CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

Medical Review(s)

Medical Officer's Review of NDA 21-184 Amendment

SEP 25 2000

NDA 21-184

Submission Date: 9/07/00 (Electronic)
Review Completed: 9/08/00

Drug name: TAZORAC™

Generic name: tazarotene creams 0.05% and 0.1%

Applicant:
Allergan
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Pharmacologic Category: retinoid

Indication(s): plaque psoriasis

Resume: This submission contains a clinical trial outline (CTO) to collect pregnancy outcome information.

Background:
NDA 21-184 is a pending application for tazarotene creams. The proposed label is consistent with the current label for tazarotene gels in categorizing the product as being in Pregnancy Category X, since tazarotene is a retinoid and a teratogen as shown in animal studies. There is a lack of well documented human data on pregnancy outcomes. Because many pregnancies may be unintended, and women may have inadvertent exposure to tazarotene in pregnancy, the Applicant has been encouraged to collect pregnancy outcome data as a potential phase 4 commitment. This submission is a response to the Agency's proposal to obtain adequate pregnancy outcome information.

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%*

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

- 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 (e.g., product, dose, duration, dates of administration for all medical products used, including OTC medications)
- Maternal information (e.g., 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 (e.g., smoking, alcohol use, illicit drug use).
- Environmental factors (e.g., 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.
- Congenital 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.

NO. SITES/PATIENTS: 10 to 12 psoriasis treatment centers in the U.S. 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). Sample size is determined empirically.

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.

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 (e.g. 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

Comments on the CTO

1. This investigation proposes to study tazarotene creams but not tazarotene gels. As the purpose of the information to be collected is for ascertaining the developmental risks of topical tazarotene use in pregnancy, the Applicant is encouraged to include pregnant women who have used tazarotene gels as well.
2. The control group includes pregnant females with psoriasis not exposed to tazarotene cream. The protocol should have exclusion criteria which exclude women using other retinoids and becoming pregnant.
3. In this protocol, the patient need not still be pregnant at the time of enrollment. The Applicant is recommended to distinguish prospective from retrospective cases in this study. ~~Only~~ Prospective cases are useful for data analysis and should be sought.
4. "Psoriasis-treatment center" should be defined.
5. Pregnancy information, including concomitant conditions and arising complications, as well as their treatment, should be part of the follow-up for study outcome.
6. The Applicant is encouraged to base sample size determination on proper power considerations. Sizing the study to detect increases ranging from doubling to quadrupling of the background rate with 80% power at alpha=0.05 would be appropriate.
7. The rationale of studying for 5 years has not been presented. Duration of the study should be consistent with predetermined enrollment of an adequate sample size.
8. In addition to elective terminations after a diagnosis of a fetal anomaly, fetal pathological evaluation should be extended to all fetuses whenever available.
9. While it is reasonable to stop the study in a case of abortion/non-live birth, the rationale of following up a live-born infant one month post-delivery but not beyond has not been presented. Neurologic and behavioral development beyond the first month may also be important outcome data for risk assessment.
10. The methodologies of data analysis should be addressed.
11. Privacy issues should be addressed.
12. The Applicant is recommended to refer to the Draft Guidance, *Guidance For Industry: Establishing Pregnancy Registries*, which is available on the World Wide Web.

Recommenation:

It is recommended that the above comments be conveyed to the Applicant.

/S/ 9-8-00

Hon-Sum Ko, M.D.

cc: NDA 21-184
HFD-540
HFD-540/CSO/Bhatt
HFD-540/CHEM/Timmer
HFD-540/PHARM/Nostrandt
HFD-880/BIOPHARM/Ghosh
HFD-540/MO/Walker/Ko
HFD-710/BIOMETRICS/Lawrence

Not in DFS

9/21/00 SW.

/S/ 9/25/00

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Addendum to Medical Officer's Review of NDA 21-184
Second Addendum

NDA 21-184
Original
DDDDP#994245

Submission Date: 9/30/99
Received Date: 9/30/99
Assigned Date: 10/8/99
Review Completed: 6/30/00
Second Addendum Dated: 7/26/00

AUG 15 2000

Drug name: "TAZORAC™"

Generic name: tazarotene creams 0.05%, 0.1%

Applicant: Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Pharmacologic Category: retinoid

Indication: plaque psoriasis

Reason for Addendum: Post-labeling meeting modifications

On 7/20/00, a labeling meeting was held to discuss the draft label for NDA 21-184. A revised draft label has been obtained from Ms Kalyani Bhatt and further modified. This addendum addresses modifications on the revised draft.

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I. Proposed Changes on Draft Label Obtained from Ms. Bhatt After Labeling Meeting of 7/20/00

In addition to editorial changes, the following lists the key modifications.

In the PI:

DESCRIPTION:

1. Cream or Creams have been added after TAZORAC® when it refers specifically to the current drug product.
2. Inactive ingredients have been rearranged to fit alphabetical order.

CLINICAL PHARMACOLOGY:

1. The mechanism of action paragraph combines the data from different experiments to make it continuous. Since the paragraph ends with ' [redacted] , the clinical significance of these findings is unknown."

2. The paragraph on therapeutic monitoring blood levels has been modified by the addition of the sentence:

[redacted]

3. Clinical Studies section:
   a. Primary efficacy variable in the clinical studies is defined and new Table created to show the data.
   b. Sentence added to show that plaque thickness responds best.
   c. Removal of asterisks for values not statistically significant vs those of vehicle in the Table on clinical signs.

INDICATIONS AND USAGE:

The proposed tazarotene creams label removes the word ' [redacted] ' (present in the label for tazarotene gels) before "plaque psoriasis". *Patient enrollment in phase 3 studies for tazarotene creams excluded those with spontaneously improving or rapidly deteriorating disease. Therefore, the wording ' [redacted] ' should be restored.*

CONTRAINDICATIONS:

PRECAUTIONS:

In these sections, the repeated references to a human psoriatic patient or the human psoriatic patient have had the word ' [redacted] dropped.

Carcinogenesis, mutagenesis, impairment of fertility:

The second sentence in the first paragraph has been changed to clarify the dosing comparison with human usage.

Geriatric Use:

The reference to [redacted] has been corrected since there is no [redacted] for tazarotene creams.

