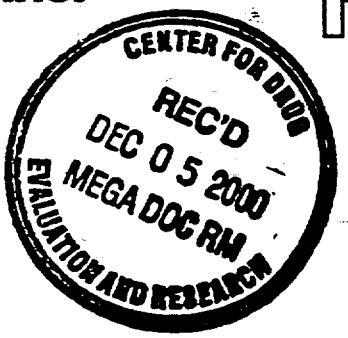
Donald E. Baker
Senior Director, Regulatory Affairs

DEB:kjg
attachment

cc: Ms. Millie Wright, Project Manager (desk copy)

APPEARS THIS WAY
ON ORIGINAL

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286



Fujisawa

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

December 2, 2000

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

ARCHIVAL

NDA [illegible]

BL

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Response to FDA Proposed Draft Packaging Insert (PI)
And Draft Patient Package Insert (PPI)

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc., (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to the Division's proposed draft Package Insert (PI) and draft Patient Package Insert (PPI) for Protopic Ointment, which was revised by FHI and submitted to FDA on November 30, 2000, for review and discussion during the Labeling negotiation conference held on December 1, 2000.

FHI has revised the Package Insert (PI) and Patient Package Insert (PPI) for Protopic Ointment in accordance with the specific agreements reached during the Labeling negotiations on December 1, 2000, with the following FDA representatives:

Dr. Wilkin, Division Director
Dr. Okun, Medical Team Leader
Dr. Labib, Medical Reviewer
Dr. Al-Osh, Clinical Statistical Team Leader
Dr. Tandon, Biopharmaceutic Reviewer
Dr. Jacobs, Pharmacology Team Leader
Dr. Mathis, Regulatory Review Officer
Ms. Wright, Project Manager

APPEARS THIS WAY
ON ORIGINAL

Therefore, this submission is to address specific areas of the Package Insert and to provide our comments to support the following revisions proposed by FHI for which further clarification and supporting information were requested.

1. In the Precaution Section, on **Page 10, Lines 280 to 284**, we have shown the durations of pruritus and burning in terms of the medians accompanied by the interval in which 90% of the durations fell. Our previous version of the Package Insert showed the — interval. Note also that to compute these numbers, we have pooled the data from the 12 week controlled and long-term studies. Thus the medians changed slightly from the previous version which used only the — controlled studies.

2. In the Carcinogenesis, Mutagenesis and Pregnancy Sections of the Package Insert, FHI had revised the calculations for the oral dosing of tacrolimus in rats and topical dosing in humans, to clarify the MRHD values. See: **Page 12, Lines 367, 375, 390 and 399.**

   Please note that the MRHD values were recalculated based on AUC comparisons. For atopic dermatitis patients, the highest mean AUC was 20.4 ng*hr/mL. In rats receiving oral tacrolimus, the AUC at a dose of 1.0 mg/kg was 38 ng*hr/mL and at a dose of 3.2 mg/kg was 266 ng*hr/mL (See **Reference 1**). In rabbits receiving oral tacrolimus, at 2.0 mg/kg, the AUC was 599 ng*hr/mL. (See **Reference 2**). The AUCs for the 0.32 mg/kg and 1.0 mg/kg doses were calculated assuming linear pharmacokinetics.

   As a result, the calculations supporting the MRHD values in the revised Package Insert are as follows:

RATS		**Atopic Dermatitis Patients**	
Dose (mg/kg)	*AUC (ng*hr/mL)*	*AUC (ng*hr/mL)*	*MRHD*
1.0	38	20.4	2
3.2	266	20.4	13

RABBITS		**Atopic Dermatitis Patients**	
Dose (mg/kg)	*AUC (ng*hr/mL)*	*AUC (ng*hr/mL)*	*MRHD*
0.32	599*0.32/2.0 = 96	20.4	5
1.0	599*1.0/2.0 = 300	20.4	15

3. In the Pregnancy Section of the Package Insert, **Page 12, Lines 383 to 384**, FHI has modified the first sentence to read:

[redacted]

However, FHI has recommended that the following statement be deleted:

[redacted]

FHI appreciates and supports the FDA's efforts to communicate meaningful risk information about drug effect on pregnancy outcomes to physicians so that women can be advised of more relevant information about pregnancy outcomes than can be derived from animal models. In this instance, however, the pregnancy data from Protopic clinical studies are sparse at best and simply do not provide any meaningful guide for physicians in advising their patients. The goal of this section of the package insert is to provide an accurate and current assessment of the risk of using the drug during pregnancy. For Protopic, pregnancy outcome was not a prospectively studied event in the clinical trials and although FHI was diligent in following up on the outcomes of the unplanned pregnancies, the data collected are not sufficient to be meaningful. Even when interpreted in their broadest terms, the data from the small number of women who became pregnant are not sufficient to conclude a reassuring result should a woman become pregnant while using our product. While FHI will freely disclose the information on pregnancy outcomes to health care professionals who contact the medical information department, including this information in the product labeling conveys an imprimatur of proven data that could be unintentionally misleading to physicians and patients.

Further, if any data are received reporting adverse pregnancy outcomes, FHI would be compelled to change this labeling section, even if there is no evidence of casual relationship to the drug. This places FHI in an unacceptable legal position.

We appreciate the Division's comments provided during Labeling negotiations on December 1, 2000, for the Protopic Ointment proposed Package Insert and Patient Package Insert. We look forward to further collaborative review during the next Labeling negotiations.

Should you have any questions regarding this submission, please do not hesitate to contact the undersigned at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898.**

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

DEB:kjg
attachment

cc: Ms. Millie Wright, Project Manager
(desk copy)

APPEARS THIS WAY
ON ORIGINAL

(176)

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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

NDA ... ENT

BL

November 30, 2000

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Response to FDA Proposed Draft Packaging Insert (PI)
And Draft Patient Package Insert (PPI)

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc., (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to the Division's proposed draft Package Insert (PI) and draft Patient Package Insert (PPI) for Protopic Ointment, provided to FHI by Ms. Millie Wright on November 29, 2000 and November 30, 2000, respectively. During a telephone conference on November 29, 2000 with Dr. Okun, Dr. Labib, and Ms. Wright, the Division Medical Reviewers requested specific additional information for the proposed draft labeling.

FHI has revised the Division's proposed Package Insert and Patient Package Insert for Protopic Ointment.

For ease of review, an annotated redlined version of your proposed draft Package Insert which incorporates FHI's recommended changes and additions is provided in **Attachment 1**. In addition, reference comments to support our rationale for our recommended revisions or additions to the draft PI are provided in **Attachment 2**. Our suggested revisions to your proposed draft PPI are written in the margins of the draft copy provided in **Attachment 3**.

Please note that a disk containing the revised proposed draft Package Insert is provided as an electronic review aid. The electronic files provided in desk and review copies were checked with Norton Antivirus (version 7.0) and found to be virus free.

We are prepared to discuss our rationale for the recommended changes and additions to the draft Package Insert during the labeling negotiation conference tentatively scheduled for Friday, December 1, 2000, from 3:00 pm – 5:00 pm EST.

