

- (3) From a project management perspective, is this NDA fileable? If "no". please state on the reverse why it is not.

THIS APPLICATION IS FILEABLE FROM A PROJECT MANAGEMENT PERSPECTIVE.

/S/

Project Manager

/S/

Supervisory Project Manager

**APPEARS THIS WAY
ON ORIGINAL**

Efficacy endpoints (Primary and secondary) and how measured:

Primary: Clinical Success Rate, defined as an Overall Lesional Assessment score of none, minimal, mild (6-point static scale)

Secondary: Overall plaque elevation, overall scaling, overall erythema (all three being 5-point scales), body surface area involvement (%), global response to treatment (7-point scale, improvement from baseline)

Pivotal Study #2: Protocol Number: 190168-017C

Page Location in NDA: Protocol: vol 1.51

Study Report: vol 1.50

Is this an adequate multi-centered trial? YES

Center Patients Enrolled
17 635

Study Title: Multicenter, Double-Blind, Randomized, Vehicle-Controlled Study Of The Safety And Efficacy Of 0.05% And 0.1% Tazarotene Creams Applied Once Daily For 12 Weeks In The Treatment Of Plaque Psoriasis

Study design: Randomized YES Double Blind YES Placebo controlled YES
Multicentered YES

Indication: Plaque psoriasis

Study arms (dosage, duration, treatment length for each arm):
Same as in 190168-016C

Efficacy endpoints (Primary and secondary) and how measured:
Same as in 190168-016C

6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling? YES

Proposed indication from sponsor's draft labeling: the topical treatment of patients with plaque psoriasis

As designed, could endpoints in pivotal trial #1 support labeling? YES

As designed, could endpoints in pivotal trial #2 support labeling? YES

7. Are all data sets for pivotal efficacy studies complete for all indication(s) requested? (this is a stat question?) For Biometrics Reviewer to answer

8. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?

PreIND Mtg: YES

IND number/s:

PreIND Mtg Date: 7/9/97; direct entry into phase 3

EP2 Meeting Date: N/A

Agency response to Phase 3 protocols: Numerous discussions; agreement reached 11/24/97

PreNDA meeting date: 6/14/99

Do endpoints as described by sponsor in pivotal Study 1 conform to previous agency commitments? YES

Do endpoints as described by sponsor in pivotal Study 2 conform to previous agency commitments? YES

Are the pivotal trials multi-centered? YES

Are there adequate numbers of patients enrolled? YES

9. Has the Applicant submitted line listings in a format to allow reasonable review of the patient data? Has the Applicant submitted line listings in the format agreed to previously by the Division? YES

10. Has the Application submitted a rationale for assuming the applicability of foreign data (disease specific microbiologic specific) in the submission to the US population? N/A (Domestic)

11. Has the Applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? No previous request

12. Has the Applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? YES

13. Has the Applicant presented a safety assessment based on all current world-wide knowledge regarding this product? YES (incomplete description in text, a summary Table listing postmarketing events for Tazorac gels 0.05%, 0.1% should be provided)

14. Has the Applicant submitted draft-labeling consistent with 21CFR 201.56 and 21CFR 201.57, current divisional policies, and the design of the development package? YES

15. Has the Applicant submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? YES

16. Has the Applicant complied with the requirements of the Pediatric Rule? YES (Waiver requested)

a) Is this an indication that would be applicable to the pediatric population? YES

b) What pediatric ages are included in the protocol? NONE

c) Does the Applicant request pediatric labeling? What age groups? NO, waiver requested

It should be noted that tazarotene is on the pediatric "list". Thus, request of a waiver rather than request for deferral may be interpreted as unwillingness to conduct pediatric studies in accordance to the Final Rule, and may become an issue for filing. However, the Agency has the authority to defer submission on its own initiative or at the request of the applicant (21 CFR 314.55(b)(1)). As there are fewer patients with psoriasis in the pediatric age group, it is recommended that the this issue not be an obstacle for approval for adult use, and submission of pediatric data be deferred but not waived.

17. Financial disclosure of investigator

a) Does the NDA contain the appropriate form to comply with the filing requirement for Financial Disclosure for Investigators? YES

18. From a clinical perspective, is this NDA fileable? YES

If certain claims are not fileable please state which claims they are and why they are not fileable. N/A

15/
10-29-99

Reviewing Medical Officer (H.S. Ko, M.D.)

15/
11-2-99

Dermatology Team Leader (S. Walker, M.D.)