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

Addendum to Medical Officer's Review of NDA 21-184

NDA 21-184
Original
DDDDP#994245

Submission Date: 9/30/99
Received Date: 9/30/99
Assigned Date: 10/8/99
Review Completed: 6/30/00
Addendum Dated: 7/14/00

AUG 17 2000

Drug name: "TAZORAC™"

Generic name: tazarotene creams 0.05%, 0.1%

Applicant: Allergan, Inc.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Pharmacologic Category: retinoid

Indication: plaque psoriasis

This addendum addresses several issues since completion of the Medical Officer's Review of 6/30/00:

1. Potential systemic retinoid effects from topical tazarotene use,
2. Pregnancy registry,
3. DDMAC review of PPI, and
4. Labeling of tazarotene creams vs tazarotene gels.

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1. Potential Systemic Retinoid Effects from Topical Use of Tazarotene Creams

1.1 Issue. In the phase 1 studies for tazarotene creams, there were some adverse events that might have been due to systemic retinoid effects.

1.2. Background. Systemic retinoid effects may involve the following abnormalities:

- Mucocutaneous - Cheilitis/Dry skin/Dry nose and mouth/Pruritus/Hair loss
- Musculoskeletal - Arthralgia/Myalgia/Skeletal hyperostosis/extraskeletal ossification/premature epiphysis closure
- Nervous system and special senses - Headache/Pseudotumor cerebri/Depression/Corneal opacification
- Metabolic and lab tests - Hyperkalemia/Liver enzyme elevation/Hyperlipidemia
- Teratogenicity

1.3. Observations and Analyses.

1.3.1. Data from Phase 1 Studies

1.3.1.1. Adverse Events. The following adverse events in phase 1 studies could possibly be related to systemic retinoid effect:

Study	Possible Systemic Retinoid Adverse Event	Incidence
190168-024C PK study	Headache Pruritus Dry skin Dry eye Alopecia Myalgia	7/9 (78%) 6/9 (67%) 4/9 (44%) 1/9 (11%) 1/9 (11%) 1/9 (11%)
190168-023C PK study	Heachache Pruritus Arthritis	5/11 (45%) 5/11 (45%) 2/11 (18%)
190168-503C Formulation selection study*	Rash Cheilitis Stomatitis	3/100 (3%) 2/100 (2%) 1/100 (1%)
190168-019C Irritancy study	[Local irritancy reactions at patch site not considered as adverse events]	–
190168-020C Sensitization study	Headache Severe depression	3/230 (1%) 1/230 (<1%)
190168-021C Phototox/Photoallergenicity study	Headache	2/30 (7%)
190168-032C Photoallergenicity study	[None reported]	–

*Studies using semi-occluded patch application of test medications are highlighted.

- Headache. The significance of the high incidence of headache in the two PK studies is hard to evaluate. However, it is not unduly increased in the dermal safety studies, which used semi-occluded patch administration.
- Mucocutaneous adverse events, including cheilitis. Cutaneous adverse events are anticipated with topical retinoid treatment, and are therefore difficult to interpret, unless they occur outside the area of administration. Pruritus is also a symptom of psoriasis patients (Studies 190168-024C and -023C). "Cheilitis" and "stomatitis" occurred in Study 190168-503C in the following patients:
  - #05: F Caucasian aged 53, with history of mild arthritis, developed *dry lips* and tingling sensation of tongue. Concomitant med: Lexotan (benzodiapepine, bromazepam). Daily tazarotene dose: 270 µg.
  - #35: F Caucasian aged 63, developed "*stomatitis*". Discontinued study because irritation resulted in inability to sleep. Concomitant med: E45 cream for varicose veins. Daily tazarotene dose: 330 µg.
  - #71: F Caucasian aged 46, with hypertension under control with atenolol 25 mg qd, developed a "cold" with sore throat and *dry lips*. Daily tazarotene dose: 410 µg.

It is noted that the term "cheilitis" is the code word used for "dry lips" in the two patients who had this adverse event. There are no further details on the nature of the "stomatitis" in the patient with this event.

- Myalgia and arthritis occurred in the PK studies where the application was not occluded. These adverse events are not uncommon, and arthritis may be a manifestation of psoriasis (psoriatic patients required in PK studies).
- Severe depression occurred in a patient (#2420-157 in Study 190168-020C) with known history of bipolar disorder.

1.3.1.2. Observed and Potential Systemic Exposure.

1.3.1.2.1. PK Studies. Data on exposure to "tazarotenic acid" in the PK studies 190168-024C and -023C can be summarized as follows:

Bioavailability Data (on "Tazarotenic Acid") at Day 15 in PK Studies

Study	Dose	Cmax (ng/mL)	Tmax (hr)	AUC_{24} (ng.hr/mL)	$T_{1/2}$ (hr)
190168-024C	2 mg/cm^2	0.4 (0.1-0.6)	8 (6-9)	8.3 (4.4-10.9)	NC
	10 mg/cm^2	1.9 (0.7-3.4)	7 (6-9)	26.6 (10.0-41.8)	20.3 (13.3-33.8)
190168-023C	2 mg/cm^2	2.3 (0.1-6.9)	8 (6-12)	31.2 (1.0-88.3)	15.4
	10 mg/cm^2	3.1 (0.7-6.4)	7 (6-9)	46.4 (14.0-97.1)	31.3 (24.1-65.0)

BSA= Body surface area; NC=not calculable. Values are means with ranges in parentheses

1.3.1.2.2. Dermal Safety Studies. The dermal safety studies used semi-occluded patches (0.1 mL of test medication). Exposure can be calculated as follows:

Study	Tazarotene concentrations	Tazarotene per patch	Exposure per day	Total application	Total exposure in entire study
190168-503C Formulation selection study*	0.01% 0.05% 0.1%	10 µg 50 µg 100 µg	700 µg* (maximum)	15x	10.5 mg (maximum)
190168-019C Irritancy study	0.01% 0.025% 0.05% 0.1%	10 µg 25 µg 50 µg 100 µg	185 µg	18x	3.33 mg
190168-020C Sensitization study	0.01% 0.025% 0.05% 0.1%	10 µg 25 µg 50 µg 100 µg	185 µg	9x induction Ix challenge	1.67 mg induction 0.185 mg challenge
190168-021C Phototox/Photoallergenicity study	0.01% 0.025% 0.05% 0.1%	10 µg 25 µg 50 µg 100 µg	370 µg**	6x induction 1x challenge	2.22 mg induction 0.37 mg challenge
190168-032C Photoallergenicity study	0.05% 0.1%	50 µg 100 µg	300 µg**	6x induction 1x challenge	1.8 mg induction 0.3 mg challenge

*Each patient received 8 patches with active ingredients, but only 6 test drugs were of tazarotene 0.1%, and the next concentration was 0.05%; **duplicate patches in these studies.