Should you have any questions regarding this submission, please do not hesitate to contact the undersigned at (847) 317-8872 or Jerry D. Johnson, Ph.D. at (847) 317-8898.

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

DEB:kjg
attachment

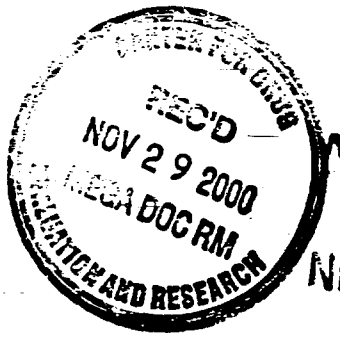
cc: Ms. Millie Wright, Project Manager
(desk copy)

APPEARS THIS WAY
ON ORIGINAL

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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



ARCHIVAL

NDA

November 28, 2000

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Response to Information Request – FDA Fax Memo dated November 22, 2000

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc., (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to the facsimile dated November 22, 2000 from Millie Wright (Project Manager) requesting specific information relating to your revisions to the Protopic Ointment draft product labeling.

To facilitate ease of review, we are providing the requested information as tabbed attachments in the order requested in the FDA Fax Memo as indicated below.

(1) **The outcome of the pregnancies – for subjects on vehicle and tacrolimus.**

Information on the outcome of fifteen (15) reported pregnancies are provided in **Tab 1**. As you are aware, no reproductive toxicity studies were performed with tacrolimus ointment. However, based on the results of reproductive studies of oral and intravenous tacrolimus formulations, tacrolimus is not considered a teratogen. Tacrolimus is also not a mutagen. Tacrolimus (Prograf®) is labeled as pregnancy category C. We also suggest the same category for Protopic.

(2) **Examples of patients with erythroderma.**

Pursuant to the instructions from Ms. Wright, information request No. 2 has been withdrawn by your Division.

(3) **Literature references for the use of topical tacrolimus in the treatment of Netherton's syndrome, with special reference to clinical studies in which whole blood levels of tacrolimus were analyzed.**

Provided in **Tab 2** is a summary of available information and references pertaining to Netherton's syndrome. In light of the potential risks for higher blood levels in patients with Netherton's syndrome treated with tacrolimus ointment, FHI recommends that the use of tacrolimus be contraindicated in patients with this condition.

Should you have any questions regarding this submission, please do not hesitate to contact the undersigned at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898**.

Sincerely,

Donald E.Baker
Senior Director, Regulatory Affairs

DEB:kjg
attachment

cc: Ms. Millie Wright, Project Manager (fax copy)

APPEARS THIS WAY
ON ORIGINAL

167

NDA ORIG AMENDMENT

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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

REVIEW

November 10, 2000

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

BZ

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Response to Request for Information from Clinical and Statistical Reviewers, During the October 26, 2000 Telephone Conference

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc., (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to the telephone conference on October 26, 2000. During that telephone conference, the Division Reviewers requested the following specific additional clinical and statistical information. Following each information request is our response:

Information Request No. 1

(1) **Plot the 8 secondary endpoints (not EASI score but include components, BSA and pruritus) over time on a graph (not differences from baseline). Show the mean and 95% confidence interval at each time point. Use the ITT population with last observation carried forward. For the 97-0-037 pediatric study, only include the vehicle and 0.03% groups. For the 97-0-035/036 adult studies, include vehicle, 0.03% and 0.1%.**

DUPLICATE

Response:

The information provided in **Attachment 1** are graphs plotting the 8 secondary endpoints showing the mean and 95% confidence interval at each time point for the ITT population for both the 97-0-037 pediatric and the 97-0-035/036 adult studies.

Information Request No. 2

(2) **Create an Access and SAS database for all patients in the 97-0-035/036/037 who had a measurable blood level at any point in time. Include in the database the patient's age, severity of disease, BSA, whether head/neck were treated, and the response to treatment at each time a level was measured.**

Response:

The information provided in **Attachment 2** is a database of all patients in the 97-0-035/036/037 who had a measurable blood level at any point in time including patient's age, disease, BSA and response to treatment measuring a level at each time.

Please note, this information is provided in electronic media only (electronic review aid):

"FDA146a.mdb" – Access dataset which include data of all patients in studies 97-0-035, 97-0-036 or 97-0-037 who had a measurable blood level at any point in time.
"FDA146b.mdb" – Access dataset which include data of all patients in studies 97-0-035, 97-0-036 or 97-0-037 who did not have any measurable blood levels at any point in time.
"FDA146.xpt" – SAS transport file which contains 2 SAS datasets: "FDA146a.sd2" and "FDA146b.sd2."

Information Request No. 3

(3) **For the FG-06-12, and 96-0-025 (long-term safety) studies, provide data on recurrences in a data table. Also provide data on how much ointment was used and/or the # of days on treatment. No Access file needed.**

Response:

The information in **Attachment 3** provides information and data tables showing information on recurrences, how much ointment was used and the number of days on treatment. (See electronic review aid, file name 1026rec.doc).

Information Request No. 4

(4) **Create a table of AEs which includes 4 columns: 97-0-035/036 pooled data from the 0.03% and 0.1% groups, 97-0-037 pooled data from the 0.03% and 0.1% groups, FG-06-12, and 96-0-025 studies. All AEs with an incidence of 1% or greater in any of the four groups should be included in the table.**

Response:

The information provided in **Attachment 4** are 2 AE tables. The first table consists of the pooled data from the 0.03% and 0.1% showing all AEs with an incidence of 1% or greater (see electronic review aid, file name Ae1.doc).

The second table provides for adjusted rates from the three (3) double blind vehicle controlled studies (97-0-035, 97-0-036 and 97-0-037). This analysis adjusts for the difference in dropout between vehicle and tacrolimus ointment groups, which were used for all statistical inferences in NDA 50-777 and allows for direct comparison of the active and vehicle groups.

Information Request No. 5

(5) **For the cases of lymphadenopathy draft a full description of each of the cases.**

Response:

Please note that our response to the specific request for the lymphadenopathy information [(5) above] was submitted to the FDA on Tuesday, November 7, 2000.

Information Request No. 6

(6) **For the proposed package insert, provide the FDA with a definition of the term "short duration" in reference to the local adverse events. Re-draft the label and provide supportive data to show how long the events last.**

Response:

The information provided in **Attachment 5** defines "short duration" in the proposed label and provides supportive data tables (see electronic review aid, file name 1026dur.doc).

Also note that the archival copy (hard copy format) as well as one desk copy and one review copy (hard copy and electronic review aids) of this submission are being provided. The electronic files provided in desk and review copies were checked with Norton Antivirus (version 7.0) and found to be virus free.

We hope that the information provided in our response are sufficient to satisfy the Division Reviewers' requests.

Should you have any questions regarding this submission, please do not hesitate to contact the undersigned at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898**.