Office of New Drug Chemistry
 Division of New Drug Chemistry III

6661 2 2 100

NDA FILEABILITY CHECKLIST

OCT 22 1999

NDA Number: 21-184

Drug Name: Tazorac (tazarotene) Cream, 0.05%, 0.1%

Applicant: Allergan

Previously approved: NDA 20-600, gel, 0.1% & 0.05% psoriasis
 0.1% acne

Stamp Date: 30-SEP-99

Today's Date: November 22, 1999

IS THE CMC SECTION OF THE APPLICATION FILABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, *i.e.*, complete enough to review but may have deficiencies.

	PARAMETER	YES	NO	COMMENT
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are all of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		IR request to Allergan: Will _____ _____
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		CE to EA requested
7	Does the section contain controls for the drug substance?	X		Refer to NDA 20-600
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	--	--	See next table (below)
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		See last page; discussion with Tony

11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		Vol I pg. 237
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included? Is a micro consult needed?	X		MLT and PET part of release testing

Regarding the stability data: see pg. 047 in volume 2; no stat consult indicated at this time

	YES	NO
Does the NDA include 12 months or more of stability data?	X	
Is the stability data for the full shelf-life?	X	
Does the stability data include all package sizes?	X	
Does the stability data include only the largest and smallest sizes?		X
Are there tabular presentations of the data for each size and batch?	X	
Are there graphical presentations of the data for each size and batch?	X	
Have different batches of different sizes been pooled?	X	
Is there a statistical analysis of the assay data (i.e., slope and intercept of the regression curve, 95% confidence limits, etc.)	X	
Is there a statistical analysis of the impurity data?	X	
Is the specific method used in the statistical analysis reference or described?	X	

Regarding the DMFs:

DMF NUMBER	HOLDER	DESCRIPTION	LOA INCLUDED	DATE OF LAST REVIEW
1	Allergan	Type I	NA	NA
		Type III	10/26/99	9/15/99
		Type I	NA	NA

Has a tradename been submitted? Marketed drug; tradename approved

Has an EER been submitted for all the facilities? Yes; submitted 11/22/99

Note: During the Pre-NDA meeting Allergan was requested the specification for tazarotene related substances from ~~_____~~ (which is the release spec in NDA 20-600). They have changed the spec to ~~_____~~ and not the requested ~~_____~~. This is more of a review issue, but it is noted here.

EXPLAIN IF THE THE NDA IS NOT FILEABLE FROM A CMC PERSPECTIVE STATE:

/S/

William C. Timmer, Ph.D.
Review Chemist:

oo November 99

/S/

Wilson H. DeCamp, Ph.D.
Team Leader

cc:

Original NDA 21-184

HFD-540/Division File
HFD-540/Chem/WCTimmer
HFD-540/ChemTL/WHDeCamp
HFD-540/PM/OCintron

HFD-830/DD/CWChen

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21184/000
Stamp: 30-SEP-1999 Regulatory Due: 31-JUL-2000
Applicant: ALLERGAN
2525 DUPONT DR
IRVINE, CA 926239534

Priority: _____ Org Code: 540
Action Goal: _____ District Goal: 01-JUN-2000
Brand Name: TAZORAC(TAXOROTENE)0.05%/0.1%
TOPICAL CR
Established Name:
Generic Name: TAZAROTENE
Dosage Form: CRM (CREAM)
Strength: 0.05% AND 0.1%

FDA Contacts: K. BHATT (HFD-540) 301-827-2020 , Project Manager
W. TIMMER (HFD-540) 301-827-2048 , Review Chemist
W. DECAMP II (HFD-540) 301-827-2041 , Team Leader

Overall Recommendation:

Establishment: 1643525
ALLERGAN INC
8301 MARS DR
WACO, TX 76712

DMF No:
AADA No:

Profile: OIN OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date 22-NOV-1999

Responsibilities: FINISHED DOSAGE
MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER

Establishment: 9610728
ALLERGAN PHARMACEUTICALS IR
WESTPORT, COUNTY MAYO, EI

DMF No:
AADA No:

Profile: CIN OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date 22-NOV-1999

Responsibilities: FINISHED DOSAGE STABILITY
TESTER

Establishment: _____

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: SUBMITTED TO OC
Milestone Date 22-NOV-1999

Responsibilities: _____

Division of Dermatologic and Dental Drug Products (HFD-540)
Pharmacology/Toxicology Forward Planning Meeting