The volume of distribution of "tazarotenic acid" from semi-occluded topical exposure has not been determined and the actual systemic exposure in these studies is not known. However, *assuming complete absorption*, the dose of tazarotene in the studies using the to-be-marketed formulation was between 0.185 mg to 0.37 mg per day. In the formulation selection study (190168-503C), subjects were given 8 active and one vehicle patches. The active patches were

with different concentrations of drug, and the maximum tazarotene one could get was from 6 patches of 0.1% and 2 of 0.05%, or 0.7 mg per day. For comparison, the following sections provide information on systemic exposure from oral administration of tazarotene and from non-occluded administration in the phase 3 trials for tazarotene creams.

1.3.2. Data from Oral Tazarotene Use. To put in perspective, data on systemic exposure with oral tazarotene [redacted], show that -

1.3.2.1. Study 190168-015P. After 6 days of oral dosing, the following PK parameters (means) were observed for "tazarotenic acid":

Dose (mg/d)	Cmax (ng/ml)	AUC_{0-} (ng*hr/ml)
0.2	4.51	30.2
0.7	18.9	90.6
1.4	36.6	187
2.1	47.9	234

Possible systemic retinoid effects in the 13 treated patients (all dosing groups combined) were: headache 6, ecchymosis 2, and 1 of each for dry mouth, dermatitis, sun induced erythema, eye dryness and eye pruritus.

1.3.2.2. Study 190168-018P. After 30 days of oral tazarotene 1.1 mg qd, the following PK values were observed for "tazarotenic acid":

PARAMETER	Cmax (ng/mL)	Tmax (hr)	AUC_{0-24} (ng.hr/mL)	K_{el} (l/hr)	T½ (hr)
Mean	28.9	1.5	120.6	0.059	14.3
Min	4.6	1	44.3	0.021	6.24
Max	49.0	4	166.5	0.111	33.4

Possible systemic retinoid effects in the 27 treated patients were: headache 9, dry skin 5, erythema 5, pruritus 4 and rash 4.

Assuming that the oral tazarotene PK data can be extrapolated to topical use under semi-occluded conditions, and using the most conservative estimate (*complete absorption*), the Cmax and AUC for "tazarotenic acid" from the *greatest exposure applications* (0.7 mg/day in 190168-503C) in the dermal safety studies would be 18.9 ng/mL and 90.6 ng.hr/mL respectively. However,

(i) most subjects in these studies received an amount substantially lower than 0.7 mg (approximately 50% to 75% lower for 0.37 mg and 0.185 mg doses in the patch studies using the to-be-marketed formulations), and

(ii) absorption is not expected to be complete (non-occluded application giving only 0.6% to 2.5% bioavailability in Study 190168-023C).

Thus, it appears unlikely that the potential systemic retinoid adverse events in the dermal safety studies were really attributable to absorbed "tazarotenic acid".

1.3.3. Adverse Event Data in Phase 3 Studies and Plasma "Tazarotenic Acid" Levels

1.3.3.1. Adverse Event Data. The following Table illustrates the incidence of potential retinoid adverse events in the phase 3 trials for tazarotene creams:

	Tazarotene 0.1%		Tazarotene 0.05%		Vehicle	
	190168-016C*	190168-017C	190168-016C*	190168-017C	190168-016C*	190168-017C
Mucocutaneous –						
Cheilitis	0	0	0	0	0	0
Dry skin	3 (1%)	3 (1%)	0	4 (2%)	2 (<1%)	1 (<1%)
Dry nose and mouth	0	0	0	0	1 (<1%)	0
Pruritus	66 (30%)**	35 (17%)**	53 (24%)**	30 (14%)	32 (14%)	19 (9%)
Hair loss	0	0	1 (<1%)	0	1 (<1%)	0
Musculoskeletal –						
Arthritis	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0
Joint disease	1 (<1%)	1 (<1%)	0	2 (<1%)	1 (<1%)	2 (<1%)
Myalgia	2 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)	2 (<1%)
Skeletal hyperostosis	0	0	0	0	0	0
extraskeletal ossification	0	0	0	0	0	0
premature epiphysis closure	0	0	0	0	0	0
Nervous system/special senses –						
Headache	12 (5%)	6 (3%)	11 (5%)	4 (2%)	6 (3%)	6 (3%)
Pseudotumor cerebri	0	0	0	0	0	0
Manic-depressive reaction	1 (<1%)	0	0	0	0	0
Depression	1 (<1%)	0	0	0	1 (<1%)	0
Corneal opacification	0	0	0	0	0	0
Metabolic and lab tests –						
Pancreatitis	0	0	1 (<1%)	0	0	0
Hyperkalemia	0	1 (<1%)	0	0	0	0
Liver enzyme elevation	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0
SGOP increase	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0
SGPT increase	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Hyperlipemia	0	0	1 (<1%)	0	1 (<1%)	0
Hypercholesterolemia	1 (<1%)	1 (<1%)	0	1 (<1%)	0	1 (<1%)
Hypertriglyceridemia	4 (2%)	3 (1%)	1 (<1%)	9 (4%)	1 (<1%)	5 (2%)
Teratogenicity	0	0	0	0	0	0

*Treatment period only; **significantly different from vehicle ($p<0.05$).

There are no significant differences between the active and vehicle groups, except for the incidence of pruritus. Also, significant differences between the two tazarotene concentrations have not been observed.

1.3.3.2. Therapeutic Blood Monitoring. In the phase 3 trials, supervised dosing and pre- and post-dose sampling were done to determine levels of tazarotene and "tazarotenic acid" after an evening of no dosing.