Sincerely,

Donald E.Baker
Senior Director Regulatory Affairs

DEB:kjg
attachment

cc: Ms. Millie Wright, Project Manager
(cover letter only)

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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

NDA ORIG AMENDMENT

November 10, 2000

REVIEW
CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 13 2000
MEGA

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

BM

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Response to Request for Information from Clinical and Statistical Reviewers, During the October 26, 2000 Telephone Conference

Dear Dr. Wilkin:

Reference is made to the telephone conference on October 26, 2000 and Fujisawa Healthcare, Inc.'s response submitted November 7, 2000 regarding lymphadenopathy. The specific request made by the FDA during the conference call is stated below:

> **For the cases of lymphadenopathy draft a full description of each of the cases.**

The data on lymphadenopathy in patients treated with tacrolimus ointment was recently re-reviewed. Our written response of November 7, 2000 included information on one patient (Patient #25-1816) who was diagnosed with cutaneous T cell lymphoma (CTCL) two years after entry in the study. We have reviewed this patient's original medical records and are writing to clarify this patient's history and clinical course.

On September 27, 1997, this patient was enrolled in protocol #97-0-036. At enrollment, the patient had a 7 year history of an eczematous dermatitis which began when the patient was 51 years old, and was diagnosed as "atopic dermatitis." The patient did not have a life-long history of atopic dermatitis as stated in our previous correspondence. The criteria for this patient's enrollment included: pruritus,

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

lichenification, chronic or relapsing course, and a sibling with a history of atopy. Minor criteria at study entry included: xerosis, a history of HSV, hand-foot dermatitis, and itch when sweating. The patient was enrolled in the long-term follow up study (#97-0-038) on April 7, 1998. In April, 1999, his skin disease flared and 3 biopsies were performed. The routine histology was suggestive of CTCL; subsequent immunophenotypic marker studies were non-confirmatory. As noted in our previous correspondence, the patient was terminated from the tacrolimus study and responded to topical nitrogen mustard.

The investigator believed the CTCL was unrelated to the use of tacrolimus ointment and felt that the patient may have had CTCL that was misdiagnosed as atopic dermatitis. The history in this patient of an eczematous dermatitis for the preceding 7 years would support this hypothesis. Epstein et al reported that the average length of time from clinical onset of symptoms to diagnosis for CTCL is 6.1 years (*Medicine 51:61, 1972).*

In addition, please note that this patient (#25-1816) was age 59 when he initially enrolled in study 97-0-036 and received 0.03% tacrolimus ointment. The patient subsequently enrolled in extension study 97-0-038. The patient, now 60 years old, applied 0.1% tacrolimus ointment during his participation in the extension study.

Furthermore, please note that we have further information on a second patient (patient #231801 in the November 7, 2000 submission. This patient's B-cell lymphoma of the parotid is of the low grade follicular type which is generally not associated with immunosuppression.

Provided as **Attachment 1** is the errata sheets identifying the changes. The replacement pages with the correct information can be found in **Attachment 2.**

Thank you for the opportunity to clarify the history of this patient.

Should you have any questions regarding this submission, please do not hesitate to contact the undersigned at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898.**

Sincerely,

Donald E. Baker
Senior Director Regulatory Affairs

cc: Millie Wright, Project Manager

APPEARS THIS WAY
ON ORIGINAL

166

NDA [illegible] AMENDMENT

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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

November 9, 2000

ARCHIVAL

BB

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Response to Request for Information from Biopharmaceutics Reviewers

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc., (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to a FDA facsimile memo dated November 1, 2000 (see attached) requesting specific information in preparation for the upcoming Protopic Advisory Committee meeting.

To facilitate ease of review, we are providing the requested information as attachments in the order requested in the FDA facsimile memo as indicated below.

Information Request No. 1.

1. **For the pediatric subjects in the clinical trials (95-0-009 and 97-0-037) who had detectable levels of tacrolimus, please provide a listing of the individual body surface areas (including both the treated surface area per subject in m^2 and the % involvement).**

   The information provided in **Appendix A** is a data listing for the patients who were in pediatric studies 95-0-009 or 97-0-037 and who had detectable levels of tacrolimus. [see electronic review aid, file name "Req1.doc"].

ORIGINAL

Information Request No. 2.

2. **Similar information should also be provided for the adult study FJ-111, 97-0-035, 97-0-036 and FG-06-12 for those subjects that had tacrolimus concentrations higher than 5 ng/mL.**

   The information provided in **Appendix B** is a data listing for patients who were in adult studies FJ-111, 97-0-035, 97-0-036 or FG-06-12 and who had tacrolimus concentrations greater than 5 ng/mL. [see electronic review aid, file name "Req2.doc"].

Information Request No. 3.

3. **An issue has been raised as to whether or not topically applied tacrolimus would participate in drug-drug interactions with known CYP3A4 inhibitors. In order to evaluate this potential, please provide the results of any in vitro studies done using tacrolimus.**

   The information in **Appendix C** will provide further clarification that it is unlikely for topically applied tacrolimus to participate in drug-drug interactions with known CYP3A4 inhibitors. In addition, information for in vitro studies on the metabolism of tacrolimus is presented. (see electronic review aid, file name "Req3.doc"].

Please note that the archival copy (hard copy format) as well as one desk copy and one review copy (hard copy and electronic review aids) of this submission are being provided. The electronic files provided in desk and review copies were checked with Norton Antivirus (version 7.0) and found to be virus free.

Should you have any questions regarding this submission, please do not hesitate to contact the undersigned at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898**.

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

DEB:kjg
attachment

163

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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

BM

REVIEW

November 7, 2000

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Response to Request for Information from Clinical and Statistical Reviewers, During the October 26, 2000 Telephone Conference

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc., (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to the telephone conference on October 26, 2000 with the following Division Reviewers, Dr. Okun, Dr. Labib, Dr. Al-Osh and Ms. Millie Wright, Project Manager and FHI representatives. During that telephone conference, the Division Reviewers requested the following specific additional clinical and statistical information:

(1) Plot the 8 secondary endpoints (not EASI score but include components, BSA and pruritus) over time on a graph (not differences from baseline). Show the mean and 95% confidence interval at each time point. Use the ITT population with last observation carried forward. For the 97-0-037 pediatric study, only include the vehicle and .03% groups. For the 97-0-035/036 adult studies, include vehicle, .03% and .1%

(2) Create an Access and SAS database for all patients in the 97-0-035/036/037 who had a measurable blood level at any point in time. Include in the database the patient's: age, severity of disease, BSA, whether head/neck were treated, and the response to treatment at each time a level was measured.

(3) For the FG-06-12, and 96-0-025 (long-term safety) studies, provide data on recurrences in a data table. Also provide data on how much ointment was used and/or the # of days on treatment. No Access file needed.

(4) Create a table of AEs which includes 4 columns: 97-0-035/036 pooled data from the .03% and .1% groups, 97-0-037 pooled data from the .03 and .1% groups, FG-06-12, and 96-0-025 studies. All AEs with an incidence of 1% or greater in any of the four groups should be included in the table.

(5) For the cases of lymphadenopathy draft a full description of each of the cases.

(6) For the proposed package insert, provide the FDA with a definition of the term "short duration" in reference to the local adverse events. Re-draft the label and provide supportive data to show how long the events last.

