12 pages redacted from this section of the approval package consisted of draft labeling

ALLERGAN INC.
REGULATORY AFFAIRS
2525 Dupont Drive
Irvine, California 92612

FAX COVER SHEET

TO:	Kalyani Bhatt	**FROM:**	Thomas Walton
FAX:	301 827 2091	**FAX:**	(714) 246-4272
TELEPHONE:	301 827 2049	**TELEPHONE:**	(714) 246- 4470
CC:		**DATE:**	9-28-00

Pages being sent including this cover page: 7

Message:

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ALLERGAN

25 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

50 years GROWTH & INNOVATION

September 28, 2000

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

REF: TAZORAC® (tazarotene) Cream 0.05%, 0.1%
NDA 21-184
Submission of DRAFT Clinical Trial Outline(CTO) for Pregnancy Data Capture

Dear Doctor Wilkin:

Allergan is amending the above-referenced NDA with the submission of the DRAFT CTO as previously submitted by electronic mail to the Project Manager and Medical Reviewer. This is being submitted at the request of the Project Manager, Kalyani Bhatt.

At this stage of development, this submission is only in DRAFT stage. The clinical study protocol will be finalized following receipt of comments from your Division.

Should you have any questions or require any further information, please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy A. Rumbaugh
Director,
Global Regulatory Affairs, Retinoids

TR/tww

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 last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
ALLERGAN	9/28/2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
800-347-4500	

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

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 21-184

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Tazarotene (USAN)	Tazorac®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate	AGN 190168

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Topical Cream	0.05% 0.1%	Topical

(PROPOSED) INDICATION(S) FOR USE:
Once daily treatment of plaque psoriasis.

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 Submit DRAFT Clinical Trial Outline--Pregnancy Data Capture

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

NUMBER OF VOLUMES SUBMITTED _____ 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)

	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 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) DRAFT Clinical Trial Outline--Pregnancy Data Capture

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 applications 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
T. Rumbaugh	Trudy A. Rumbaugh, MD, Director, Global Regulatory Affairs	9/28/00

ADDRESS (Street, City State, and ZIP Code)	Telephone Number
2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534	(714) 246-4292

Allergan - Confidential

CLINICAL TRIAL OUTLINE

Study Number: 190168-043C

TITLE: A multi-center, open, non-randomized epidemiology study to evaluate the potential for adverse health effects in women, fetuses and live-born infants following inadvertent exposure to tazarotene cream 0.1% or 0.05% for psoriasis during pregnancy, compared with a similar group of psoriatic women not exposed to tazarotene and compared with background levels in the general population.

OBJECTIVE(S): To evaluate the potential for adverse health effects in women, fetuses and live-born infants following inadvertent exposure to tazarotene cream 0.1% or 0.05% for psoriasis during pregnancy compared with a similar group of psoriatic women not exposed to tazarotene and compared with background levels in the general population.

TEST PRODUCT(S): *Tazarotene Cream 0.1%*
Tazarotene Cream 0.05%

CLINICAL HYPOTHESIS(ES): The potential for adverse health effects in women, fetuses and live-born infants following inadvertent exposure to tazarotene cream for psoriasis during pregnancy is not different from that in women, fetuses and live-born infants not exposed to tazarotene (based upon levels of pregnancy outcome in a similar cohort of psoriatic women not exposed to tazarotene or in women in the general population).

DESIGN:

Structure: Multi-center, open, non-randomized epidemiology study with control group

subjects: Enrollment of 100 female psoriatic patients inadvertently exposed to tazarotene cream during pregnancy and 100 female psoriatic patients not exposed to tazarotene during pregnancy (enrollment limited to a period of 5 years from approval of the drug for marketing by FDA).

Duration: From recognition of pregnancy until one month post-outcome of pregnancy (in the event of both a live- or non-live birth).

Dosage/Dose Regimen: No actual treatment with tazarotene cream during the study (Note: treatment with tazarotene cream 0.1% or 0.05% **must stop** immediately when pregnancy is determined, for the duration of pregnancy and subsequent nursing [in the event of a live birth and mother choosing to nurse]).

STUDY POPULATION:

Inclusion Criteria

The following are requirements for entry into the study:

- Female psoriasis-treatment-center patient treated for psoriasis with tazarotene cream 0.1% or 0.05% at some time between the last menstrual period and conception **or** female psoriasis-treatment-center patient who becomes pregnant and was not exposed to tazarotene cream at any time between the last menstrual period and conception.
- Medical confirmation of pregnancy, e.g. a positive urine pregnancy test or ultrasound (note: patient need not still be pregnant at time of enrollment into the study).
- Patient is willing to provide information pertinent to the progress and outcome of her pregnancy, including information on the health status of her

child (up to one month) in the event of a live birth.
- Written informed consent.

