CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-600

CHEMISTRY REVIEW(S)

CHEMIST'S NOTES Gilman

NDA 20-600

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS (HFD-540)

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-600 CHEM. REVIEW#: 01 REVIEW DATE: 1 May 1996

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	16 Jun 95	19 Jun 95	Jan 2 96

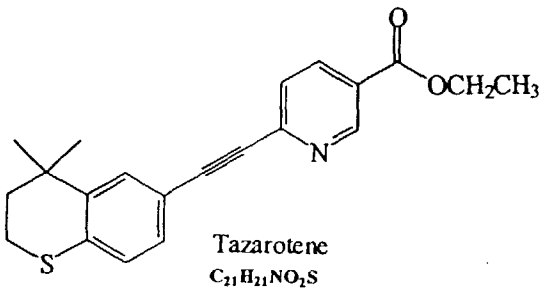
NAME & ADDRESS OF APPLICANT:

Allergan Inc.
P.O. Box 19534
2525 Dupont Drive
Irvine, CA 92713-9534

Trudy Rumbaugh, MD
Tom Walton
714 246 4292 fax 714 246 4272

DRUG PRODUCT NAME	
PROPRIETARY:	None
NONPROPRIETARY/USAN:	Tazarotene 0.05%/0.1% Topical Gel
CHEM ABSTRACT NUMBER	118292-40-3
CODE NAME/#:	AGN 190168
CHEM. TYPE/THER. CLASS	1s
PHARMACOL. CATEGORY/INDICATION:	topical treatment of plaque psoriasis and the the topical treatment of acne vulgaris
DOSAGE FORM:	Ointment, nonsterile-*
STRENGTH(S):	0.1% or 0.05%
ROUTE OF ADMINISTRATION:	dermatologic
DISPENSED:	X Rx ____Otc

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynl]nicotinate



Tazarotene
$C_{21}H_{21}NO_2S$
351.46
351.129300
C 71.8% H 6.0% N 4.0% O 9.1% S 9.1%

AGN 190168

SUPPORTING DOCUMENTS:
IND
DMF
DMF

DMF

CONSULTS:
Environmental Assessment HFD-102, consult issued on or before July 10, 1995.
Tradename Request sent on 30 January 1996
REMARKS/COMMENTS:

Inspection Status:

DMF on file. The last cGMP inspection conducted at was in November 1994. It involved a follow-up pre-approval inspection. This inspection was classified NAI and no 483 Notice of Observations was issued. On or about July 11, 1995 MIN-DO received a request to conduct a cGMP inspection covering the manufacture of the bulk drug substance used to manufacture Tazarotene Topical Gel, NDA 20-600. On July 17, 1995, a memo was sent to the appropriate individuals recommending that be approved for the manufacture of this bulk drug substance for NDA 20-600, Tazarotene Topical Gel, 0.05%/0.1%. Based on findings by the respective investigators at Allergan, it is strongly advisable that a product specific inspection be conducted.
the period of inspection was January 18 - 22, 1996. DMF is on file. A 483 was issued on the last day of inspection. The agent noted that identity testing of raw materials and method validation of the drug substance were inadequate.

Allergan in Waco: the inspection was initiated on January 15, 1996. An extensive 483 was issued to the firm on January 22, 1996.

Allergan in Irvine: the inspection was completed on April 24, 1996 ; a Notice of Observations, form 483, was issued to the company for evaluation and comment.

Allergan (IE) This site in Wesport Ireland will be used for post-approval stability testing of tazarotene gel. At this time, regardless of a paper approval issued on July 7, 1995, this firm is not recognized as a manufacturing facility for NDA 20-600.

Drug Substance:

The impurity profiles at for individual steps and its flow through the entire synthetic sequence were inadequately addressed.
Variability in reaction yields for each procedure may indicate a control issue for consistency in the amount of product prepared.
The methods validation package was incomplete.
The testing site for release and stability data was not disclosed in this submission.
No draft label of the bulk drug product was submitted.