We were also notified that our response to the specific request for the lymphadenopathy information [(5) above] should be submitted to the FDA by Tuesday, November 7, 2000, in anticipation of the Division's preparation for the upcoming Protopic Advisory Committee meeting.

Accordingly, FHI is hereby providing in the attached, a summary report of thirty-three (33) cases of lymphadenopathy including the twenty-three (23) cases of lymphadenopathy reported in NDA 50-777 and an additional ten (10) cases reported in the 120 day safety update.

As agreed, FHI's response to the remaining information requests will be provided to FDA as soon as possible.

Please note that the archival copy (hard copy format) as well as one desk copy and one review copy (hard copy and electronic review aids) of this submission are being provided. The electronic files provided in desk and review copies were checked with Norton Antivirus (version 7.0) and found to be virus free.

We trust that our understanding of the specific requests expressed by the reviewers during the teleconference on October 26, 2000 are consistent with yours, and that the information provided in this response has satisfactorily addressed the Divisions' questions, regarding lymphadenopathy [request (5)].

Should you have any questions regarding this submission, please do not hesitate to contact the undersigned at (847) 317-8872 or Jerry D. Johnson, Ph.D. at (847) 317-8898.

Sincerely,

Donald E.Baker
Senior Director Regulatory Affairs

DEB:kjg
attachment

cc: Ms. Millie Wright, Project Manager
(cover letter only)

APPEARS THIS WAY
ON ORIGINAL

(297)

AMENDMENT DUPLICATE

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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

October 21, 1999

REVIEW

Jonathan Wilkin, M. D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd. 2nd Fl., N-214
Rockville, Maryland 20850-3202

RE: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

AMENDMENT
Pharmacology/Toxicology

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc.'s (FHI) new drug application (NDA 50-777) submitted under Section 505(b) to the FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to a telephone conference on September 29, 1999, with Ms. Millie Wright and the Division's Biostatistics reviewers, Dr. Srinivasan and Dr. Freidlim. During that teleconference, the Biostatistics reviewers requested that FHI re-submit the SAS transport file for the tumor dataset (tumor.xpt) from the two (2) year dermal oncogenicity study of Protopic ointment, in the format described in the FDA's Electronic Submissions Guidance. This information was previously submitted to the FDA on February 3, 1999, in IND ——— (Amendment Serial No. 122), and was also included in NDA 50-777, which was submitted to FDA on September 8, 1999.

Accordingly, we are re-submitting the SAS transport file for the tumor dataset provided by the contract lab, ——————————— which is in the format requested. This electronic submission was checked with Norton Antivirus (version 4.04) and is virus free.

Please note that this Amendment is also being submitted as an Information Amendment to IND ——— (Serial No. 132).

Should you have any question or require further information regarding this submission, please do not hesitate to contact me at (847) 317-8872 or Jerry D. Johnson, Ph.D. at (847) 317-8898.

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

K:\kim\protopic\nda\tumor dataset.doc
NDA_Dev\archive\protopic\nda\amend\991021.pdf

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Fujisawa Healthcare, Inc.	10/21/99
TELEPHONE NO. *(Include Area Code)* (847) 317-8872	FACSIMILE (FAX) Number *(Include Area Code)* (847)317-7286
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: Parkway North Center, Three Parkway North, Deerfield, IL 60015-2548	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 50-777

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
tacrolimus ointment	PROTOPIC

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: Please refer to package insert

CODE NAME *(If any)*: FK506, FK 506, FK-506, FR900506

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Ointment	0.03% and 0.1%	Topical

(PROPOSED) INDICATION(S) FOR USE: Short and long term treatment of the signs and symptoms of atopic dermatitis.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION: Resubmission of tumor dataset for Study 9-0055

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

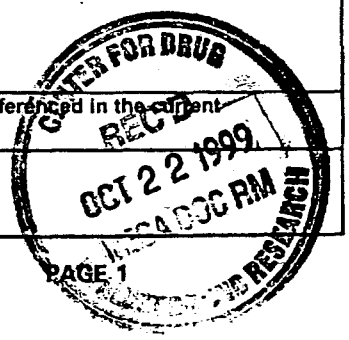
NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

NDA 50-708
NDA 50-709



This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Resubmission of tumor dataset for Study 9-0055

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Donald E. Baker	Donald E. Baker, JD Senior Director, Regulatory Affairs	10/21/99

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
3 Parkway Center North Deerfield, IL 60015-2548	(847 317-8872

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Washington, DC 20201

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141

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Telephone (847) 317-8800 Telefax (847) 317-7286

Fujisawa

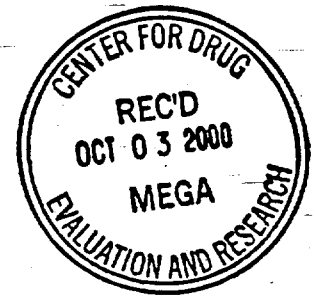
NEW CORRESPONDENCE

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

October 2, 2000

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Product, HFD-540
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd., 2nd Fl., N-214
Rockville, MD 20850-3202

NC



RE: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

CROSS-REFERENCE LETTER

Dear Dr. Wilkin:

Please incorporate by cross-reference the contents of the October 2, 2000 submission to NDA 50-708 (Prograf® (tacrolimus) capsules into NDA 50-777. This submission is a request for review of proposed manufacturing process changes for tacrolimus (FK506) bulk drug substance.

Should you have any questions regarding this submission please do not hesitate to contact me at (847) 317-8872.

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

ORIGINAL

(95)

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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

August 21, 2000

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

ARCHIVAL

NDA ORIG AMENDMENT

EZ

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Response to Request for Information from Clinical, Biopharmaceutics and Pharmacology/Toxicology Reviewers, During the July 10, 2000 Telephone Conference

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc., (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to the telephone conference on July 10, 2000 with you, the Division's Clinical, Biopharmaceutics and Pharmacology/Toxicology reviewers, and FHI representatives. During that teleconference, you informed FHI that the Advisory Committee meeting for Protopic Ointment, previously scheduled for August 16, 2000, would be rescheduled for the second week in November 2000. You indicated that the main reason for this delay was the volume of data submitted by FHI on June 28, 2000 in response to the Division's request for additional pharmacokinetics data from two studies from Europe; one in adults (FG-06-22) and one in children, 6 to 12 years of age (FG-06-23).

During the teleconference you also mentioned the following two areas of concern with respect to tacrolimus ointment:

1. Tacrolimus blood concentrations in pediatric patients (2 to 6 years of age), to model safety margins particularly with respect to lymphoreticular disorders.
2. Photocarcinogenicity potential.

ORIGINAL

Accordingly, you requested the following:

1. Additional PK data for pediatric patients (2 to 6 years).
2. Responses to the concern regarding the potential for photocarcinogenicity following topical application of tacrolimus ointment.
3. Responses to article in Nature 1999; 397:530 entitled "Cyclosporine Induces Cancer Progression by Cell-Autonomous Mechanism."