KEY VARIABLES:

Data collection at enrollment

- Product exposure information (eg product, dose, duration, dates of administration for all medical products used, including OTC medications)
- Maternal information (eg initials, patient number in study, age, obstetrical history, medical history [including family medical history], current medical conditions, contact information, health care provider and their contact information, date of last menstrual period, estimated delivery date)
- Behavioral factors (eg smoking, alcohol use, illicit drug use).
- Environmental factors (eg maternal and parental occupation, residence)

Study Outcomes

- Maternal adverse events, labor and delivery complications, major categories of pregnancy outcomes including spontaneous abortion, elective termination, fetal death/stillbirth and live born infants.

- Congential anomalies in each of the major categories of pregnancy outcomes, autopsy results (if available) on late fetal deaths and stillbirths. Fetal pathologic evaluations (if available) for elective terminations after a diagnosis of a fetal anomaly.

- Upon a live-birth delivery, minimum information will include date of birth, length of pregnancy, birth weight and length, sex of the infant, major and minor anomalies identified at birth, and whether a single or multiple birth occurred. For multiple births, this information should be collected for each infant along with the birth order. Instances of the more common neonatal conditions such as hyperbilirubinemia, apnea and conditions related to prematurity will also be collected.

POWER CALCULATION:

The sample size of 100 patients per group was determined empirically.

NO SITES:

10 to 12 psoriasis treatment centers

COUNTRIES:

USA

NO. PATIENTS:

100 psoriasis-treatment-center women inadvertently exposed to tazarotene cream 0.1% or 0.05% during pregnancy and 100 female psoriasis-treatment-center patients not exposed to tazarotene cream during pregnancy (enrollment limited to a period of 5 years from approval of the drug for marketing by FDA).

VISITS/SCHEDULE:

An initial telephone "interview" with the patient as soon as possible after it is known that the patient is pregnant, with a further 4 telephone contacts (typically a telephone contact with each patient in the study towards the end of the first trimester, followed by another telephone contact towards the end of the second trimester, a telephone contact a few weeks prior to expected parturition and a

final telephone contact one month following the outcome of pregnancy).

Other contacts with health care professionals may be made as appropriate.

END POINT: One month following the outcome of pregnancy.

LAB TESTS: Confirmatory pregnancy tests will be conducted at the start of the study .

PLANNED DATES: Start Date: Jan 2001
End Date: Sep 2005
Interim Reports: Yearly intervals based on Jan to Dec data.
Final Topline Date : Feb 2006
Final Report Date: July 2006

SCHEDULE OF VISITS AND MEASUREMENTS:

	Enrollment	Pregnancy period (telephone contacts every trimester)	Pregnancy outcome (one month post-pregnancy telephone contact)
Informed Consent	X		
Qualification and maternal information	X		
Confirmation of pregnancy (eg Urine Pregnancy Test)	X		
Medical product exposure information	X	X	X
Behavioral information/ environmental factors	X	X	X
Maternal adverse events		X	X
Labor/delivery complications			X
Pregnancy outcomes/congenital anomalies			X
Mother and child adverse events			X

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 26, 2000 Number of Pages 2 (Including cover sheet)

TO: Tom Walton
COMPANY: Allergan
FAX #: 1-714-246-4272

MESSAGE: Please see comments from the medical officer.

FROM: Kalyani Bhatt
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

The following comments are as follows:

1. The Agency will be granting you a partial waiver for pediatric psoriasis studies for the age group from birth to 11 under 21 CFR 314.55 (c) (4).

2. The Agency further allows you to defer submission of information for the age group 12-17 under 21 CFR 314.55 (b) (2). Allergan should make a Phase 4 commitment to provide safety information.

Please submit a statement of commitment to the following:

- To submit safety information, including the effects on epiphyses, for tazarotene creams in the treatment of psoriasis in the age group 12-17 by September 30, 2001.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: August 24, 2000 Number of Pages 1(Including coversheet)

TO: Thomas W. Walton / Trudy A. Rumbaugh, M.D.
COMPANY: Allergan
FAX #: 1-714-246-4272

MESSAGE: **NDA 21-184, Tazorac Cream, % 0.05% & 0.1%**
Please see comments from the Chemistry Reviewer. Clarification regarding the draft label. The preferred forms are:

TAZORAC (tazarotene) Cream 0.05%
TAZORAC (tazarotene) Cream 0.1%

FROM: Kalyani Bhatt
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

cc:
Division File/NDA 21-184
HFD-540/Decamp
HFD-540Timmer
HFD-540/ Bhatt

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

FACSIMILE TRANSMISSION RECORD

DATE: 8-17-00 Pages (including cover) 3

TO: Tom Walton

COMPANY:

ADDRESS: 4272

FAX PHONE#: 714-246-4470 Our Fax # (301) 827-2075

Voice # (301) 827-2020

MESSAGE:

Tom.
I hope these tables are clear

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: /S/

TITLE:

TELEPHONE: 301-827-2020

Patient Numbers and Percentages for Overall Lesional Assessment Scores and "Clinical Success" at Baseline (BL), End of Treatment (Week 12) and 12 Weeks After Stopping Therapy (Week 24)‡ in Two Controlled Clinical Trials for Psoriasis

	Taz 0.05% Cream					Taz 0.1% Cream					Vehicle Cream				
	Study 1 N = 218			Study 2 N = 210		Study 1 N = 221			Study 2 N = 211		Study 1 N = 229			Study 2 N = 214	
Score	BL	wk 12	wk 24	BL	wk 12	BL	wk 12	wk 24	BL	wk 12	BL	wk 12	wk 24	BL	wk 12
None (0)	0	1 (0.5%)	1 (0.5%)	0	2 (1%)	0	0	0	0	6 (3%)	0	0	1 (0.4%)	0	1 (0.5%)
Minimal (1)	0	11 (5%)	12 (6%)	0	7 (3%)	0	12 (5%)	14 (6%)	0	11 (5%)	0	7 (3%)	6 (3%)	0	1 (0.5%)
Mild (2)	0	79 (36%)	60 (28%)	0	76 (36%)	0	75 (34%)	53 (24%)	0	90 (43%)	0	49 (21%)	43 (19%)	0	54 (25%)
Moderate (3)	141 (65%)	86 (39%)	90 (41%)	100 (48%)	74 (35%)	122 (55%)	97 (44%)	107 (48%)	96 (45%)	62 (29%)	139 (61%)	119 (52%)	114 (50%)	97 (45%)	99 (46%)
Severe (4)	69 (32%)	39 (18%)	51 (23%)	80 (38%)	36 (17%)	91 (41%)	36 (16%)	46 (21%)	86 (41%)	29 (14%)	81 (35%)	51 (22%)	61 (27%)	93 (44%)	47 (22%)
Very severe (5)	8 (4%)	2 (0.9%)	4 (2%)	30 (14%)	15 (7%)	8 (4%)	1 (0.5%)	1 (0.5%)	29 (14%)	13 (6%)	9 (4%)	3 (1%)	4 (2%)	24 (11%)	12 (6%)
"Clinical Success"	0	91 (42%*)	73 (33*%)	0	85 (40%*)	0	87 (39%*)	67 (30*%)	0	107 (51%*)	0	56 (24%)	50 (22%)	0	56 (26%)

0 - no plaque elevation above normal skin level; may have residual non-erythematous discoloration; no psoriatic scale
1 - essentially flat with possible trace elevation; may have up to moderate erythema (red coloration); no psoriatic scale
2 - slight but definite elevation of plaque above normal skin level; may have up to moderate erythema (red coloration); fine scales with some lesions partially covered
3 - moderate elevation with rounded or sloped edges to plaque; moderate erythema (red coloration); somewhat coarser scales with most lesions partially covered
4 - marked elevation with hard, sharp edges to plaque; severe erythema (very red coloration); coarse, thick scales with virtually all lesions covered and a rough surface
5 - very marked elevation with very hard, sharp edges to plaque; very severe erythema (extreme red coloration); very coarse, thick scales with all lesions covered and a very rough surface

Clinical Success defined as an overall lesional assessment score of none, minimal or mild.

‡Study 1 had post-treatment period observations for 12 weeks after stopping therapy, which were not part of Study 2.

***Denotes statistically significant difference for "Clinical Success" compared with vehicle.**

Mean Decreases in Plaque Elevation, Scaling and Erythema in Two Controlled Clinical Trials for Psoriasis