Drug Product:

Although the formulations remained consistent, the manufacturing process of combining aqueous and nonaqueous phases has been evolving from primary small batch studies to isothermal additions with high efficiency mixers (Fryma) on large scale. Evidence is clear through company contact and informal submissions addressing modifications to the manufacturing procedure that the applicant continues to approach a "consistency level," based on analytical control, of the manufacturing batch.
These changes have been leading to an inhomogeneity effect where tazarotene at 25°C migrates out of the gel formulation to the walls of the container; the assay for the drug product is out of specification within 10 to 12 months.
Allergan continues to monitor the progress of its stability batches.
The applicant claims that there is no reprocessing of the batch, but data contained in this application suggests that Allergan is struggling with making a qualification lot that meets proposed specifications.
Data which supports qualification batches of Tazarotene Gel formulations and meets the current release and stability specifications is an ongoing struggle for the applicant.

CONCLUSIONS & RECOMMENDATIONS:

From a chemistry viewpoint of the CMC section presented, this application is not approvable. The deficiencies are summarized in the chemist's letter.

cc:
Orig. NDA 20-600
HFD-160/S.A. Gilman/1 May 1996/Date Revised: 1 May 1996
HFD-541/CSO/F.Cross
HFD-541/CSO/K.Chapman
HFD-540/N.Rejali
HFD-160/CHEM SUPERVISOR/E. W. DeCamp
HFD-830 E.Sheinin [#1 ONLY]
R/D INIT BY : 5/7/96

S.A.GILMAN, REVIEW CHEMIST
filename: NDA20600.SAM

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CHEMIST'S NOTES Gilman NDA 20-600

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS (HFD-540)

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-600 **CHEM. REVIEW#:** 02 **REVIEW DATE:**14 November 1996

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AZ	27 Jun 96	03 Jul 96	01 Aug 96
BZ	30 Jul 96	01 Aug 96	23 Aug 96
BB	18 Sep 96	20 Sep 96	23 Sep 96

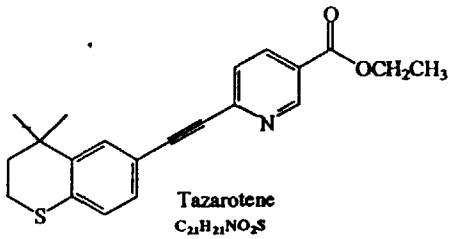
SUBMISSIONS PROVIDE FOR:
Responses to non-approval letter issued on June 6, 1996.

NAME & ADDRESS OF APPLICANT: Allergan Inc.
P.O. Box 19534
Trudy Rumbaugh, MD 2525 Dupont Drive
Tom Walton Irvine, CA 92713-9534
714 246 4292 fax 714 246 4272

DRUG PRODUCT NAME	
PROPRIETARY:	None
NONPROPRIETARY/USAN:	Tazarotene 0.05%/0.1% Topical Gel
CHEM ABSTRACT NUMBER	118292-40-3
CODE NAME/#:	AGN 190168
CHEM. TYPE/THER. CLASS	1s
PHARMACOL. CATEGORY/INDICATION:	topical treatment of plaque psoriasis and the the topical treatment of acne vulgaris
DOSAGE FORM:	Topical Gel, nonsterile-*
STRENGTH(S):	0.1% ~~or~~ and 0.05%
ROUTE OF ADMINISTRATION:	dermatologic
DISPENSED:	X Rx Otc

CHEMIST'S NOTES Gilman NDA 20-600

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynl]nicotinate



Tazarotene
$C_{21}H_{21}NO_2S$
351.46
351.129300
C 71.8% H 6.0% N 4.0% O 9.1% S 9.1%

AGN 190168

SUPPORTING DOCUMENTS:
IND
DMF
DMF
DMF

REMARKS/COMMENTS:
Inspection Status:
To date, all facilities meet preapproval inspection requirements.

Drug Substance:
The CMC requirements at are nearly complete. The accuracy parameter of the method validation for the stability indicating assay requires further information.

Drug Product:
The CMC requirements for the drug product in this application are nearly complete. Again, further clarification on the accuracy parameter in the method validation is requested.