Based on the concerns discussed and the clarification provided by the Division during the teleconference, FHI is hereby providing the following responses and additional information requested as follows:

1. Tacrolimus blood concentration in Pediatric Patients

The information provided in **Attachment 1**, addresses the specific questions and requests from the Biopharmaceutics reviewers. This document summarizes the information provided in NDA 50-777 and subsequent submissions in response to the Division's questions regarding blood concentrations following topical application of tacrolimus ointment in young pediatric patients (2 to 6 years of age).

In support of **Attachment 1**, individual patient blood concentrations at various timepoints for these young patients are listed in an index table (Table 1, 4 patients in Study 94-0-008) and Appendix 1 (remaining 57 patients in Studies 95-0-009 and 97-0-037) of **Attachment 1**.

For the reviewer's convenience, the EXCEL files containing the information provided in Appendix 1 of **Attachment 1** are also included (LEV009.xls US phase II 95-0-009 blood level data for 2 to 6 years old patients; LEV037.xls US phase III blood level data for 2 to 6 years old patients).

As requested, an EXCEL file containing blood concentration data in Japanese Study FJ-106 is also provided (LEV106.xls). Please note that the investigators in FJ-106 did not collect percent BSA affected; therefore, we are unable to provide this data for Dr. Tandon.

Also, please note that all three EXCEL files are provided on a floppy located in the desk and review copies of this submission.

2. Photocarcinogenicity Potential

The information provided in **Attachment 2** is in response to your stated concern regarding the potential for photocarcinogenicity following topical application of tacrolimus ointment. This document is a summary of the photocarcinogenicity assessment by the two leaders in

the area of photobiology, Drs. ——— and ——— and provides a description and interpretation of the study in the context of related studies and other supporting information.

3. Article in Nature regarding Cyclosporine

The information provided in **Attachment 3** is in response to the comment from the Medical Reviewer, Dr. Labib, regarding an article in Nature 1999; 397:530 entitled "Cyclosporine Induces Cancer Progression by Cell-Autonomous Mechanism."

This document presents FHI's clarification and additional reference material pertinent to the differential effects of cyclosporine as compared to tacrolimus on TGF-ß in humans.

Please note that the archival copy (hard copy format) as well as one desk copy and one review copy (hard copy and electronic review aids) of this submission are being provided. The electronic files provided in desk and review copies were checked with Norton Antivirus (version 7.0) and found to be virus free.

We trust that our understanding of the concerns expressed by the Division during the teleconference on July 10, 2000 are consistent with yours, and that the additional information provided and our responses have satisfactorily addressed the Division's concerns regarding tacrolimus ointment. Should there be additional information or responses outstanding, please let us know immediately.

We look forward to continued cooperative interaction with your Division during your evaluation of our NDA and during our efforts to finalize all information necessary for the FDA Advisory Committee for our new drug application for Protopic (tacrolimus ointment) for the treatment of atopic dermatitis.

Should you have any questions or require further clarification regarding this submission, please do not hesitate to contact the undersigned at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898**.

Sincerely,

Donald E.Baker
Senior Director Regulatory Affairs

DEB:kjg
attachment

**APPEARS THIS WAY
ON ORIGINAL**

(66)

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
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Fujisawa

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

June 28, 2000

NDA ORIG AMENDMENT

ARCHIVAL

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

BE

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Response to Request for Information from Biopharmaceutics Reviewer

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc., (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to our June 2, 2000 submission which provided responses to your letter dated March 29, 2000 requesting additional safety information in order to continue your evaluation of our NDA.

Venecta

In addition, reference is made to a telephone communication on June 14, 2000, from Dr. ~~Anita~~ Tanden, requesting additional pharmacokinetic data from two studies from Europe; one in adults (FG-06-22) and one in children, 6-12 years of age (FG-06-23). In order to clarify the content and format of the pharmacokinetic data requested, a teleconference between FHI and Dr. Tanden was held on June 20, 2000. Accordingly, FHI is hereby providing the following information:

1. In response to the FDA March 29, 2000 information request from the Biopharmaceutic reviewer, we indicated in our June 2, 2000 submission response to the FDA that FHI was conducting a population pharmacokinetic analysis (Non-MEM analysis) of blood concentration data from Phase 2 and 3 clinical trials for tacrolimus ointment to obtain rough estimates of AUC. The report is provided in **ATTACHMENT 1**.

ORIGINAL

With this submission, we are also providing a CD (in desk and review copies) containing four files used for the population pharmacokinetic analysis (Non-MEM analysis) of blood concentration data from these clinical trials.

Three of the files are Excel spreadsheets (US001B.CSV, US49B.CSV, and USNOZER5.CSV) containing information for dosing (variable AMT) and blood levels (variable DV). Beginning from the day of first dose, the time in hours from the first dosing event is given for every dosing or blood draw event up to the time of the last blood draw event (variable TIME).

These 3 files correspond to the three methods of analysis which differed as values were assumed for blood level values below the level of quantitation (LOQ).

i) In US001B.CSV, all blood draw events with result <LOQ are set to 0.001, i.e., slightly greater than 0.

ii) In US49B.CSV, all blood draw events with result <LOQ are set slightly less than the LOQ: — for protocols 950003, 950009, 950013 (Phase II protocols) and — for protocols 970035, 970036, 970037 (Phase III protocols).

iii) In USNOZER5.CSV, all blood draw events with result <LOQ are deleted. Consequently, this file has many fewer records

Finally, the fourth file, 007.ctl, contains the model used for the analysis.

2. Errata sheets for Attachment 1.1 in our June 2, 2000 submission response to the FDA March 29, 2000 information request are being provided. These errata sheets correct Tables 8 & 9 on pages 60, 61 and 62 of this submission based upon recently-received pharmacokinetic information from Fujisawa Germany since the submission was made. We are including a second errata sheet for the same table as Table 9 which also appears as Table 2.1 on page 26 of this June 2, 2000 submission. We have also included red-lined sheets showing the specific values that were corrected in the tables. **ATTACHMENT 2.**

3. A draft interim data report for FG-06-23 (enrollment ongoing, interim analysis completed) is provided in **ATTACHMENT 3**, and is followed by the study protocol.

4. A draft study report for FG-06-22 (enrollment completed) is provided in **ATTACHMENT 4**, and is followed by the study protocol.

The following electronic datasets in Excel format for individual patient demographic and PK data for FG-06-22 and FG-06-23 studies conducted in Europe are provided in desk and review copies.

(a) FG622dem.xls, FG623dem.xls - These files contain demographic and other patient information including dosing for each profile.

(b) PK622c.xls, PK623c.xls - These files contain PK parameters calculated for individual patient per profile.

(c) FG622lev.xls, FG623lev.xls - These files are datasets containing individual blood concentration data obtained from each patient.

The parameter labeled "Actual Time (h)" was populated with data used in the calculation of the PK parameters (AUC, Cmax etc.) only when the actual time of the blood draw differed substantially from the scheduled draw time.