		TAZORAC® 0.05% Cream						TAZORAC® 0.1% Cream						Vehicle Cream					
Lesion		Trunk/Arm/ Leg lesions		Knee/Elbow lesions		All Treated		Trunk/Arm/ Leg lesions		Knee/Elbow lesions		All Treated		Trunk/Arm/ Leg lesions		Knee/Elbow lesions		All Treated	
		Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
		N=218	N=210	N=218	N=210	N=218	N=210	N=221	N=211	N=221	N=211	N=221	N=211	N=229	N=214	N=229	N=214	N=229	N=214
Plaque elevation	BL	2.29	2.50	2.40	2.52	2.28	2.51	2.34	2.52	2.35	2.49	2.32	2.51	2.28	2.51	2.35	2.51	2.29	2.51
	C-12	-0.83*	-0.98*	-0.91*	-1.04*	-0.75*	-0.90*	-1.08*	-1.25*	-0.96*	-1.21*	-0.83*	-1.08*	-0.59	-0.69	-0.57	-0.68	-0.48	-0.61
	C-24	-0.75*		-0.73*		-0.60*		-0.87*		-0.73*		-0.63*		-0.57		-0.49		-0.42	
Scaling	BL	2.26	2.45	2.47	2.60	2.32	2.47	2.37	2.45	2.40	2.57	2.36	2.53	2.34	2.46	2.45	2.61	2.31	2.53
	C-12	-0.75	-0.90	-0.78*	-0.98*	-0.67*	-0.80	-0.84*	-1.06*	-0.76*	-1.13*	-0.73*	-1.03*	-0.66	-0.79	-0.62	-0.76	-0.46	-0.70
	C-24	-0.68		-0.62*		-0.51*		-0.79*		-0.61*		-0.59*		-0.56		-0.45		-0.45	
Erythema	BL	2.26	2.51	2.17	2.40	2.23	2.48	2.25	2.53	2.17	2.42	2.21	2.51	2.24	2.47	2.17	2.34	2.24	2.47
	C-12	-0.49	-0.65*	-0.44	-0.66*	-0.40	-0.62	-0.49	-0.82*	-0.57*	-0.82*	-0.42	-0.78*	-0.42	-0.46	-0.38	-0.44	-0.37	-0.47
	C-24	-0.52		-0.44		-0.41		-0.55		-0.52*		-0.39		-0.43		-0.34		-0.33	

Plaque elevation, scaling and erythema scored on a 0-4 scale with 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe.

BL=Mean Baseline Severity:

C-12=Mean Change from Baseline at end of 12 weeks of therapy:

C-24=Mean Change from Baseline at week 24 (12 weeks after the end of therapy).

***Denotes statistically significant difference compared with vehicle.**

APPEARS THIS WAY
ON ORIGINAL

ALLERGAN INC.
REGULATORY AFFAIRS
2525 Dupont Drive
Irvine, California 92612

FAX COVER SHEET

TO:	Kalyani Bhatt	**FROM:**	/S/
FAX:	301-827-2075	**FAX:**	(714) 246-4272
TELEPHONE:	-2020	**TELEPHONE:**	(714) 246-4292
CC:		**DATE:**	7/25/00

Pages being sent including this cover page: 3

Message:

Kalyani – Here is the information that will be sent hard copy by — tomorrow (with a form 356h), to address the NPF query from you. I will call tomorrow to make sure all is in order.

/S/

If you do not receive entire document, please call:

APPROPRIATE EXPORT LICENSE SYMBOL:

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(For BOTOX® manufacturing and development information, contact Corporate Import/Export Compliance Dept., X 2277/4628)

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

50 years
GROWTH & INNOVATION

July 25, 2000

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

REF: TAZORAC® (tazarotene topical cream) 0.05%, 0.1%
NDA 21-184
Response to FDA Request for NPF Authorization Letter

Dear Doctor Wilkin:

Allergan is amending the above-referenced NDA with a response to a FDA request for information. Attached is a copy of a letter from the National Psoriasis Foundation that permits Allergan to reference their organization in our labeling for Tazorac®. The original copy of this letter was submitted to NDA 20-600 for Tazorac® 0.05%, 0.1% Gels on May 28, 1997.

Should you have any further questions or require additional information, please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

T. Rumbaugh M.D.

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

NATIONAL
PSORIASIS
FOUNDATION
NPF

May 22, 1997

Ms. Gail Duner
Director of Marketing
Allergan Skin Care
2525 Dupont Drive
Irvine, CA 92713

Dear Ms. Duner:

The National Psoriasis Foundation (NPF) agrees to allow Allergan Skin Care to include information about the NPF as part of the patient package insert for the new psoriasis drug Tazorac. We appreciate this opportunity to acquaint people with our educational services.

Sincerely,

Sheri Decker
Associate Director

APPEARS THIS WAY
ON ORIGINAL

6600 SW 92ND AVENUE • SUITE 300 • PORTLAND, OR • 97223-7195 • USA • 503-244-7404 • FAX 503-245-0626
E-MAIL 76135.2746@COMPUSERVE.COM • WEB SITE HTTP://WWW.PSORIASIS.ORG

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: July 24, 2000 Number of Pages 1(Including coversheet)

TO: Thomas W. Walton / Trudy A. Rumbaugh, M.D.
COMPANY: Allergan
FAX #: 1-714-246-4272

MESSAGE: **NDA 21-184, Tazorac Cream, % 0.05% & 0.1%**
Please see comments from the Pharmacology-Toxicology Reviewer.