CONCLUSIONS & RECOMMENDATIONS:
From a chemistry viewpoint of the CMC section presented, this application is approvable pending satisfactory response to the chemist's information request.

cc:
Orig. NDA 20-600
HFD-820/S.A. Gilman/October 14, 1996/Date Revised: 22 October 1996
HFD-541/CSO/F.Cross
HFD-540/Medical/H.Ko
HFD-540/Pharmacology/H.Sheevers
HFD-830/N.Rejali
HFD-830/CHEM SUPERVISOR/W. DeCamp

S.A.GILMAN, REVIEW CHEMIST
filename: NDA20600.SAM

R/D INIT BY : WD 11/6/96

12/4/96

CHEMIST'S NOTES Gilman NDA 20-600

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS (HFD-540)

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-600 **CHEM. REVIEW#: 03** **REVIEW DATE:3 December 1996**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BC	14 Nov 96	19 Nov 96	19 Nov 96
FAX	28 Oct 96	28 Oct 96	28 Oct 96
FAX	07 Nov 96	07 Nov 96	07 Nov 96

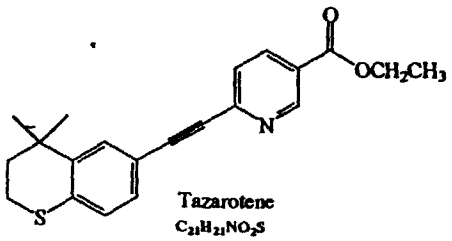
SUBMISSIONS PROVIDE FOR:
Review of responses to an information request issued via fax on October 24, 1996.

NAME & ADDRESS OF APPLICANT: Allergan Inc.
P.O. Box 19534
2525 Dupont Drive
Irvine, CA 92713-9534

Trudy Rumbaugh, MD
Tom Walton
714 246 4292 fax 714 246 4272

DRUG PRODUCT NAME	
PROPRIETARY:	None
NONPROPRIETARY/USAN:	Tazarotene 0.05%/0.1% Topical Gel
CHEM ABSTRACT NUMBER	118292-40-3
CODE NAME/#:	AGN 190168
CHEM. TYPE/THER. CLASS	1s
PHARMACOL. CATEGORY/INDICATION:	topical treatment of plaque psoriasis and the the topical treatment of acne vulgaris
DOSAGE FORM:	Topical Gel, nonsterile-*
STRENGTH(S):	0.1% or 0.05%
ROUTE OF ADMINISTRATION:	dermatologic
DISPENSED:	X Rx Otc

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynl]nicotinate



Tazarotene
$C_{21}H_{21}NO_2S$
351.46
351.129300
C 71.8% H 6.0% N 4.0% O 9.1% S 9.1%

AGN 190168

SUPPORTING DOCUMENTS:
IND
DMF
DMF
DMF

REMARKS/COMMENTS:
Inspection Status:
To date, all facilities meet preapproval inspection requirements.

Drug Substance:
The CMC requirements at have been adequately addressed. The accuracy parameter of the method validation for the stability indicating assay is sufficient.

Drug Product:
The CMC requirements for the drug product in this application are complete. The accuracy parameter for AGN 190168, BHA, and BHT in the final formulation has been adequately addressed.

CONCLUSIONS & RECOMMENDATIONS:
From a chemistry viewpoint of the CMC section presented, an approval of this application is recommended. We recommend that method AP-L217-2E serve as an addendum to the original method validation package.

cc:
Orig. NDA 20-600
HFD-820/S.A. Gilman/December 3, 1996/Date Revised: 3 December 1996
HFD-541/CSO/F.Cross
HFD-540/Medical/H.Ko
HFD-540/Pharmacology/H.Sheevers
HFD-830/N.Rejali
HFD-830/CHEM SUPERVISOR/W. DeCamp

S.A.GILMAN, REVIEW CHEMIST
filename: 20600r3.lwp

R/D INIT BY : 12/3/96

12/19/96

CHEMIST'S NOTES Gilman NDA 20-600

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS (HFD-540)

DEC 19

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-600 **CHEM. REVIEW#: 04** **REVIEW DATE:18 December 1996**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BL	05 Dec 96	06 Dec 96	
BC	11 Dec 96	12 Dec 96	
BC	14 Nov 96	19 Nov 96	19 Nov 96
FAX	28 Oct 96	28 Oct 96	28 Oct 96
FAX	07 Nov 96	07 Nov 96	07 Nov 96

Miscellaneous Submissions to NDA 20-600 not included in previous reviews:

BL	22 Jun 95	29 Jun 95
BC	26 Jul 95	27 Jul 95
BC	22 Sep 95	25 Sep 95
BC	27 Feb 96	29 Feb 96
BC	21 May 96	22 May 96

SUBMISSION SUBMITTED BETWEEN DEC 05 - DEC 11, 1996

Amendments consisting of draft labeling (aluminum tube with screw top closure and the outer carton) and the 24-month stability report for tazarotene gel along with 12 months of manufacturing validation lots (- 1300 kg scale) in support of a 24 month expiration date.