The parameter labeled "Extrapolated Value (ng/mL)" was populated with data used in the calculation of the PK parameters (AUC, Cmax etc.) in some cases where a blood draw was missing.

The parameter labeled "Collected Blood Level (ng/mL)" contains many values which were less than the limit of quantitation (LOQ, e.g. [redacted] . These LOQ values were set to zero for calculation of the PK parameters (AUC, Cmax etc). These LOQ values were set to half the LOQ for calculating the daily blood level means and medians.

Please note that the archival copy (hard copy format) as well as one desk copy and one review copy (hard copy and electronic review aids) of this submission are being provided. The electronic files provided in desk and review copies were checked with Norton Antivirus (version 7.0) and found to be virus free.

We trust that the draft study reports and datasets for the FG-06-22 and FG-06-23 will allow your Division to continue its review of the suggested studies and that the population pharmacokinetic analysis (Non-MEM analysis) of blood concentration data have satisfactorily addressed the Agency's request for this information.

We look forward to continued cooperative interaction with your Division during your evaluation of our NDA. Should you have any questions or require further clarification regarding this submission, please do not hesitate to contact the undersigned at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898**.

Sincerely,

Donald E.Baker
Senior Director Regulatory Affairs

DEB:bw
attachment

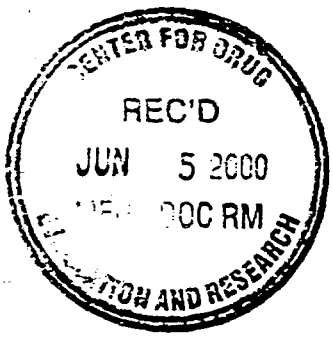
APPEARS THIS WAY
ON ORIGINAL

NDA ORIG AMENDMENT

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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



June 2, 2000

ARCHIVAL
(HARD COPY)

BZ

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Response to Request for Information from Clinical, Biopharmaceutics and Pharmacology/Toxicology Reviewers

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc., (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to your letter dated March 29, 2000 (attached) which provided comments and specific requests for additional safety information in order to continue your evaluation of our NDA.

Your comments and requests were organized according to scientific disciplines within the reviewing division. We have carefully reviewed the issues and questions and herein are providing our responses to the specific questions and comments in the order provided in your letter. These responses are based on Fujisawa global safety data as well as the literature and data obtained from Fujisawa company-sponsored clinical trials.

For ease of review, our responses to the FDA information request are being provided in the submission as follows:

ORIGINAL

PART I: CLINICAL INFORMATION

The information contained in this section addresses the specific questions and comments provided by the Clinical and Biopharmaceutics Reviewers. To address the concern for pharmacokinetic information in the patient population, actual data from ongoing pharmacokinetic trials in Europe that have just become available are provided. The availability of these actual data may reduce the relevance of the population pharmacokinetic modeling. Nevertheless, we are still pursuing the NONMEM modeling which will be provided in a subsequent submission no later than June 30, 2000.

PART II: NONCLINICAL PHARMACOLOGY/TOXICOLOGY QUESTIONS

The information contained in this section addresses the specific questions provided by the Pharmacology/Toxicology Reviewers.

Also included in Part I. as Attachment 1.1 is a white paper reviewing lymphoproliferative disease and attendant risk factors. The paper presents additional material pertinent to the discussion of immunosuppression and lymphoproliferative disease. It reviews the risk factors for, and incidence of, lymphoproliferative disease in general and, specifically, for transplant recipients administered Prograf® as a reference for a relative risk assessment for atopic dermatitis patients applying topical tacrolimus ointment.

Please note that one archival copy (electronic and hard copy formats) as well as one desk copy and three review copies (hard copy) of this submission are being provided. The electronic copy and the hard copy review/desk copies are identical. The electronic files were checked with Norton Antivirus (version 7.0) and found to be virus free.

In summary, there has been no clinical evidence of lymphomas related to tacrolimus ointment use. Atopic dermatitis patients have minimal systemic exposure to tacrolimus following topical application. Based on a large patient base (6,906 patients), there is no clinical evidence of either systemic immunosuppression or lymphoma related to tacrolimus ointment in these patients.

Based on the questions posed by your Division and the anticipated FDA acceptance of the responses submitted, there do not appear to be any remaining issues related to the potential risk of lymphoproliferative disease disorders from the use of topical tacrolimus ointment.

We plan to include the pertinent data and carcinogenicity study results in the product labeling and obtain Division occurrence on the labeling. As such, Fujisawa is not anticipating presentation of this topic at the FDA advisory committee for tacrolimus ointment.

However, to be complete, we do plan to include a summary of the "potential risk" issues in our Advisory Committee briefing package. We will also include the "white paper" (Attachment 1.1 of this submission) in our reference binder accompanying the briefing document. This will ensure that information pertinent to the discussion of lymphoproliferative disease and the relative risk for atopic dermatitis patients applying tacrolimus ointment is available to committee members.

We believe that it may be beneficial to FHI and the Division to convene a pre-Advisory Committee meeting in an effort to have your Division fully aware of the content of the FHI presentation at the committee meeting. This meeting would also allow us to coordinate key issues to be presented at the committee meeting such as clinical efficacy and safety and systemic exposure. Accordingly, we request that the Division schedule a pre-Advisory Committee meeting with FHI at least one month prior to the scheduled meeting (probably during mid-July 2000) to discuss the primary clinical issues and focus our attention on the salient points to be addressed at the FDA Advisory Committee meeting scheduled for August 16, 2000. For your information and review, we have attached to this cover letter a proposed agenda of the material we plan to present at the meeting, primarily addressing critical clinical issues. Since time is of the essence, we plan to contact your Division on June 26, 2000 to schedule this pre-Advisory Committee meeting.

We look forward to continued cooperative interaction with your Division during your evaluation of our NDA and during our efforts to finalize all information necessary for the FDA Advisory Committee for our new drug application for Protopic (tacrolimus ointment) for the treatment of atopic dermatitis.

Should you have any questions or require further clarification regarding this submission, please do not hesitate to contact the undersigned **at (847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898.**

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

DEB:bw
attachment

APPEARS THIS WAY
ON ORIGINAL

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

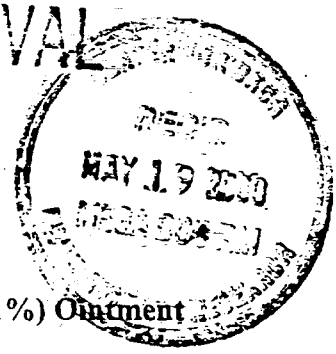
Donald E. Baker, J.D.
Senior Director
Regulatory Affairs

May 18, 2000

NDA ORIG AMENDMENT

ARCHIVAL

B2



Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Floor, N-214
Rockville, Maryland 20850-3202

Re: NDA 50-777
Protopic® (tacrolimus 0.03% & 0.1%) Ointment

Response to Request for Information from Clinical and Statistical Reviewers

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc., (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to FHI's submission dated April 21, 2000, which provided specific safety analyses and efficacy information requested in the FDA facsimile dated March 15, 2000 (**Attachment 1**).