Clarification is requested for study TX99008. The ophthalmology reports are identical for animals 302 and 351. Both have a set of lesions that are unlikely to be exactly duplicated. Please recheck the ophthalmology reports for all animals in the study.

FROM: Kalyani Bhatt
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

cc:
Division File/NDA 21-184
HFD-540/Jacobs
HFD-540/Nostrandt
HFD-540/ Bhatt

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

FACSIMILE TRANSMISSION RECORD

DATE: 8-15-00 Pages (including cover) 9

TO: Tom Walton

COMPANY: ALLERGAN

ADDRESS:

FAX PHONE#: 1-714-246-4272 Our Fax # (301) 827-2075

Voice # (301) 827-2020

MESSAGE:

Tom,

Here is the proposed Draft Label

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: /S/

TITLE:

TELEPHONE:

8 pages redacted from this section of the approval package consisted of draft labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 25, 2000 Number of Pages 2 (Including coversheet)

TO: Thomas W. Walton / Trudy A. Rumbaugh, M.D.
COMPANY: Allergan
FAX #: 1-714-246-4272

MESSAGE: BioPharm comments regarding the electronic submission of NDA. 21-184

1.) Please clarify the exposure time with Tazorac crème in the studies PK-99-044, PK-99-060 & PK-099-085.
2.) Please submit information on how the cream was applied and how & when it was removed from the patients.
3.) If you could submit this information within one week via fax and then formally submit it to the Division File.

FROM: Kalyani Bhatt
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

cc:
Division File/NDA 21-184
Bashaw/HFD-540
Ghosh/HFD-540
Bhatt/HFD-540

·MESSAGE CONFIRMATION

BEST POSSIBLE COPY

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: March 13, 2000 Number of Pages 2 (Including coversheet)

TO: Thomas W. Walton / Trudy A. Rumbaugh, M.D.
COMPANY: Allergan
FAX #: 1-714-246-4272

MESSAGE: BioPharm comments regarding the electronic submission of NDA. 21-184

1.) Please clarify the exposure time with Tazorac crème in the studies PK-99-044, PK-99-060 & PK-099-085.
2.) Please submit information on how the cream was applied and how & when it was removed from the patients.
3.) If you could submit this information within one week via fax and then formally submit it to the Division File.

FROM: Kalyani Bhatt
TITLE: Project Manager
PHONE #: 301-827-2020

ALLERGAN INC.
REGULATORY AFFAIRS
2525 Dupont Drive
Irvine, California 92612

FAX COVER SHEET

TO: Ms. Kalyani Bhatt **FROM:** /S/
Project Manager-DDDDP Regulatory Specialist
FAX: 301-827-2075 **FAX:** (714) 246-4272
TELEPHONE: 301-827-2020 **TELEPHONE:** (714) 246-6802

CC: T. Rumbaugh, NDA 21-184 FDA Files. **DATE:** May 5, 2000

Pages being sent including this cover page: 31

Message: Dear Ms. Bhatt,

Attached, please find Allergan's response to the BioPharm Comments for NDA 21-184, dated March 13, 2000 (subsequently revised to April 25, 2000). Thank you very much for your prompt assistance and co-operation with this correspondance.

If you do not receive entire document, please call:

Sincerely,
/S/

APPROPRIATE EXPORT LICENSE SYMBOL:

N/A Information that is publicly available and/or items such as credit cards, airline tickets, etc.
NLR Proprietary Information/Company Confidential
DOC License

(For BOTOX® manufacturing and development information, contact Corporate Import/Export Compliance Dept., X 2277/4628)

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 last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
ALLERGAN	5/5/2000
TELEPHONE NO. *(Include Area Code)* 800-347-4500	**FACSIMILE (FAX) Number** *(Include Area Code)* 714.246.4272

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

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 21-184

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Tazarotene (USAN)	Tazorac®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate	AGN 190168

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Topical Cream	0.05% 0.1%	Topical

(PROPOSED) INDICATION(S) FOR USE:
Once daily treatment of plaque psoriasis.

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 Response to FDA Fax of 3/13/00 (Clinical)

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)

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 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Response to FDA Fax (BioPharm)

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 applications 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
Gayatri Mohanraj for	Trudy A. Rumbaugh, MD, Director, Global Regulatory Affairs	5/5/2000

ADDRESS *(Street, City State, and ZIP Code)*	Telephone Number
2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534	(714) 246-4292

ALLERGAN

25 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

May 5, 2000

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

REF: TAZORAC® (tazarotene topical cream) 0.05%, 0.1%
NDA 21-184
Response to FDA Fax of April 25, 2000 (BioPharm Comments)

Dear Doctor Wilkin:

Allergan is amending the above-referenced NDA with a response to the fax (dated March 13, 2000) with BioPharm comments received by Allergan on April 25, 2000.