OCT 21 1999

NDA Number: 21-184 Date: 10/7/99
Drug Name: Tazorac (tazarotene) 0.05%/0.1% topical cream
Reviewer: Amy Nostrandt
CAS Number: not provided in pharm/tox volumes
Drug Type: (i.e. NME, new formulation, new indication) new formulation
Drug Class: acetylenic retinoid
Indication: treatment of plaque psoriasis
Route of Administration: topical to the skin
Date CDER Received: 9/30/1999
User Fee Date: 7/30/2000
Expected Date of Draft Review: 5/1/2000
Sponsor: Allergan

Fileability:

On initial overview of the NDA application:

YES NO

(1) On its face, is the pharmacology/toxicology section of the NDA organized in a manner to allow substantive review to begin?
Comments? X _____

(2) Is the pharm/tox section of the NDA indexed and paginated in a manner to allow substantive review to begin?
Comments? X _____

There is a separate index for each volume, but no overall index for the pharm/tox section. A master index was included in the desk copy of the 1.1 volume.

(3) On its face, is the pharm/tox section of the NDA legible so that substantive review can begin?
Comments? X _____

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute studies*, chronic studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?
Comments? X _____

The only study requested was one to bridge data after the formulation change.

(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the Sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required?
Comments? X _____

- (6) Are the proposed labeling sections relative to pharm/tox appropriate (including human dose multiples expressed in either mg/m² or comparative serum/plasma levels) and in accordance with 201.57? X
Comments?

Comparisons appear to be on the basis of pharmacokinetic data or body surface area adjusted doses.

- (7) Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor?
Comments? not applicable

- (8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the Sponsor submitted a rationale to justify the alternative route? X
Comments?

- (9) Has the Sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? X
Comments?

The statement is that *most* studies were conducted under GLP's. This is appropriate, as nonclinical pharmacology and ADME studies do not have to be conducted under GLP's.

- (10) Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics?
Comments? not applicable

Carcinogenicity studies for the drug substance have been reviewed with NDA 20-600 for tazarotene gels.

- (11) Has the Sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? X
Comments?

- (12) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. X

- (13) If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify: X

(14) Issues that should not be conveyed to the Sponsor:
none

IS/
Reviewing Pharmacology Officer 10/1/99

IS/
Pharmacology Team Leader 10/21/99

APPEARS THIS WAY
ON ORIGINAL



Cross-540

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: November 23, 1999 Number of Pages (including cover sheet) - 9

TO: Tom Walton, Specialist, Regulatory Affairs
COMPANY: Allergan, Inc.
FAX #: 714-246-4272

MESSAGE: Please find attached to this facsimile transmission, minutes of our meeting of June 14, 1999.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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Meeting Date: June 14, 1999
Meeting ID# 4210

Time: 1000

Location: N225

IND — Tazorac (tazarotene topical cream) Cream, 0.05%, 0.1%

Indication: Topical Treatment of Plaque Psoriasis

Sponsor: Allergan, Inc.

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Hon Sum Ko, M.D., Medical Officer, DDDDP, HFD-540
Bonnie Dunn, Ph.D., Deputy Division Director, DNDCIII, HFD-830
Jim Vidra, Ph.D., Acting Chemistry Team Leader, DNDCIII, HFD-830
Bill Timmer, Ph.D., Chemist, DNDCIII, HFD-830
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540
Sue Chih-Lee, Ph.D., Biopharmaceutist, DPEIII, HFD-880
R. Srinivasan, Ph.D., Biostatistics Team Leader, DOBIII, HFD-725
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Trudy Rumbaugh, M.D., Director, Global Regulatory Affairs, Retinoids
Patricia Walker, M.D., Ph.D., Director, Medical Affairs
John Sefton, Ph.D., Director, Skin Care Clinical Research and Development
John Lue, M.S., Principal Biostatistician, Biostatistics
Brian Short, D.V.M., Ph.D., Director, Safety Evaluation
Gary Ewing, Ph.D., Senior Scientist, Pharmaceutical Sciences
John Worsley, Section Manager, Pharmaceutical Analysis
Richard Matsumoto, Ph.D., Principal Scientist, Pharmacokinetics and Drug Metabolism
Thomas Walton, Specialist, Pharmaceutical Regulatory Affairs, Retinoids

Discussion:

With reference to IND — SN 028, Request for pre-NDA Meeting and SN 029, Briefing Package for Pre-NDA Meeting, the Agency made the following recommendations:

Chemistry, Manufacturing and Controls:

1. Chemistry Manufacturing and Controls Question 1 of May 21, 1999, Meeting Briefing Package: The Sponsor can cross-reference previous filings for the API but cross-references must be explicit to page and volume numbers. We request that there be no updates to the DMF within the last 3 months of the NDA review cycle.
2. Chemistry Manufacturing and Controls Question 2 of May 21, 1999, Meeting Briefing Package: The manufacturing process of the container-closure system needs to be validated before submission. The container-closure facility should be ready for inspection at the time of submission. If a second container/closure system is desired, the Sponsor should submit it as a Pre Approval Supplement.
3. Chemistry Manufacturing and Controls Question 1 of May 21, 1999, Meeting Briefing Package: The stability data appears to be acceptable; however, it would be best to submit the stability data in tabular form. The Sponsor is reminded that they can bracket containers, but not concentrations for stability. The registration stability was not defined. There was no reference to relative humidity in the stability protocol. No pooled data should be submitted. What expiration dating period is going to be requested?

Sponsor: The Sponsor said that they would be requesting a _____ expiration.

4. The specification for 'tazarotene related substances,' at _____ appears to be high based on the data you submitted. This high of a value will require a justification. We would prefer for this value to be reduced. (In fact, the specification is _____ for tazarotene related substances [i.e., the oxidation and hydrolysis products] in NDA 20-600 Tazarotene Gel 0.05% and 0.1%).
5. Is the Sponsor aware of how to apply for a categorical exclusion to an environmental assessment?

Sponsor: The Sponsor said that they are aware.

6. The issue of _____ was discussed at a previous meeting. The Agency assumes that the Sponsor is using _____

Sponsor: The Sponsor claims to be using _____

7. Will all facilities be ready for inspection at the time of the NDA submission?

Sponsor: The Sponsor said that all facilities will be ready for inspection at the time of the NDA submission.

Pharmacology/Toxicology:

1. Toxicology/Pharmacology/Nonclinical Pharmacokinetics Question 1 of May 21, 1999, Meeting Briefing Package: It is acceptable to cross-reference NDA 20-600 for nonclinical studies of tazarotene that are not formulation-based. Please provide an executive summary of those studies in the proposed NDA and cross-reference submission volumes where the reports can be found.
2. Toxicology/Pharmacology/Nonclinical Pharmacokinetics Question 2 of May 21, 1999, Meeting Briefing Package: At this time, the nonclinical data package does appear to be sufficient for NDA filing.

Biopharmaceutics:

1. With regard to Study 190168-024C, the Sponsor stated that there were gross errors in dosing and, therefore, the study was abandoned. The Sponsor should clarify what the errors were and submit the available data in the NDA.

Sponsor: As requested by the Agency, the Sponsor agreed to analyze the plasma samples and will submit the data. A discussion on toxicity (local and systemic) as related to dose or plasma concentration will also be provided in the submission. This information will be submitted to the NDA within two months after the original NDA submission.

2. With regard to Study 190168-023C, the Sponsor should ensure that patients completing the study have acceptable total surface area of involved skin.

Sponsor: The Sponsor said that they have studied patients with a large surface area of psoriatic skin.

3. With regard to therapeutic drug monitoring, it is unclear whether patients actually missed an evening dose prior to blood collection.

Sponsor: The Sponsor clarified that patients did miss an evening dose, but the patients did have a morning dose prior to blood collection.

Agency: The Agency commented that this missed evening dose will result in lower plasma concentrations of the active metabolite, tazarotenic acid.

4. The Sponsor should provide in the original NDA submission in vitro percutaneous absorption data comparing the tazarotene cream and the approved Tazorac Gel formulations.

Clinical:

1. Clinical Pharmacokinetics/Clinical Safety and Efficacy Question 1 of May 21, 1999, Meeting Briefing Package: The information in the "clinical package" contains study synopses in the ICH E3 format, together with Tables for the Phase 3 trials. Such information alone would not be adequate for filing. The Sponsor should follow the Clinical/Biostatistics Guidelines in presenting full study reports, plus integrated summaries of effectiveness, safety and benefits and risks. All safety data must be presented, including postmarketing data for marketed formulation(s), data from studies on indications not sought and on formulations not marketed, and data from ongoing studies not yet completed (domestic and foreign).

Sponsor: The Sponsor agreed.

2. Clinical Pharmacokinetics/Clinical Safety and Efficacy Question 2 of May 21, 1999, Meeting Briefing Package: "Allergan has accepted the Division's recommendation of May 7, 1999 (FDA fax, Comment#1) for photoallergenicity testing and we are undertaking activities to repeat the study utilizing both UVA and UVB in the challenge phase. Allergan proposes submission of this study in the 120-day Safety Update. Does the FDA concur?"