In response to item #4 of FDA's fax memo dated March 15, 2000 and clarification provided during the April 10, 2000 telephone conference between FHI and the Division's reviewers, we agreed to provide additional data to supplement the Quality of Life (QOL) data previously submitted to the Division on April 21, 2000. Accordingly, we are hereby providing in **Attachment 2** the corrected analysis for the QOL report previously submitted. The corrections only affect the "Personal Relationships" QOL scale for adults.

Please note that one electronic archival copy (pdf format) and two desk copies of this submission are being provided. The electronic copy and the hard copy desk copies are identical. The electronic files were checked with Norton Antivirus (version 7.0) and found to be virus free.

ORIGINAL

Should you have any questions or require additional information concerning this submission, please do not hesitate to contact the undersigned at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898.**

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

DEB:bw
attachments

cc: Ms. Millie Wright, FDA, Project Manager (desk copy)

APPEARS THIS WAY
ON ORIGINAL

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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

April 21, 2000

REVIEW

NDA ORIG AMENDMENT

Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd., 2nd Fl., N-214
Rockville, Maryland 20850-3202

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

Response to Request for Information from Clinical and Statistical Reviewers B2

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc. (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to a FDA facsimile memo dated March 15, 2000 **(Attachment 1)** requesting specific safety analysis and efficacy information for NDA 50-777. In order to clarify our understanding of the FDA's request, FHI submitted to the Division on March 22, 2000, a list of questions for which we desired clarification and feedback. As a result, a teleconference between FHI and the Division's clinical and statistical reviewers was held on April 10, 2000. Based on the clarifications provided by the Division during the teleconference, FHI is hereby providing the specific safety analysis and efficacy information requested in the FDA facsimile dated March 15, 2000.

To facilitate ease of reviews, we are providing the requested information as attachments in the order requested in the FDA facsimile memo as indicated below:

Attachment 2: In response to item #1 & #2 of FDA's Fax Memo dated March 15, 2000, a comparison of adverse event rates between the 0.03% and 0.1% tacrolimus ointment treated patients from the three double-blind 12-week studies (97-0-035, 97-0-036, 97-0-037) is provided. No adverse event occurred at a statistically significantly higher rate in the 0.1% group compared to the 0.03%.

The electronic file requested in Word and the SAS program file are included in the desk copies only (table1.doc and advit.sas).

DUPLICATE

Attachment 3: In response to item #3 of FDA's Fax Memo dated March 15, 2000 and clarification provided during the April 10, 2000 teleconference, analysis of adverse event hazard rates over time (0-3 months, 3-6 months, 6-12 months) is provided for the three double-blind 12-week studies (97-0-035, 97-0-036, 97-0-037) and the two long-term safety studies (96-0-025, FG-06-12). Also, please refer to ISS Appendix 8.4.13.9 for additional hazard rate analysis for selected adverse events of clinical interest.

The electronic file requested in Word and the SAS program file are included in the desk copies only (table2.doc and adhzd1t.sas).

Attachment 4: In response to item #4 of FDA's Fax Memo dated March 15, 2000 and clarification provided during the April 10, 2000 teleconference, SAS datasets (one record per patient) including demographic, disposition, quality of life and efficacy variables are provided for each of the double-blind 12-week studies (97-0-035 – effqol35.sd2, 97-0-036 – effqol36.sd2, 97-0-037 – effqol37.sd2). The format catalog information is provided in a SAS dataset (ndafmts.sd2) in a PROC FORMAT CNTLIN structure and also in hard copy. The 4 SAS datasets are provided as a transport file using PROC COPY with the XPORT engine (effdata.xpt) and are included electronically in the desk copies only. During validation of the quality of life data a minor discrepancy in the original report was discovered. The "Personal Relationships" QOL score at end of treatment in adults was in reality the week 12 analysis. The corrected analyses will be submitted to you shortly.

Attachment 5: In response to item #5 of FDA's Fax Memo dated March 15, 2000, the efficacy results for the MITT population are provided for each of the three double-blind 12-week studies (97-0-035, 97-0-036, 97-0-037) in the requested format. The requested word file (attach5.doc) is included in the desk copies only.

Please note that one archival copy and two desk copies (includes electronic media) of this submission are being provided. The electronic files included in desk copies were checked with Norton Antivirus (version 7.0) and found to be virus free.

We look forward to continued communications with the Division during your review and evaluation of our NDA. Should you have any questions or require additional information concerning this submission, please do not hesitate to contact the undersigned at (847) 317-8872 or Jerry D. Johnson, Ph.D. at (847) 317-8898.

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

attachments

cc: Ms. Millie Wright, FDA, Project Manager (desk copy)

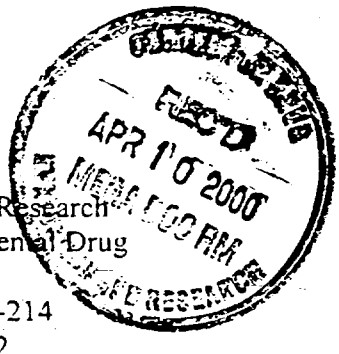
20

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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

April 7, 2000



Jonathan Wilkin, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug
Products, HFD-540
9201 Corporate Blvd., 2nd Fl., N-214
Rockville, Maryland 20850-3202

REVIEW
NC

Re: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

GENERAL CORRESPONDENCE

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc.'s (FHI) new drug application (NDA 50-777) submitted under Section 505(b) of the FD&C Act to FDA on September 8, 1999 for Protopic (tacrolimus 0.03% and 0.1%) Ointment.

Reference is also made to your letter dated March 29, 2000 regarding your request for information based on comments from the Clinical, Bio-pharmaceutics and Pharmacology/Toxicology reviewers (see attached).

Please be advised that FHI is actively working on responses to the questions and within two weeks we intend to provide your Division with a definitive timeline for providing the information requested. In an effort to provide thorough and complete responses to the reviewers comments, we intend to develop an overall plan of action for addressing all of the issues identified in your letter dated March 29, 2000 and also referenced in the minutes of the Executive Carcinogenicity Assessment Committee (ECAC) Meeting held on March 14, 2000.

Accordingly, please be assured that complete responses will be provided to the Division on a timely manner, and we look forward to a continued cooperative interaction with your Division during your evaluation of our NDA.