Bioavailability Data of Phase 3 Trials

	Tazarotene Levels (ng/mL)	"Tazarotenic Acid" Levels (ng/mL)
190168-016C		
tazarotene 0.05% group (N=32)	all undetectable	12 (38%) detectable, up to 0.636
tazarotene 0.1% group (N=38)	one Week 8 sample at 0.091	24 (63%) detectable, up to 2.38
190168-017C		
tazarotene 0.05% group (N=37)	all undetectable	19 (51%) detectable, up to 0.334
tazarotene 0.1% group (N=32)	two Week 4 samples: 0.091 & 0.0838	23 (72%) detectable, up to 0.874

The highest level attained was in a patient using tazarotene 0.1% cream (2.38 ng/mL). It is noted that there have been patients in studies for other tazarotene formulations (gel and oral capsules) who achieved levels a log higher without apparent adverse effects. There is also a suggestion of dose-dependence:

	Week 4					Week 8				
	Dose	%BSA	Cpre	Cpost	Time	Dose	%BSA	Cpre	Cpost	Time
190168-016C										
Tazarotene 0.05%	4.74	12	0.030	0.083	4.05	4.45	8	0.064	0.130	5.18
Tazarotene 0.1%	3.88	7	0.185	0.311	4.86	3.80	7	0.157	0.348	4.58
190168-017C										
Tazarotene 0.05%	2.26	10	0.028	0.040	4.38	2.08	10	0.023	0.043	4.48
Tazarotene 0.1%	2.13	11	0.072	0.155	3.92	2.43	11	0.047	0.111	3.97

Dose=dose of test drug in Gm, %BSA= percent body surface area involvement, Cpre=pre-dose mean plasma "tazarotenic acid" level in ng/mL, Cpost=post-dose mean plasma "tazarotenic acid" level in ng/mL, Time=time of sampling in hours.

These adverse event data and plasma levels suggest that the potential systemic retinoid adverse effects observed in the phase 3 studies are unlikely attributable to tazarotene, because of:

(i) the relatively low plasma levels of "tazarotenic acid" attained, and
(ii) the apparent dose-dependence of plasma levels, but not of the incidence of these adverse events (no significant differences between groups except for pruritus).

1.4. Conclusions

1.4.1. Although some of the adverse events distant to the semi-occluded patch sites in phase 1 studies for tazarotene creams could have been systemic retinoid effects, this proposition appears to be unlikely. The systemic exposure arising from such dosing is substantially lower than that associated with these effects upon oral administration, even by very conservative estimates.

1.4.2. Exposure due to non-occluded dosing in the phase 3 trials and in the PK studies appears to be low (AUC for exaggerated topical application equivalent to that from approximately 0.3 mg - 0.4 mg oral dosing) and not likely to be causing overt systemic retinoid toxicity.

1.4.3. The threshold for some systemic toxicities in humans, e.g., skeletal effects and teratogenicity, has not been determined. Data from short-term clinical studies may not be adequate to rule out these effects because of either selection criteria (for fetal toxicity) or the duration of these studies (for skeletal effects). Despite some technical difficulties, an earlier study for tazarotene gels (R168-128-8606; previously submitted to NDA 20-600) suggests no significant bone changes with topical use for 52 weeks in psoriasis patients. However, exposure from topical dosing with tazarotene creams and tazarotene gels may reach levels associated with teratogenicity in animals.

1.5. Recommendations.

1.5.1. There are no specific recommendations regarding tazarotene systemic toxicity associated with topical use, since (1) none have been conclusively documented in clinical studies, and (2) adequate systemic exposure is not anticipated.

1.5.2. The key systemic effect whose risk from topical use of tazarotene has not been adequately determined in humans but is believed to be substantial is teratogenicity,

because of potentially high exposure compared to preclinical data showing fetal toxicity. Therefore, (1) similar to tazarotene gels, Pregnancy Category X for tazarotene creams, and (2) establishment of a pregnancy registry for topical use of tazarotene, are recommended.

2. [redacted]

2.1. Issue. [redacted] is recommended for topical use of tazarotene.

2.2. Background.

- Tazarotene is a retinoid, with teratogenic effect documented in animals when exposure is adequate.
- Use of tazarotene by topical administration may lead to systemic exposure levels equivalent to those associated with teratogenicity in animals.
- The threshold exposure to tazarotene in humans to induce teratogenicity is unknown.
- At the time of approval of tazarotene gels, Allergan was requested to conduct a [redacted] to clarify whether teratogenic effects might be demonstrated with topical use of tazarotene gels. If there were adequate data showing an absence of such effects, the Pregnancy Category for tazarotene gels might be reconsidered. The Applicant declined this request.

2.3. Observations and Analyses.

2.3.1. Data from the Applicant. Since the approval of tazarotene gels 0.05% and 0.1%, first in Europe in 1996, Allergan has received 16 reports of pregnancy occurring in patients using the drug.

2.3.1.1. Allergan's Global Medical Surveillance. There were 7 cases:

- Six reported no associated adverse events. All six patients stopped drug use upon learning pregnancy. Two were about 8 weeks pregnant and one 4 weeks pregnant. Allergan has received no other information about these pregnancy outcomes.
- One was a case of trisomy 18 in a fetus from a pregnancy terminated at ten weeks gestation. The mother used etretinate ten years previously, and tazarotene gel (strength not mentioned) from approximately 2 months prior to becoming pregnant to about 2 weeks after conception.

These data are not adequate to draw any conclusions because the extent of exposure (indication, degree of skin involvement and severity of disease) is unknown and cannot be correlated with the lack of adverse events in those reports. In addition, trisomy 18 is not a known teratogenic effect of retinoids.

2.3.1.2. Reports from Clinical Trials. Nine reports were from clinical trials:

- 2 reports involved use of products other than tazarotene: tretinoin 1, vehicle 1.
- 5 cases used tazarotene gel 0.1%
- 2 cases used tazarotene cream 0.1%.