The Agency concurs.

3. Biostatistics Questions of May 21, 1999, Meeting Briefing Package:

(These questions from the Sponsor are discussed here because they are relevant items for the clinical reviewer):

For the Integrated Summary of Safety (combined analysis of Phase 3 Trials):

- a. Is a summary statistical table of the number (%) of patients with a medical disorder prior to the start of tazarotene treatment required?

No, but this should be provided in the individual studies.

- b. Is a summary statistical table of patient's concomitant medication use before and during the study required?

No, but this should be provided in the individual studies.

- c. Is analysis of clinical laboratory data by demographics required?

No, but this may be "useful" and "should be explored" (Clinical/Biostatistics Guidelines pp 43-44). The Sponsor can combine the studies to look at demographic subsets.

Sponsor: The Sponsor said that they will also analyze the Adverse Events, demographically.

- d. Is it helpful to provide data electronically on CDs?

This question will be answered by the Biostatistics Reviewer.

2. Additional Comments:

- a. The Sponsor should answer whether protocol and investigator information for 190168-023C have been submitted to the IND; and if not, provide an explanation.
- b. The Sponsor should supply CRTs and CRFs as per 21 CFR 314.50(f)(1) and (2).
- c. The Sponsor should give proper rationale for the dose (concentration, frequency and duration) selected for marketing. In general, the drug product showing best effectiveness and not worse in toxicity when compared to others should be selected. Multiple adjustment for the Phase 3 studies will be discussed by the Biostatistics Reviewer.
- d. Any published reference to support the application should be provided as hard copies rather than simply quoted.
- e. Explanations for all dropouts should be provided. It is not acceptable to just designate a dropout as being "administrative" or "protocol violation". It is noted that some of them listed under "other" were dropped for "personal" reason, which would make them "administrative".
- f. The Agency may request to review photography of the endpoint "Overall Lesional Assessment". The Agency said that photographs proposed to be used in advertising should be submitted to the Agency for review prior to their use.

Sponsor: The Sponsor said that they will submit the photographs to the Division of Dermatologic and Dental Drug Products and to the Division of Drug Marketing, Advertising & Communications.

- g. The Sponsor should correlate data from "Overall Lesional Assessment" with those from more traditional endpoints such as physician global and clinical signs.

Sponsor: The Sponsor asked whether it is acceptable to only submit the analysis for Week 12.

Agency: The Agency agreed.

- h. A claim of "maintenance of therapeutic effect" based on data from the post-treatment period in a vehicle-controlled study would not be acceptable.
- i. If the Sponsor wishes to submit any clinical study report in abbreviated format, prior agreement should be reached with the Agency.

Sponsor: The Sponsor asked if Study 190168-024C could be submitted in abbreviated format.

Agency: The Agency said that the full report should be submitted. At the time of initial NDA submission, the report may be in abbreviated format with the full report to follow.

Biostatistics:

1. SAS Datasets in v. 6.12 on 3.5 inch media are preferred, however, datasets on CD's are also acceptable.
2. Perhaps because the methods of analysis agree with those preferred by this reviewer, the Sponsor's proposed analyses seem to be quite appropriate and well thought out.
3. The DDDDP definition of "intent-to-treat" is all subjects dispensed treatment, not all subjects randomized to treatment as on page 106. But either definition seems defensible to this reviewer.

4. The Sponsor states (e.g. see page 106, ninth line of text) "Within-group comparisons to baseline were performed by the Wilcoxon signed rank test". Because of regression, placebo, and secular effects, and the difficulties of disentangling these effects from treatment effect, to this reviewer within group differences from baseline would seem to be of questionable scientific utility. But they only waste time, and would not hurt the Sponsor's case.
5. If the request is for either of the two concentrations to be marketed, and if only one is superior to vehicle, then the claims of superiority over vehicle should be tested at 0.025 level, using Bonferroni or any other appropriate type of adjustment for multiple comparisons.