SUBMISSIONS SUBMITTED BETWEEN OCT 28 - NOV 14, 1996 PROVIDE FOR:

Responses to the chemist's information requests issued via fax on October 24, 1996 which include draft labeling and stability of all qualification batches.

SUBMISSIONS SUBMITTED BETWEEN JUN 25, 1995 AND MAY 21 1996 PROVIDE FOR:

Amendments which have been reviewed in the Chem Review 1 and 2. Specifically, contents of each amendment are as follows:

BL 22 Jun 95 29 Jun 95
Real annotated labeling submitted in place of old labeling in original submission.
BC 26 Jul 95 27 Jul 95
A minor change in the sample preparation for the benzyl alcohol assay that has been validated.
BC 22 Sep 95 25 Sep 95
The correction and clarification of issues with tazarotene gel which affect the preservative efficacy test (a microbiology review issue), the amendment for SOP HQC-002 for receipt of incoming components, and the reissuing of stability protocols to be utilized for accelerated testing.

CHEMIST'S NOTES Gilman NDA 20-600

BC 27 Feb 96 29 Feb 96
Amendment consisting of the 12-month stability report for tazarotene gel. A request for an 18 month expiration date was introduced.
BC 21 May 96 22 May 96
Amendment consisting of the 18-month stability report for tazarotene gel along with 6 months of stability data for 1300 kg manufacturing validation lots. A request for an 24 month expiration date was introduced.

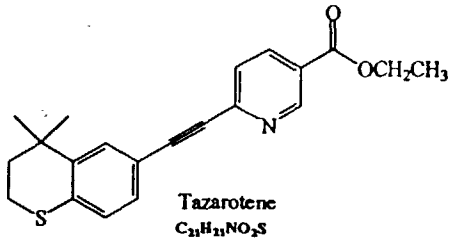
NAME & ADDRESS OF APPLICANT: Allergan Inc.
P.O. Box 19534
Trudy Rumbaugh, MD 2525 Dupont Drive
Tom Walton Irvine, CA 92713-9534
714 246 4292 fax 714 246 4272

DRUG PRODUCT NAME
PROPRIETARY: None
NONPROPRIETARY/USAN: Tazarotene 0.05%/0.1% Topical Gel
CHEM ABSTRACT NUMBER 118292-40-3
CODE NAME/#: AGN 190168

CHEM. TYPE/THER. CLASS 1s
PHARMACOL. CATEGORY/INDICATION: topical treatment of plaque psoriasis and the topical treatment of acme vulgaris
DOSAGE FORM: Topical Gel, nonsterile
STRENGTH(S): 0.1% or 0.05%

ROUTE OF ADMINISTRATION: dermatologic
DISPENSED: X Rx Otc

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynl]nicotinate



Tazarotene
$C_{21}H_{21}NO_2S$
351.46
351.129380
C 71.8% H 6.0% N 4.0% O 9.1% S 9.1%
AGN 190168

SUPPORTING DOCUMENTS:
IND
DMF
DMF
DMF

REMARKS/COMMENTS:
Inspection Status:
To date, all facilities meet preapproval inspection requirements.

Drug Substance:
The CMC requirements at have been adequately addressed. The accuracy parameter of the method validation for the stability indicating assay is sufficient.

Post approval commitment requested:

A phase IV post approval commitment to provide detailed manufacturing procedures at is requested.

Drug Product:
The CMC requirements for the drug product in this application are complete. The accuracy parameter for AGN 190168, BHA, and BHT in the final formulation has been adequately addressed. We recommend that the method validation package of the original NDA submission along with amendment BC (modification of method AP-L217 to AP-L217-2E), letter date November 14, 1996, be submitted to the appropriate field laboratory for evaluation.