Among the 7 cases involving tazarotene use,

- *3 of the pregnancy outcomes have not been determined*
- *2 pregnancy terminations did not have details of the products of conception.*
- *2 cases with healthy babies associated with use of tazarotene gel 0.1% lack details of exposure.*

2.3.2. Draft *Guidance for Industry. Establishing Pregnancy Registries* (published June, 1999). It is recognized that tazarotene gels are under Pregnancy Category X, and this Category is also being recommended for tazarotene creams. However, according to the Draft *Guidance for Industry. Establishing Pregnancy Registries*, some 60% of pregnancies are unintended; the patterns and extent of exposure to drugs often do not differ between women of childbearing age and those in the first trimester of pregnancy. For chronic conditions, exposures may continue even after recognition of pregnancy. The draft guidance further stipulates that:

- Pregnancy registries are recognized as one method for ascertaining major risks associated with a drug or biologic exposure during pregnancy. [*Currently such risks associated with topical tazarotene use has not been ascertained.*]

- A pregnancy registry design is not appropriate for products where the goal is to monitor and evaluate programs intended to prevent pregnancy exposures. [*It is not the intention to establish a pregnancy prevention program for topical tazarotene use. On the contrary, the aim is to acquire information on the magnitude of the risk of abnormal pregnancy outcome for topical tazarotene.*]

The draft guidance provides following criteria to evaluate the need of a registry:

- Any product expected to be used commonly by women of reproductive potential
- Products continued during pregnancy because they are necessary for conditions associated with high morbidity or mortality
- Products suspected of adverse effects in human pregnancy based on structure, pharmacologic activity, pharmaceutical class, findings from laboratory animal studies, or spontaneous human case reports
- Products known to be harmful if used during human pregnancy, but for which the magnitude or other risk characterization is unknown

Topical tazarotene dosage forms fit these criteria, except that harm if used in human pregnancy has not been documented.

2.4. Conclusions

2.4.1. There is a current lack of adequate human data on the risks to the fetus in association with topical tazarotene use.

2.4.2. Topical tazarotene dosage forms fit the criteria for drugs needing pregnancy registries.

2.5. Recommendation

A properly designed pregnancy registry is highly recommended for topical use of tazarotene. Such a registry should be requested of the Applicant, albeit not as a mandatory phase 4 commitment. If the Applicant declines, an acceptable rationale for the refusal and alternative plans for collection of adequate data on pregnancy outcomes should be provided. A consult to OPDRA has been requested.

3. DDMAC Review of Patient Package Insert (PPI)

3.1. Issue. The proposed label for tazarotene creams includes a PPI. Ms. Karen Lechter of DDMAC reviewed the PPI and provided comments.

3.2. Background. It is the current policy of the Center that all proposed MedGuides and PPIs be reviewed by DDMAC.

3.3. Observations and Analyses.

3.3.1. Changes by Ms. Lechter.

- created headings and an order consistent with recommendations DDMAC makes for all current PPI's;
- reorganized material to fit into appropriate sections with the most important information first;
- [redacted]
- eliminated the phrase " [redacted] , but indicating in the beginning of the PPI that it does not take the place of discussions with the doctor. [*The only places with this phrase* [redacted]

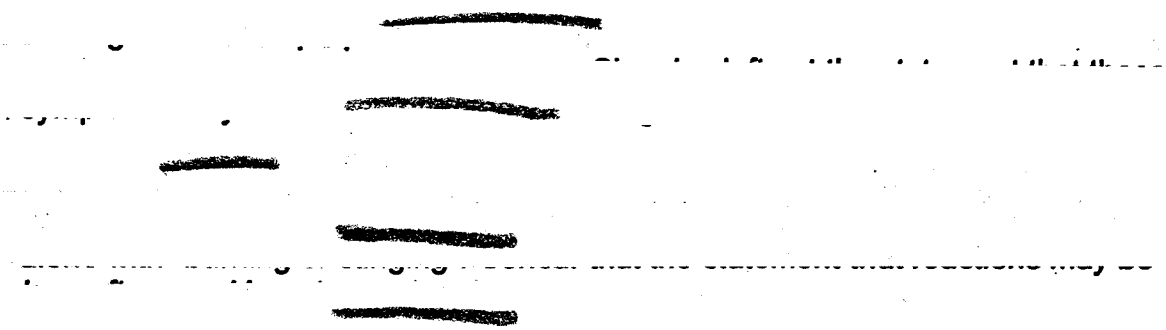
3.3.2. Questions by Ms Lechter.

[redacted]

3.3.2.2. Products to be Used Carefully while Using Tazorac. In the section on what to avoid while using Tazorac, the second bullet contains a list of products to be used carefully while using Tazorac but not mentioned in the PI.

- The review division should examine the list to be sure the items are appropriate for inclusion in the second bullet.

Answer: Appropriate and may be included.



3.3.2.4. Statement that Effectiveness with Less Than Once-a-Day Use Has not been Proven. Ms Lechter left out this statement, which was in the section indicating that the doctor may change the dosing of the medicine if side effects become a problem, as it may distress patients if dosing is reduced due to side effects.

- If the review division wants to retain this sentence, Ms Lechter recommends it be the last sentence in the first paragraph under "What are the possible side effects of TAZORAC?" to read: '

Answer: The statement may be retained at the end of the paragraph under "What are the possible side effects of TAZORAC?"

3.3.2.5. Storage Information. The PPI indicates that "excursions" from the normal storage temperature are permitted.

- To be useful, the PPI should specify how long the medication can be kept at more extreme temperatures. Ms Lechter left a blank in the text on this time.

Answer: This question should be addressed by the Chemistry Reviewer.

3.3.2.6. Reference to the National Psoriasis Foundation.

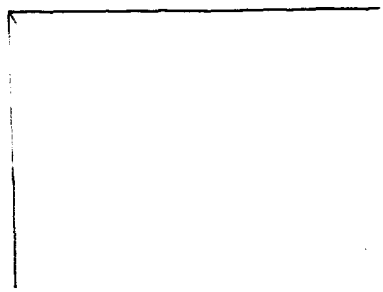
- Is it appropriate to have a reference to the NPF in the PPI?

Answer: Appropriate. The NPF may provide valuable information to patients.

3.3.2.7. Information for Patients Subsection of the PI.

- It is not sufficient, as it is now written, to refer the prescriber to the attached PPI, as we cannot be sure that the PPI will always be attached to the PI.

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



3.4. Conclusion and Recommendation.
DDMAC's revised PPI is acceptable with modifications incorporating the above comments.