Addendum:

Project Management:

1. Pediatric Rule:
 - a. Under 21CFR, Section 314.50, the NDA application is required to include the following: (d)(7) Pediatric Use Section. Requires that an NDA contain "a section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (3) and (5), and information required to be submitted under Section 314.55."
 - b. Under 21CFR Section 314.55, Pediatric Use Information. (a) Required Assessment. "Except as provided in paragraphs (b), (c), and (d), each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective...." Orphan drugs are exempted from this requirement.
 - c. For additional information, please refer to the following CDER web site, www.fda.gov/cder/pediatric

2. Financial Disclosure:

For applications submitted after February 2, 1999, the Applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to the following CDER web site, www.fda.gov/cdrh/modact/112098a.html

Signature, minutes preparer: _____

/S/

Concurrence Chair (or designated signatory): _____

/S/

cc:

HFD-540
HFD-540/DIV DIR/Wilkin
HFD-540/DERM TL/Walker
HFD-540/MO/Ko/6.14.99
HFD-830/DEP DIV DIR/Dunn
HFD-540/CHEM TL/DeCamp
HFD-540/ACT CHEM TL/Vidra
HFD-540/CHEM/Timmer/6.14.99
HFD-540/PHARM TOX TL/Jacobs/6.14.99
HFD-540/PHARM TOX/Nostrandt
HFD-880/BIOPHARM TL/Bashaw
HFD-880/BIOPHARM/Lee/6.14.99
HFD-725/BIOSTAT TL/Srinivasan/6.14.99
HFD-725/BIOSTAT/Thomson
HFD-540/PM/Cross

Drafted by: fhc/June 14, 1999

c:\word\tazorac\

Initialed by:

final:

MEMORANDUM OF MEETING

COMPANY: Allergan, Inc.
FAX #: 714-246-4272

MESSAGE: Please find attached to this facsimile transmission, minutes of our meeting of June 14, 1999.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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11/23/99 13:52

BEST POSSIBLE COPY MESSAGE CONFIRMATION

Electronic Mail Message

Date: 8/31/00 11:49:30 AM
From: Walton_Thomas (Walton_Thomas@Allergan.com)
To: See Below
Subject: FDA/Allergan Teleconference/NDA 21-184/August 29, 2000

Dear Ms. Bhatt and Drs. Timmer and Ko:

These are Allergan's interpretations of the Key Decisions and Understandings from our Teleconference:

<<Pregnancy Labeling CMC 082900.doc>>

To: 'Bhatt, Kalyani (e-mail)' (BhattK@A1)
To: 'Timmer_William, FDA' (TimmerW@A1)
To: 'Hon-Sum Ko 301-827-2021 FAX 301-82' (KOH@A1)
Cc: Sefton_John (Sefton_John@Allergan.com)
Cc: Rumbaugh_Trudy (Rumbaugh_Trudy@Allergan.com)
Cc: Kresel_Peter (Kresel_Peter@Allergan.com)
Walton_Thomas (Walton_Thomas@Allergan.com)
Quell_Janine (Quell_Janine@Allergan.com)

Due to the limitations of the Pregnancy Category classifications in the CFR, FDA has requested that Allergan prospectively identify women who inadvertently become pregnant while on TAZORAC Cream therapy in order to build a database on such exposure.

This data would eventually be included in the labeling to help women and their doctors make informed decisions and would be presented in a fashion that would not encourage exposure.

Allergan has proposed that we identify 10-12 specialized psoriasis treatment centers nationwide and initiate a protocol that would prospectively identify inadvertent pregnancies and enter those women into the protocol and monitor the health of the mother, fetus and newborn.

Allergan will submit a Clinical Trial Outline designed to capture these data to FDA for review within 2 weeks.

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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;
- removed inactive ingredients; [*The DDMAC version asks the patient not to use the product if "you are allergic to the ingredients in TAZORAC. The active ingredient is tazarotene. Ask your doctor or pharmacist about the inactive ingredients." It would be more convenient to the consumer to have the excipients listed in the PPI.*]
- eliminated the phrase _____, 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 pertain to complete sunlamp avoidance. The physician may prescribe UV therapy in conjunction with tazarotene for psoriasis. Although this practice is not in the label, elimination of this phrase potentially casts doubt on the physician's judgment.*]

3.3.2. Questions by Ms Lechter.

3.3.2.1. Vitamin A.

in other appropriate sections with some explanation about them. In the PI, there is only a mention that ingesting Tazorac can result in symptoms similar to Vitamin A overdose.

- Should the advice to tell a doctor about Vitamin A use be left out, or
- Should it be in the section on what to avoid while using Tazorac, or
- Should it be in the section about who should not use the product?
- If it is left in, what should it say?

Answer: The patient should tell the prescriber about Vitamin A usage, including its dose. The decision should depend on the judgment of the prescriber.

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.

Answer: Stinging and burning are related sensations. Suggest replacing " " alone with "burning or stinging". Concur that the statement that reactions may be less often as skin gets used to the drug can be left out, unless the Applicant can substantiate this with data.