FDA Comment

1.) Please clarify the exposure time with Tazorac cream in the studies PK-99-044, PK-99-060 &PK-099-085.

Allergan Response

a. For all patients with therapeutic drug monitoring (TDM) data from Study PK-99-044 (PK-99-044 is the PK report for clinical Study **190168-016C**), the time from the last dose to the trough level blood sampling is listed in Table 1 (refer to header "last dose to trough [a]"). Note that the study protocol did not specify requirements regarding bathing/showering during this period of time. General bathing/showering guidelines outlined in the protocol were related to the non-TDM portion of the study (i.e., "If patients bathe or shower in the evening, they will be instructed to apply the study medication after they have allowed their skin to dry").

   For all patients with TDM data from Study PK-99-044, the study medication "exposure" time, defined as the difference between the time of dosing at the clinic and the time of subsequent blood sampling is listed also in Table 1 (refer to header "exposure time [b]"). Patients were instructed not to wash or shower until after the blood collection was performed.

b. For all patients with TDM data from study PK-99-060 (PK-99-060 is the PK report for clinical Study **190168-017C**), the time from the last dose to the trough level blood sampling is listed in Table 2 (refer to header "last dose to trough [a]"). Note that the study protocol did not specify requirements regarding bathing/showering during this exposure time. General bathing/showering guidelines outlined in the protocol were related to the non-TDM portion of the study (i.e., "If patients bathe or shower in the evening, they will be instructed to apply the study medication after they have allowed their skin to dry.").

   For all patients with TDM data from Study PK-99-060, study medication "exposure" time, defined as the difference between the time of dosing at the clinic and the time of subsequent blood sampling is listed in Table 2 (refer to header "exposure time [b]"). Patients were instructed not to wash or shower until after the blood collection was performed.

c. For study PK-099-085 (PK-99-085 is the PK report for clinical Study **190168-023C**), all patients were instructed to bathe/shower 12 hours after application of tazarotene cream. Therefore, the exposure time for all patients participating in this study was 12 hours.

FDA Comment

2.) Please submit information on how the cream was applied and how & when it was removed from the patients.

Allergan Response

a. For studies PK-99-044 and PK-99-060 (PK-99-044 and PK-99-060 are the PK reports for clinical studies 190168-016C and 190168-017C respectively), the application procedure of study medication at the clinic was as follows:
   (1) patients were given a tube of study medication that had been pre-weighed by study personnel at the site
   (2) patients were asked to apply the study medication as they normally would
   (3) application of the study medication was witnessed by study personnel and the time of application noted
   (4) the tube of study medication was re-weighed by study personnel at the site
   (5) patients were instructed not to wash or shower until after their blood sample had been collected

(6) patients were instructed to return to the site approximately 3 to 10 hours later on the same day for collection of their blood sample, the time of which was noted.
(7) patients were instructed to resume their application of the study medication the following evening.

As stated previously, specific requirements regarding bathing/showering prior to the "trough" blood draw was not included in the protocol. General bathing/showering guidelines outlined in the protocol were related to application of study medication during the non-TDM portion of the study (i.e., "If patients bathe or shower in the evening, they will be instructed to apply the study medication after they have allowed their skin to dry.").

b. For Study PK-099-085 (PK-99-085 is the PK report for clinical Study **190168-023C**), application of tazarotene cream was conducted by site personnel, as described under Section 7.1.2 (Instructions for use and administration) of the Protocol 190168-023C (original NDA 21-184, Volume 12, Pages 266-267). Patients were instructed to bathe or shower 12 hours after tazarotene cream application. For your convenience, the relevant pages of the NDA 21-184 are attached following this cover memo.

3.) ***If you could submit this information within one week via fax and then formally submit it to Division File.***

Per my voice mail update to Kalyani Bhatt of your Division on May 4, 2000, we have compiled the requested data diligently in the earliest possible manner.

Should you have any further questions or require additional information, please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/sm

7.0 MATERIALS

7.1 Study treatment

7.1.1 Study treatments/formulations

Tazarotene 0.1% Cream will be supplied in [redacted]

Tazarotene 0.1% Cream ([redacted]) contains the following inactive ingredients: benzyl alcohol NF, carbomer 1342 NF, carbomer 934P NF, edetate disodium USP, mineral oil USP, medium-chain triglycerides [redacted], purified water USP, sodium hydroxide NF, sorbitan monooleate NF and sodium thiosulfate USP.