Should you have any questions regarding this matter, please do not hesitate to contact the undersigned at **(847) 317-8872** or Jerry D. Johnson, Ph.D. at **(847) 317-8898.**

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

DUPLICATE

attachment

Ms. Millie Wright, Project Manager – Desk Copy

REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Fujisawa Healthcare, inc.	April 7, 2000
TELEPHONE NO. *(Include Area Code)* (847) 317-8872	**FACSIMILE (FAX) Number** *(Include Area Code)* (847) 317-7286
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* Parkway North Center Three Parkway North Deerfield, IL 60015-2548	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 50-777

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
tacrolimus ointment	Protopic®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Please refer to package insert

CODE NAME *(If any)* FK506, FK 506, FK-506, FR900506

DOSAGE FORM	STRENGTHS	ROUTE OF ADMINISTRATION
Ointment	0.03% and 0.1%	Topical

(PROPOSED) INDICATIONS FOR USE: Short and long term treatment of the signs and symptoms of atopic dermatitis

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 31.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION: General Correspondence

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provice locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
APR 10 2000
MEGA DOC RM

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 50-708

NDA 50-709

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50(c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355 (b) (2) or (j) (2) (A)
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50(k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Letter indicating intent to respond

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Donna E Baker	Donald E. Baker, JD Senior Director, Regulatory Affairs	4/7/2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Three Parkway North Deerfield, IL 60015-2548	(847) 317-8872

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 50-777

Fujisawa Healthcare, Inc
Attention: Donald E. Baker, J.D.
Senior Director, Regulatory Affairs
Parkway North Center
Three Parkway North
Deerfield, Illinois 60015-2548

MAR 29 2000

Dear Mr. Baker:

Please refer to your new drug application dated September 8, 1999, received September 9, 1999, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Protopic (tacrolimus) Ointment, 0.03 and 0.1%.

We also refer to your submissions dated October 21, November 9, and December 9, 1999; January 10, and 31, February 11, and March 13, 2000.

We are reviewing your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

CLINICAL

1. Please provide data on the relationship of blood levels of FK506 and subsequent development of lymphomas (or posttransplant lymphoproliferative disorders) in patients treated systemically with FK506 (Prograf). Please provide any available information concerning the relative risk of EBV seroprevalence for development of lymphomas (or posttransplant lymphoproliferative disorders) in patients treated systemically with FK506.

2. Please provide data on the chronology of lymphoma (or posttransplant lymphoprolieferative disorders) development in patients treated systemically with FD506. Please characterize the chronology of lymphomas (or posttransplant lymphoprolieferative disorders) development separately in pediatric and adult populations.

3. The Sponsor should clarify whether the lymphomas noted in the recipients of Prograf were of a B-cell or T-cell origin.

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BIOPHARMACEUTICS

1. The Sponsor should conduct a population analysis of the plasma concentrations measured in Phase 2 and 3 Clinical Trials for 0.03, 0.1 and 0.3% tacrolimus ointment to obtain rough estimates of AUC. From Study 94-0-008, it appears that the plasma concentration profile is relatively flat at steady state. Hence, estimating AUCs from the random samples taken during clinical trials would provide a rough estimation of the AUCs at the to-be-marketed strengths of tacrolimus ointment.

2. The Sponsor should conduct a pharmacokinetic study in adult and pediatric patients with severe atopic dermatitis using the 0.1% tacrolimus ointment. The study should have enough patients, in both the adult and pediatric population, with acute atopic dermatitis, to evaluate any differences in pharmacokinetic parameters and should be conducted under the maximal use conditions associated with a maximum surface area coverage. Plasma sampling should be sufficient to evaluate relevant pharmacokinetic parameters.

PHARMACOLOGY/TOXICOLOGY

1. Please provide historical background incidence rates from the contract laboratory that conducted the 2 year mouse dermal carcinogenicity study for tacrolimus ointment for the following tumor types:
   a. Liver-Carcinoma
   b. Cervix-Stromal Cell Sarcoma
   c. Uterus-Leiomyoma

2. The Sponsor should clarify whether the lymphomas noted in the 2 year mouse dermal carcinogenicity study conducted for tacrolimus ointment were of a B-cell or T-cell origin, if known.

3. It is recommended that the Sponsor conduct a nonclinical study in minipigs, or other suitable species, to determine the concentration of tacrolimus in the regional lymph nodes ~~that~~ drain from the skin after topical tacrolimus ointment application to abraded or irritated skin. The purpose of this study is to determine if the concentration of tacrolimus in regional lymph nodes that drain from the skin is higher than ~~or~~ the same as the level of tacrolimus in the blood after topical administration. This information is necessary for the determination of human risk for lymphoma after topical administration of tacrolimus ointment. It is recommended that the Sponsor submit the study protocol for this study to the Division for review prior to initiation of the study.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, call Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

/S/

Jonathan Wilkin, M.D.
Director
Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

4420

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8300 • Telefax (847) 317-7288

Fujisawa

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

March 17, 2000

Jonathan Wilkin, M.D., Director
Division of Dermatologic and
Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, 2nd Fl. N-214
Rockville, MD 20850

ARCHIVAL
NDA ORIG AMENDMENT
BC

RE: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

CHEMISTRY, MANUFACTURING, AND CONTROLS AMENDMENT
NOTIFICATION OF ADDITIONAL ——— SUPPLIER

Dear Dr. Wilkin:

Reference is made to Fujisawa Healthcare, Inc. (FHI) new drug application (NDA 50-777) submitted under Section 505(b) on September 8, 1999 for Protopic® (tacrolimus 0.03% and 0.1%) Ointment.

Pursuant to 21 C.F.R. § 314.60(c), FHI herein provides notification of an amendment to the above referenced new drug application that is currently under review. As reported in the original application in Volume 3, Section 4 on page 13 (attached) the manufacturer of ——— is

This letter is to provide notification of an **additional agent** — Supplier), namely

ORIGINAL

All other information related to the ——— remains the same, in particular there are no changes to the specifications or manufacturer of the material. For ease of review, following is a copy of the referenced page (Volume 3, Section 4, page 13) of the original application, noting the agents — suppliers) and manufacturers for all the materials.

As required in 21 C.F.R. § 314.60 (c), FHI hereby certifies that a copy of this information has been forwarded to:

Ms. Brenda Holman
District Director, Buffalo District
Food and Drug Administration
300 Pearl Street, Suite 100
Buffalo, NY 14202

If you have any further questions regarding this information, please contact me at **(847) 317-8872** or Ms. Laura C. Navarre at **(847) 317-1340.**

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

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Archive\Protopic\NDA\Subm\000317.pdf

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ON ORIGINAL

Fujisawa Healthcare, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

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

March 17, 2000

COPY

Ms. Brenda Holman
District Director, Buffalo District
Food and Drug Administration
300 Pearl Street, Suite 100
Buffalo, NY 14202

RE: NDA 50-777
Protopic® (tacrolimus 0.03% and 0.1%) Ointment

CHEMISTRY, MANUFACTURING, AND CONTROLS AMENDMENT
NOTIFICATION OF ADDITIONAL ——— SUPPLIER

Dear Ms. Holman:

As required by 21 C.F.R. § 314.60 (c), Fujisawa Healthcare, Inc. (FHI) hereby provides you with a field copy that is a true copy of the Chemistry, Manufacturing and Controls (CMC) information submitted on March 17, 2000 to the Division of Dermatologic and Dental Drug Products. This field copy is provided simultaneously with the delivery of this document to the Division.

If you have any questions or concerns related to this application, please do not hesitate to contact the undersigned at (847) ~~317~~-8872 or Ms. Laura C. Navarre at (847) 317-1340.

Sincerely,

Donald E. Baker
Senior Director, Regulatory Affairs

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Kim\Protopic\NDA\CMC Field Letter.doc
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