4. Labeling of Tazarotene Creams vs Tazarotene Gels

4.1. Issue. There are some differences between the proposed labeling for tazarotene creams and the approved label for tazarotene gels.

4.2. Background. The labels for the two dosage forms would have mirrored each other if tazarotene creams are line extensions of their corresponding gels. The application for tazarotene creams could have been supported by trial(s) designed for the study of line extensions, as the to-be-marketed tazarotene creams are of the same concentrations, have the same dosing regimens, and may have the same indications as the approved tazarotene gels. However, the Applicant preferred to study the safety and efficacy of tazarotene creams 0.05% and 0.1% in psoriasis independently from their corresponding gels, even though the rationale for choosing these doses (concentrations) has been based on previous studies on the gels. No independent dose-ranging was conducted for efficacy prior to phase 3. Study 190168-503C was done primarily for the selection of formulations having different excipients by testing their irritancy.

4.2.1. Key Differences in the Phase 3 Development of Tazarotene Gels and Creams in Psoriasis.

- At the Agency's request, the two phase 3 trials for tazarotene creams in psoriasis did not have an upper limit for body surface area (BSA) involvement. The proposed label therefore does not limit usage according to BSA involvement. This is in contrast to tazarotene gels, as their phase 3 trials had an upper BSA limit (20%) and this restriction has been incorporated into the tazarotene gel label.
- Phase 3 psoriasis studies for tazarotene creams used a novel scale, an overall static global (overall lesional assessment) with dichotomization at week 12 as the primary parameter. For tazarotene gels, effectiveness is based on evaluation of clinical signs at target lesions and a physician overall global assessment, by comparison with baseline.
- For tazarotene gels, in addition to two-vehicle controlled studies, the Applicant conducted three active-controlled trials with post-treatment periods, trying to demonstrate a lasting beneficial effect of tazarotene in the treatment of psoriasis. No such studies were done for tazarotene creams. In both development programs (for the creams and for the gels), one of the two vehicle-controlled phase 3 studies had a post-treatment period to determine the state of psoriasis for 12 additional weeks upon stopping treatment.
- A long-term study with 52-week application of tazarotene gels 0.05% and 0.1% in the treatment of plaque psoriasis was conducted and submitted to NDA 20-600. A similar study was not conducted for tazarotene creams.

4.2.2. Evidence Supporting Approval of Tazarotene Creams and Gels for Psoriasis.

4.2.2.1. Demonstration of Effectiveness in Psoriasis.

The following endpoints were used in reviewing effectiveness by comparison with vehicle at the end of treatment (Week 12):

	Tazarotene Gels (NDA 20-600)	Tazarotene Creams (NDA 21-184)
Primary	• Reduction in individual clinical sign scores (plaque elevation, scaling and erythema) for target lesions • Physician's overall global (comparison vs baseline): distribution and dichotomization	• Dichotomized overall lesional assessment (static global)
Secondary	• Reduction in total clinical sign scores • Reduction in overall clinical severity score (static global)	• Reduction in individual clinical sign scores (plaque elevation, scaling and erythema); target lesions and overall • Physician's overall global (comparison vs baseline): dichotomization

In both NDAs, the 0.05% and 0.1% concentrations each demonstrated superiority over vehicle for the primary endpoint(s) at Week 12. Despite multiple primary endpoints for the studies on tazarotene gels, multiplicity adjustment was not incurred because the review required superiority shown for each primary endpoint.

4.2.2.2. Data Supporting Marketing of Two Concentrations. Data supporting the marketing of two concentrations of tazarotene gel were discussed in the Medical Officer's Review on the Amendment to NDA 20-600 submitted 6/27/96. The benefits of having both cream concentrations have also been extensively discussed in the original Medical Officer's Review of the current NDA on tazarotene creams. In neither instance were phase 3 trials designed or powered to demonstrate statistical differences between the two concentrations. Statistical significance has not been required for head-to-head comparisons between doses or concentrations of the same drug product.

4.2.2.2.1. Tazarotene Gels. In the treatment of plaque psoriasis, tazarotene gels 0.05% and 0.1% did not show significant differences for the primary efficacy endpoints at the end of treatment (Week 12) or in the post-treatment period. Approval was based on –

- *lower* (a) incidence and (b) severity of local reactions for tazarotene 0.05% gel;
- tazarotene gel 0.1% consistently giving *numerically better* (yet *statistically not significant*) results for the primary parameters than tazarotene gel 0.05%;
- tazarotene gel 0.1% giving improvement when compared to vehicle *earlier* than tazarotene gel 0.05%.
- agreement between FDA and Allergan on 12/10/92 that statistically significant differences between the two concentrations were *not required* for efficacy in order to gain approval.

4.2.2.2.2. Tazarotene Creams. The documentation of differences between the two concentrations for tazarotene creams is much more robust than that for tazarotene gels. As noted by the Division Director in the Review of NDA 21-184, "(i)n general, the most straightforward argument for supporting two concentrations is based on (1) a statistically significant superiority of the higher

concentration for the primary efficacy endpoint AND (2) a well-documented superior safety profile for the lower concentration. Although the 0.1% was not statistically significantly superior to the 0.05% for the primary efficacy endpoint, the MO has considered secondary endpoints, such as plaque thickness, based on rating scales with a limited number of clinically compelling categories to demonstrate that the weight of evidence that is clinically relevant and objective supports approval for BOTH concentrations."

The following is noted for tazarotene creams:

- *lower* (a) (i) incidence and (ii) severity of local reactions and (b) systemic bioavailability for tazarotene cream 0.05%;
- *statistically significant* superiority of tazarotene cream 0.1% vs tazarotene cream 0.05% for the primary efficacy endpoint in *one* phase 3 study (190168-017C) plus *confirmatory evidence from traditional endpoints* in both phase 3 studies, 190168-016C and -017C.
- tazarotene cream 0.1% giving improvement when compared to vehicle *earlier* than tazarotene cream 0.05%.