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: "However, effectiveness of TAZORAC when used less often than once a day has not been proven."

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.

Answer: The PPI is always attached to the PI until cut out by the Pharmacist.

Number of Pages
Redacted 4 pages



Draft Labeling
(not releasable)

Electronic Mail Message

Date: 7/6/00 6:48:46 PM
From: Walton_Thomas (Walton_Thomas@Allergan.com)
To: 'Bhatt, Kalyani (e-mail)' (BhattK@A1)
To: 'Timmer_William, FDA' (TimmerW@A1)
To: 'DeCamp_Wilson, FDA' (DeCamp@A1)
Cc: Rumbaugh_Trudy (Rumbaugh_Trudy@Allergan.com)
Cc: Fleitman_Jeffrey (Fleitman_Jeffrey@Allergan.com)
Subject: NDA 21-184/FDA-Allergan CMC Telecon/July 6, 2000

Dear Ms. Bhatt and Drs. DeCamp and Timmer:

Thank you for meeting with us this morning on the outstanding CMC issues. I have attached Allergan's Meeting Minutes and our understanding of the meeting outcome for your review and information.

Please let me have any comments or clarifications you may have.

Sincerely,

Tom

<<FDA Telecon.doc>>

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Minutes of FDA/Allergan Teleconference: July 6, 2000, 8:40 am, PDT

NDA 21-184/TAZORAC (tazarotene topical cream)

Attendees: FDA: Kalyani Bhatt, Project Manager, William Timmer, PhD, Chemistry Reviewer, DNDC, Wilson DeCamp, PhD, Supervisory Chemist, DNDC

Allergan: Thomas Walton, Regulatory Affairs, Trudy Rumbaugh, MD, Regulatory Affairs, Jeffrey Fleitman, PhD, Director, Pharmaceutical Analysis

Topics of Discussion:

- In the future, Allergan should only submit one set of "Regulatory Specifications" which will be utilized for both Release and Shelf-Life acceptance.
- Specifications for the related substances in tazarotene cream are different from tazarotene gel due to the different formulations and the different reactivity of tazarotene in the two formulations.
- The expiration date of _____ is based on the extrapolation of data for all regulatory specification parameters.
- Total tazarotene-related substances in tazarotene gel are the same overall level as in tazarotene cream _____ however the proportions are slightly different.
- Higher levels of degradants in tazarotene cream does not justify any relaxation of the specifications for tazarotene gel that could then be the basis for extension of the expiry date for tazarotene gel.
- AGN 190299 is the active metabolite of tazarotene.
- If 36-month stability data is available, fax to FDA as "unofficial correspondence." (Post-meeting note: data not available until September 2000).
- Allergan to submit stability commitment, if not already in NDA 21-184 (First 3 lots into stability program, at least one lot per year entered thereafter, notify FDA immediately for any stability failure and commitment to pull failed lots from the market if requested). (Post meeting note: commitments are contained in the stability protocols Vol 2 pp. 098-099 and pp.100-101).
- Allergan to check storage temperature on draft labeling and compare to stability report and standard requirements (Post-meeting note: labeling currently says _____)

_____ Allergan will modify the _____

storage requirement as recommended by FDA and as stated in the stability report.

- FDA to contact Allergan following discussion with Pharm/Tox, if further meetings are required.

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Electronic Mail Message

Date: 6/8/00 3:14:29 PM
From: Walton_Thomas (Walton_Thomas@Allergan.com)
To: 'Bhatt, Kalyani (e-mail)' (BhattK@A1)
To: 'Timmer_William, FDA' (TimmerW@A1)
Cc: Rumbaugh_Trudy (Rumbaugh_Trudy@Allergan.com)
Cc: Kresel_Peter (Kresel_Peter@Allergan.com)
Subject: Today's teleconference/NDA 21-184

Dear Dr. Timmer and Ms Bhatt:

Following today's teleconference among us, I have reviewed the PreNDA Meeting minutes, our NDA specifications and the 24-Month Stability Report submitted on March 7. I also spoke to our Pharmaceutical Sciences/Pharmaceutical Analysis group.

I will be contacting you shortly to arrange a teleconference with you. In a nutshell; it appears we cannot go lower than _____ based on the stability data I have (quickly) reviewed.

The PreNDA Meeting Minutes (11/23/99) states as follows

"The specification for 'tazarotene related substances,' at NMT than _____ appears to be high based on the data you submitted. This high value will require a justification. We would prefer this value to be reduced. (In _____, the specification is NMT _____ for tazarotene related substances [i.e., the oxidation and hydrolysis products] in NDA 20-600 Tazarotene Gel 0.05% and 0.1%)."