Draft labeling for the physician sample size (3.5g; strength 0.05% & 0.1%), the aluminum collapsible tubes (30 g and 100 g sizes for strengths of 0.05% & 0.1%) and the respective outer cartons of TAZORAC, the proposed tradename for tazarotene gel, is adequate. Copies of labeling for 30 g aluminum tube and its carton are shown below:

A review of stability tables for the registration stability batches (i.e., primary stability lots) with data reported up to the 24 month time interval and stability tables for the validation stability batches with data reported up to the 12 month time interval, show that all batches remain within specification. A 24 month expiration period is acceptable.

CONCLUSIONS & RECOMMENDATIONS:
From a chemistry viewpoint of the CMC section presented, an approval of this application is recommended.

cc:
Orig. NDA 20-600
HFD-820/S.A. Gilman/December 03, 1996/Date Revised: 16 December 1996
HFD-541/CSO/F.Cross
HFD-540/Medical/H.Ko
HFD-540/Pharmacology/H.Sheevers
HFD-830/N.Rejali
HFD-830/CHEM SUPERVISOR/W. DeCamp

S.A.GILMAN, REVIEW CHEMIST
filename: 20600r3.lwp

R/D INIT BY: 12/18/96

12/19/96

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CHEMIST'S NOTES Gilman NDA 20-600

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS (HFD-540)

MAR 17 1997

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-600 **CHEM. REVIEW#: 05** **REVIEW DATE: 17 March 1997**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AZ	17 Jan 97	21 Jan 97	03 Feb 97
Internal Field Inspection Report	01 Mar 96		

SUBMISSIONS PROVIDE FOR:
A phase IV commitment for drug substance scale-up procedures at Torcan and Cambridge manufacturing facilities.
Comments on EIR from field inspector Leman J. Cole

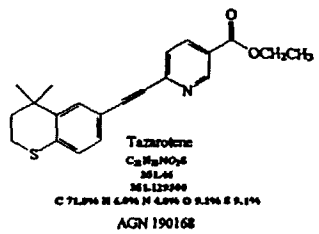
NAME & ADDRESS OF APPLICANT:

Allergan Inc.
P.O. Box 19534
2525 Dupont Drive
Irvine, CA 92713-9534

Trudy Rumbaugh, MD
Tom Walton
714 246 4292 fax 714 246 4272

DRUG PRODUCT NAME	
PROPRIETARY:	TAZARAC™
NONPROPRIETARY/USAN:	Tazarotene 0.05%/0.1% Topical Gel
CHEM ABSTRACT NUMBER	118292-40-3
CODE NAME/#:	AGN 190168
CHEM. TYPE/THER. CLASS	1s
PHARMACOL. CATEGORY/INDICATION:	topical treatment of plaque psoriasis and the topical treatment of acme vulgaris
DOSAGE FORM:	Topical Gel, nonsterile
STRENGTH(S):	0.1% or 0.05%
ROUTE OF ADMINISTRATION:	dermatologic
DISPENSED:	X Rx Otc

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynl]nicotinate



MAR 21 1997

CHEMIST'S NOTES Gilman NDA 20-600

SUPPORTING DOCUMENTS:
IND :
DMF
DMF
DMF

REMARKS/COMMENTS:
Inspection Status:

To date, all facilities, including the Waco facility, manufacturer of the drug product, meet inspection requirements.

Drug Substance:

The CMC requirements for the drug substance in this application are complete.
Allergan has agreed to provide manufacturing information on the new scaled up bulk drug substance as a phase IV commitment.
We suggest that details of the phase IV commitment be submitted to the Agency 30 days post approval of this NDA. The following information should be included:

Drug Product:

The CMC requirements for the drug product in this application are complete.

CONCLUSIONS & RECOMMENDATIONS:

From a chemistry viewpoint of the CMC section presented, an approval of this application is recommended.

cc:
Orig. NDA 20-600
HFD-820/S.A. Gilman/ March 17, 1997 /Date Revised: 17-March 1997
HFD-541/CSO/F.Cross
HFD-540/Medical/H.Ko
HFD-540/Pharmacology/H.Sheevers
HFD-830/CHEM SUPERVISOR/W. DeCamp

R/D INIT BY : 6/5/97

S.A.GILMAN, REVIEW CHEMIST
filename: 20600r5.lwp