7.1.2 Instructions for use and administration

Dosing calculations:

To calculate the amount of study medication to be applied for each patient, the site personnel will be instructed to do the following calculations prior to each dose of study medication:

1. Use the nomogram (ATTACHMENT 13.2) to determine the body surface area of the patient (BSA). Use the patient's height and weight recorded at the screening visit. (To convert from m^2 to cm^2 multiply by 10,000).
2. Multiply the percent of psoriatic involvement** by BSA to determine the treatment area:

Percent Psoriatic Involvement x BSA (cm^2) = Treatment Area (cm^2)

3. Multiply the treatment area by the dosage assigned (refer to Section 8.1.5) to determine the treatment dose weight:

Treatment Area (cm^2) x Dose (mg/cm^2) = Treatment Dose Weight (mg)
(To convert from mg to g divide by 1,000).

Site personnel will be instructed to record the above information on the patient's dosing log case report form.

Instructions for investigational site personnel:

For each patient, the site personnel assigned to apply the study medication will apply the study medication to the psoriatic lesions every evening throughout the study. All psoriatic plaques excluding the scalp and intertriginous areas will be treated.

During the study period, study medication will not be applied to those areas of the skin which have healed and no longer have psoriatic lesions. Study medication will be applied to newly developed areas of psoriasis.

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* Allergan formulation number
** The "Percent of Psoriatic Involvement" will be determined each time prior to dosing.

Allergan - Confidential

Based on the dosing calculations, the quantity of study medication for each patient will be weighed out in an appropriate weigh container prior to dosing. Appropriate gloves will be worn for each application of study medication. The quantity of study medication along with the weigh container and gloves will be weighed before and after each application, and the amounts will be recorded on the patient's dosing log case report form.

When new tubes of medication are opened, the tear-off portion of the medication label should be removed and attached to the Medication Label Sheet. All used and unused tubes will be retrieved by the sponsor after the completion of the study.

At Day 3 (Dose 2) and Day 9 (Dose 8), study medication will be applied after blood samples have been collected for pharmacokinetic analyses.

The site personnel should avoid applying the study medication to normal (i.e., non-involved) skin. If the study medication accidentally gets on normal skin, it should be washed off.

The site personnel should avoid bringing the study medication in contact with the patient's eyes, eyelids and mouth. If contact with these areas occurs, rinse the area thoroughly with water.

The site personnel should wash their hands after applying the study medication.

The site personnel should store the study medication at room temperature and protect it from freezing. Storage instructions will be included on each medication label.

Instructions for patients:

Patients will receive each dose in the evening at the investigational site. Patients will be instructed to wear loose fitting, non-occlusive clothing (preferably cotton) after application of their study medication. Patients will be instructed to allow the application site to dry (i.e., no longer feels wet to touch) prior to dressing.

After the application of study medication, patients will be instructed to avoid bringing the study medication in contact with their eyes, eyelids and mouth. If contact with these areas occurs, rinse the area thoroughly with water.

Patients will be instructed to bathe or shower in the morning 12 hours after tazarotene cream application.

Patients will be allowed to use their own non-medicated emollients during the study. If patients usually apply emollients in the evening, they will be instructed to apply their own emollient at least one hour before application of the study medication. During the period after application of the study medication and showering/bathing the next morning, patients will be instructed to not apply their own emollient.

Patients will be instructed to not apply their own emollient starting the evening prior to the psoriasis evaluation (Day 0 and 24 hours after the last dose of study medication on Day 16). However, patients may apply their own emollient after their psoriasis evaluations are completed.

Patients will be allowed to use over-the-counter tar shampoos during the study.

Patients should avoid excessive sun exposure (e.g., sunlight, tanning booths) and should wear protective clothing when exposed to sunlight (e.g., hat, long-sleeved shirt, visor).

Patients will be instructed to notify the investigator if their disease appears to be "completely cleared". The patient will be instructed to return for an evaluation, and the investigator will determine whether treatment should be continued or stopped.

Patients will be instructed to fast (i.e., only water will be allowed) for 8 hours prior to blood and urine collections for laboratory tests (hematology, blood chemistry and urinalysis). If repeat laboratory tests are needed that include testing for lipids (e.g., triglycerides, cholesterol, HDL, or LDL), patients will be instructed to fast for 12 hours prior to blood collection for repeat laboratory tests.

7.2 Other study supplies

Pregnancy Test kits will be provided to each site by Allergan. At the completion of the study, unused urine pregnancy test kits will be returned to Allergan. Laboratory kits (chemistry panel, complete blood count and urinalysis) will be provided to each site by [redacted] will not be provided by Allergan.