4.2.3. Post-Treatment Period Evaluation of Efficacy. As discussed above, for tazarotene gels, there were 3 active-controlled trials to determine the post-treatment effect by further observation for 12 weeks without treatment, after initial evaluation during a 12-week treatment period. These studies were:

- R168-125-8606 comparison with Lidex Cream 0.05%
- R168-126-8606 comparison with Lidex Cream 0.05%
- R168-145-8606 comparison with Dovonex Ointment 0.005%

They were designed to show that tazarotene was superior to other treatments in providing prolonged benefit in the treatment of psoriasis. However, the data from these studies were difficult to interpret because of different baselines for different groups for the post-treatment period. Post-treatment period observations in a vehicle-controlled study had even bigger disparities between groups because of post-randomization selection. Post-treatment period efficacy was only evaluated in a vehicle-controlled trial for tazarotene creams.

Despite the additional active-controlled studies, no claim was established for maintenance of therapeutic effect for tazarotene gels. Data of the active-controlled trials are not included in the label. The label only presents the post-treatment period data of the vehicle-controlled study in the Clinical Studies section without comments. The proposed label for tazarotene creams is modeled after the label for the gels in presenting data after treatment without comments.

4.3. Observations and Analyses.

Apart from (1) data specific to the dosage forms and (2) the fact that tazarotene creams are only proposed for the treatment of plaque psoriasis at this time, the key differences between the proposed label for the creams and the approved label for the gels are:

4.3.1. "Tazarotenic Acid". In the proposed tazarotene creams label, the term "tazarotenic acid" has replaced [redacted]

The Chemistry Reviewer should comment on the use of the term "tazarotenic acid".

4.3.2. Mechanism of Action. In the proposed tazarotene creams label, under "CLINICAL PHAMACOLOGY". new information has been added:

- [redacted]

It may be important to provide the prescriber with up-to-date information on mechanism of action. The last sentence gives balance to the information.

4.3.3. Clinical Data on Efficacy. In the proposed tazarotene creams label, under "CLINICAL STUDIES", little information is given for the primary parameter, overall lesional assessment, while the data on secondary parameters fill two Tables.

It is noted that these [redacted]

In the proposed tazarotene creams label, under "CLINICAL STUDIES" are also the statements:

- [redacted]
- [redacted]

- *The first statement pertains to the reasoning in marketing two concentrations of tazarotene cream. This issue has been discussed above in Section 4.2.2. Tazarotene creams show more robust data than tazarotene gels in the demonstration of statistically significant differences between the 0.05% and 0.1% concentrations. The language used is only slightly modified from that in the gels label, which states: "The 0.1% gel was more effective than the 0.05% gel, but the 0.05% gel was associated with less local irritation than the 0.1% gel (see ADVERSE REACTIONS section)." The cross-reference to ADVERSE REACTIONS section should be restored.*
- *The second statement has not been allowed for tazarotene gels despite observations in the post-treatment period of one vehicle-controlled and 3 active-controlled studies. It is even less supported by adequate data for tazarotene*

creams, which had post-treatment period assessment in only one vehicle-controlled trial.

4.3.4. Stability of Plaque Psoriasis. The "INDICATIONS AND USAGE" section of the proposed tazarotene creams label removes the word [redacted] (present in the label for tazarotene gels) before "plaque psoriasis".

Patient enrollment in phase 3 studies for tazarotene creams excluded those with spontaneously improving or rapidly deteriorating disease. Therefore, the wording [redacted]" should be included.

4.3.5. Extrapolation to 20% Body Surface Area Involvement. In several areas of the proposed tazarotene creams label ("CLINICAL PHARMACOLOGY" and "PRECAUTIONS" sections), human systemic exposure is extrapolated to that based on the mean obtained for dosing over 20% body surface area. This manipulation may be acceptable for tazarotene gels, as they are indicated for stable plaque psoriasis involving up to 20% body surface area.

There was no upper limit restriction for body surface area involvement in the phase 3 studies for tazarotene creams (actual maximum involvement of 95% in one study and 80% in the other). Approximately 15 to 20% of patients studied had baseline involvement of ≥20 % body area. It was the Agency that requested Allergan not to place an upper limit for body surface area involvement. As the Agency is interested in maximal exposure compatible with labeling, it does not appear to have any basis for the label to repeatedly mention an estimated exposure due to application over 20% body surface area. It may be more appropriate to use data on maximal systemic exposure attained in clinical studies (including human PK studies) for the purpose of comparison with data from animal studies.

4.3.6. Dosing Interval Adjustment. In the proposed tazarotene creams label, under "PRECAUTIONS", "General" is the statement:

- Some individuals may experience excessive pruritus, burning, skin redness or peeling. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the dosing should be adjusted to a level or interval the patient can tolerate.

The advice on adjusting medication is not in the label for tazarotene gels. It is acceptable to use a lower concentration of tazarotene cream (0.05%) if the patient has been originally using tazarotene cream 0.1%. After the approval of tazarotene gels, there have been some published data in support of adjusting the frequency of tazarotene applications, but effectiveness has not been adequately established. While it is important to let the prescriber know of this option because of safety, balance should be provided by mentioning that there are no adequate data in support of adjusting dosing interval.

In the proposed PPI for tazarotene creams, under "HOW TO USE THIS PRODUCT", is the following bullet:

- [redacted]

The same comment as above pertains here. While it is important to let the consumer know of the option of adjusting dosing because of safety, the last sentence provides balance to the bullet.

4.3.7. Changes in the "Precautions", "Carcinogenesis, Mutagenesis, Impairment of Fertility" Subsection. Three changes are noted in the proposed label for tazarotene creams:

-
-
-

These differences should be commented on by the Pharm/Tox Reviewer.

4.3.8. Geriatric Use Subsection. The proposed tazarotene creams label has a Geriatric Use subsection under "PRECAUTIONS".

4.3.9. "ADVERSE REACTIONS" Section. The proposed label for tazarotene creams has the following statement:

-

The label for tazarotene gels gives actual figures: 2 to 5% lower. The corresponding figures should be provided for the label for tazarotene creams.

4.3.10. "DOSAGE AND ADMINISTRATION" Section. Under this section in the proposed label for tazarotene creams, it is noted that in contrast to the tazarotene gels label:

See comments in Sections 4.3.5 and 4.3.6. for the first two items. As to the third item, the phase 3 studies for tazarotene creams required emollients, if used, to be applied at least one hour before administration of study medication. Thus, the statement is acceptable. For the fourth item, the phase 3 studies for tazarotene creams did not explicitly instruct administration in the evening.