Based on your comments and building on our knowledge of tazarotene, we submitted the NDA with the following lowered specs:

Lastly, we have conducted 2 toxicology safety studies with taz gel containing 3% _____ in rats and rabbits. These studies were included in the 1998 Annual Report for NDA 20-600, Taz Gel (volume 2).

I have included them here for your convenience.

<<TX97022Rat.pdf>>

<<TX97021Rabbit.pdf>>

We can have a toxicology/safety evaluation person available also.

I will telephone you soon to arrange the teleconference with our Pharmaceutical Sciences person:rel's proposal.

Sincerely,

Tom Walton

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Electronic Mail Message

Date: 10/4/99 4:49:12 PM
From: Randy Levin (LEVINR)
To: See Below
Subject: Re: Problem: Electronic Submission from Allegran 21184

The information in the CD is a review aid and should not be archived.
You can send it to the division document room.

The sponsor state that they submitted the CRTs in paper for the archive.

If there are any questions, let me know.

>Randy -

>
>The EDR has received an electronic submission of CRTs only from Allegran
>for 21184 for Division 540. Allegran states that the CRTs are submitted
>in electronic format only under the electronic signature rule - 21 CRF
>Part 11, but makes no mention of the Guidance documents.
>
>The submission includes documentation in MS Word format, .SAS and .SD2
>mat data files, SAS Proc files, and a variety of .pdf files. They
>viously are not formatted nor organized according to Guidance
>specifications. We cannot archive them.
>
>Please contact the SCSO - Division 540, Kozma-Fornaro and the sponsor -
>Trudy Rumbaugh (714 246 4292 or Thomas Walton 714 246 4470) and make
>arrangements to accept the files as ERAs or for a new set of archival
>files that meet requirements.
>
>Thanks
>
>Barry
>

To: Jega Nathan* (NATHANJ)
Cc: Thomas Tokoli * (TOKOLI)
Cc: Paul Henig (HENIGP)
Cc: Thomas Selnekovic (SELNEKOVIC)
Cc: Mary Jean Kozma-Fornaro (KOZMAFORNARO)
Cc: Greg Warzala (WARZALAG)
Cc: Barbara Murphy * (MURPHYB)
Cc: Barry Wheeler * (WHEELERB)
Cc: Jega Nathan* (NATHANJ)

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Electronic Mail Message

Date: 10/4/99 4:46:00 PM
From: Randy Levin (LEVINR)
To: Mary Jean Kozma-Fornaro (KOZMAFORNARO)
Cc: Barry Wheeler * (WHEELERB)
Subject: NDA 21-184

Mary Jean,

The sponsor states that the CRTs are provided in paper with the individual study reports in item 8 and 10. If this is true, and you should check this out, this is not a filing issue. This makes the CDROM a review aid. The sponsor sent it based on a request from the statistician, Steve Thomson. I will ask the electronic document room people to send it to the division document room so Steve can get it.

I recommended to the sponsor that in the future, they should send in the data in a format that we can archive as per the guidance.

If there are any questions or additional problems, let me know.

Thanks,

Randy

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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: September 29, 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 for NDA 21-184 Tazorac (tazarotene) Cream 0.05% & 0.1%.

FROM: Kalyani Bhatt

TITLE: Project Manager

PHONE #: 301-827-2020

FAX #: 301-827-2075/2091

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Please see comments on the Clinical Trail Outline .

- 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. Prospective cases are most 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.)

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cc

Div File NDA 21-184

HFD-540/Wilkin

HFD-540/Walker

HFD-540/Ko

HFD-540Kozma-Fornaro

HFD-540/Bhatt

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

FAX COVER SHEET

TO: K. Bhatt FROM: Tom Walton

FAX: 301 827 2091 FAX: (714) 246-4272

TELEPHONE: 301 827 2020 TELEPHONE: (714) 246-4470

CC: _____ DATE: _____

Pages being sent including this cover page: 13

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the approval package consisted of draft labeling

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**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: 9-29-00 Pages (including cover) 16
TO: Tom Walton
COMPANY: ALLERGAN
ADDRESS: 2525 Dupont Drive, P.O. Box 19534, Irvine, CA
FAX PHONE#: 714-246-4272 Our Fax # (301) 827-2075 92623-9554
Voice # (301) 827-2020

MESSAGE:

Please find your Approval Letter

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: _____
TITLE: Project Manager
TELEPHONE: 301 827-2020

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