8.0 STUDY METHODS AND PROCEDURES

8.1 Subject entry procedures

8.1.1 Overview of entry procedures

Prospective patients as defined by the criteria in Sections 5.3 and 5.4 (inclusion/exclusion criteria) will be considered for entry into this study. In the morning during the screening visit (Days -14 to -2), patients will undergo routine blood (chemistry panel and complete blood count) and urinalysis screening. Additionally, blood tests for Human Immunodeficiency Virus (HIV) and Hepatitis types B and C, and urine screens for the following substances—phencyclidine, benzodiazepines, cannabinoids, amphetamines, barbiturates, cocaine, and opiates will be conducted. Patients will be instructed to fast (i.e., only water will be allowed) for 8 hours prior to blood and urine collections for laboratory tests (hematology, blood chemistry and urinalysis). If repeat laboratory tests are needed that include testing for lipids (e.g., triglycerides, cholesterol, HDL, or LDL), patients will be instructed to fast for 12 hours

Number of Pages Redacted 22 pages

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Confidential,
Commercial Information

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: March 13, 2000 Number of Pages 2 (Including coversheet)

TO: Thomas W. Walton / Trudy A. Rumbaugh, M.D.
COMPANY: Allergan
FAX #: 1-714-246-4272

MESSAGE: Clinical comments regarding the electronic submission of NDA. 21-184

FROM: Kalyani Bhatt
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

Please find comments from the Medial Officer:

1. Please provide the distribution of (a) OLA and (b) physician global (all lesions, each target lesion) for all visits, with real numbers (not adjusted with LOCF) for studies 16C and 17C, at Allergan's earliest convenience.

2. Please provide the summary table for per protocol analysis of percent psoriasis involvement for studies 16C and 17C.

3. In the Integrated Summary of Effectiveness, there are no summary Tables. Please provide summary Tables, including Tables of combined data from the two phase 3 studies for subset analysis on race, sex and age for the efficacy variables.

4. In the Integrated Summary of Effectiveness, section 8.7.4, "Comparison and analysis of results of phase 3 studies", please provide a section on body surface area involvement.

Bhatt

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: February 8, 2000 Number of Pages 2 (Including coversheet)

TO: Thomas W. Walton / Trudy A. Rumbaugh, M.D.
COMPANY: Allergan
FAX #: 1-714-246-4272

MESSAGE: Clinical comments regarding the electronic submission of NDA. 21-184

FROM: Kalyani Bhatt
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

Div File
NDA- 21-184
HFD540- Walker
HFD540 - KO
HED-540 - Bhatt

1. In the pre-NDA minutes (the meeting dated 6/14/99), the Sponsor has been advised (Clinical Item 1) the following:

   - "All safety data must be presented, including postmarketing data for marketed formulations, data from studies on indications not sought and on formulations not marketed, and data from ongoing studies not yet completed (domestic and foreign)."

   Concerning the present request for postmarketing data, this is what has originally been conveyed to the Sponsor as information needed for filing of the NDA [The above being part of the answer to the Sponsor's question: "Allergan is assembling a clinical package, as outlined in this document, including human dermal safety, clinical pharmacokinetics
   and two Phase 3 studies which we believe fully meet the requirements for fileability, review and approval. Does the FDA concur?"].

   The Integrated Summary of Safety gave postmarketing data of tazarotene gels up to 7/15/99 only with incidence of the most common events. The Applicant needs to –

a) clarify whether the information is from U.S. sources or ALL sources;
b) provide incidence of death, serious adverse events or discontinuations due to adverse events; and
c) provide incidence of pregnancies and outcomes of pregnancies encountered in users.
d) summarize safety data from postmarketing studies (e.g., summary tables on the safety data from the long list of studies in the annual reports of NDA 20-600 would be appropriate).

   The Integrated Summary of Safety should also address the safety data of the oral tazarotene dosage forms.

2. We previously requested the following on 11/4/99:

   - p-values for adverse event data contrasting:
   - Tazarotene 0.1% cream versus vehicle cream
   - Tazarotene 0.1% cream versus Tazarotene 0.05% cream
   - Tazarotene 0.05% cream versus vehicle cream
     (ALL adverse events and treatment-related adverse events)

The Sponsor responded that they have not done so in order to save the medical reviewer time ["if all the p-values are reported, then this will produce volumes of paper for the medical reviewer to sift through.

The way it is done now is to save the medical reviewer time and effort."]. This reviewer thanks them for the consideration, but after
discussion with the statistician at that time, would still like to have the p-values for review because of their importance.