4.3.11. Data on Therapeutic Drug Monitoring. The proposed label for tazarotene creams includes such data in the "CLINICAL PHARMACOLOGY" section.

4.4. Conclusion and Recommendation.

There are significant differences between the proposed label for tazarotene creams and the approved label for tazarotene gels. Despite many similarities, tazarotene creams are not really line extensions of tazarotene gels. Thus, the labeling differences are acceptable as long as they are supported by data. The Applicant may need to substantiate some of statements in the label for tazarotene creams. These issues will be addressed at the labeling meeting scheduled for 7/20/00.

5. Overall Conclusions and Recommendations.

The purpose of this Addendum is to clarify certain issues raised since completion of the Medical Officer's Review. It does not alter the conclusions and recommendations in the original review, which stand as previously written.

/S/

Hon-Sum Ko, M.D.

cc: NDA 21-184
HFD-540
HFD-540/CSO/Bhatt
HFD-540/CHEM/Timmer
HFD-540/PHARM/Nostrandt
HFD-880/BIOPHARM/Lee
HFD-540/MO/Walker/Ko
HFD-710/BIOMETRICS/Lawrence

✓Not in DFS

Pregnancy category X is conveyed in labeling [21 CFR 201.57 (f) (6) (e)] if studies in animals have demonstrated fetal abnormalities and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit. Since both conditions obtain for this product, Pregnancy category X is an appropriate precaution to minimize fetal exposure. However, Pregnancy category X alone does not inform about the quantitative risks of teratogenicity when fetal exposure has occurred, and such information could be useful for both patient and physician in the setting where exposure has occurred. Since this product will likely be used extensively by women of child-bearing potential, it is ethical to harvest outcome data on these patients and their infants and incorporate these data into labeling. The Pregnancy category X is important for the decision to prescribe, but is is insufficient to inform the important decisions to be made once fetal exposure has occurred. Such pregnancy outcome data would be useful information for all Pregnancy category X products. The Sponsor has been encouraged to propose methodology for harvesting such data.

8/17/00

/S/

KD

Medical Officer Review for Original NDA* 21-184

DDDDP#994245

1 General Information

JUL 11 2000

1.1 NDA submission number	21-184
1.2 Applicant identification	
1.2.1 Name	Allergan, Inc.
1.2.2 Address and telephone number	2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534,
1.2.3 Name of company contact official	Trudy A. Rumbaugh, Director, Global Regulatory Affairs, Retinoids
1.3 Submission/review dates	
1.3.1 Date of submission	9/30/99
1.3.2 CDER stamp date	9/30/99
1.3.3 Date submission received by reviewer	10/8/99
1.3.4 Date review begun	10/9/99
1.3.5 Date review completed	4/30/00
1.3.6 Date review revised	5/08/00, 6/07/00, 6/30/00
1.4 Drug Identification	
1.4.1 Generic Name	tazarotene
1.4.2 Proposed Trade Name	TAZORAC
1.4.3 Chemical Name	Ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl] nicotinate
1.4.4 Chemical Formula	$C_{21}H_{21}NO_2S$
1.4.5 Molecular Weight	351.46
1.5 Pharmacologic Category	retinoid
1.6 Dosage Form	creams 0.05% and 0.1%
1.7 Route of Administration	topical

1.8 Proposed Indication & Usage Section

"TAZORAC® (tazarotene topical cream) 0.05% and 0.1% are indicated for the topical treatment of patients with plaque psoriasis."

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*Abbreviations used in this review: ADR=adverse drug reaction; AE=adverse event(s); ALT=alanine transaminase; ANOVA=analysis of variance; AST=aspartate transaminase; AUC=area under the curve; BID (bid)=twice daily; BSA=body surface area; Cmax=maximal concentration; CMC=chemistry, manufacturing and controls; CMH=Cochran-Mantel-Haenszel; COPD=chronic obstructive pulmonary disease; EP=European Pharmacopeia; HDL=high density lipoprotein; HMG-CoA=3-hydroxy-3methylglutaryl coenzyme A; ICD=irritant contact dermatitis; IND=Investigational New Drug Application; ITT=intent-to-treat; LDL=low density lipoprotein; LOCF=last observation carried forward; LSD=least significant difference; MED=minimal erythema dose; NDA=New Drug Application; NF=National Formulary; OLA=overall lesional assessment; PK=pharmacokinetic(s); QD (qd)=once daily; T½=half-life; Taz=tazarotene; Tmax=time to maximal concentration; USP=United States Pharmacopeia; UVA=ultraviolet A; UVB=ultraviolet B; Veh=vehicle.

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1.9 Proposed Dosage & Administration Section

1.10 Related Drugs

Tazarotene (TAZORAC®) Gels 0.05% and 0.1% have been approved for the indications psoriasis and acne under NDA 20-600.

under IND

1.11 Material Reviewed

1.11.1 NDA volumes reviewed 1.1, 1.11-1.15 (PK Section), 1.16-1.81 (Clinical Section)

1.11.2 Amendments reviewed Submissions dated -

- 2/3/00 120-day Safety Update
- 3/22/00 Submission of safety data from formulations other than cream and requested analysis
- 4/4/00 Submission of analysis missing in original NDA
- 5/15/00 Submission clarifying discrepancies in NDA
- 6/7/00 Submission clarifying laboratory adverse event data

Review has also been assisted with electronic documents including the draft labeling, integrated summaries, study reports and protocols.

1.12 Regulatory Background

Studies in support of this NDA were conducted under IND Important submissions/interactions between the Applicant and the Agency are shown in the following Table:

Submission	IND Serial #	Subject
07/09/97		Pre-IND meeting
09/09/97		Original IND omission
11/17/97		Telephone conference (clinical)
11/24/97		Telephone conference (clinical)
08/17/98		Submission of statistical plan
09/11/98		Request for telephone conference (statistical) – denied by FDA
11/02/98		Request for telephone conference (PK)
01/14/99		Telephone conference (PK)
03/11/99		Request for telephone conference (process validation)
		Telephone conference (process validation)
04/27/99		Request for pre-NDA meeting
06/14/99		Pre-NDA meeting

The following is an account of important guidance provided to the Applicant:

7/9/97 Pre-IND/End of Phase II meeting

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