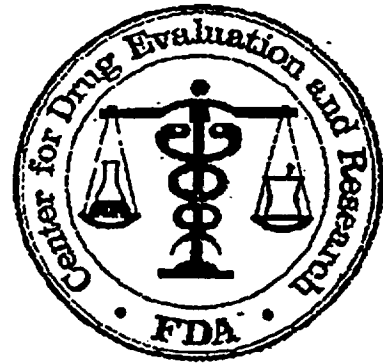


**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:  
21-056**

**CORRESPONDENCE**

# FAX



FOOD AND DRUG ADMINISTRATION  
DIVISION OF ONCOLOGY DRUG PRODUCTS  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857

---

To: Howard Holden, Ligand Pharm

From: Amy Baird, CSO

---

Fax: 858-550-1827

Fax: (301) 594-0498

---

Phone: 858-550-7600

Phone: (301) 594-5771

---

Pages, including cover sheet: 2

Date: 5-<sup>15</sup>~~10~~-00

---


Re: NDA 21-056 Targretin (bexarotene) gel 1%.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

## COMMENTS:

See the attached clinical comments. Please do not hesitate to call should you have any questions.

Thank you,

  
Amy Baird

cc: orig. NDA 21-056  
HFD-150 + Div File  
HFD-150 / Baird

1. From Study -25, please provide the CRF for patient #744.
2. Please indicate when in the protocol for Study -25 the intent-to-treat analysis plan for efficacy can be found.

---

APPROX THIS WAY  
OR ORIGINAL

# FAX



FOOD AND DRUG ADMINISTRATION  
DIVISION OF ONCOLOGY DRUG PRODUCTS  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857

---

To: Howard Holden, Ligand Pharm

From: Amy Baird, CSO

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Fax: 858-550-1827

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Phone: 858-550-7600

Phone: (301) 594-5771

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Pages, including cover sheet: 2

Date: 5-9-00

---

Re: NDA 21-056 Targretin (bexarotene) gel 1%.

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---

## COMMENTS:

See the attached clinical comments. Also, in regards to our facsimile of 5-8-00, question # 29, according to the medical officer, patient # 805 is correct. Please do not hesitate to call should you have any questions.

Thank you,

*/s/*

U  
Amy Baird

cc: Div. NDA 21-056  
HFD-150 / Div. File  
HFD-150 / Baird

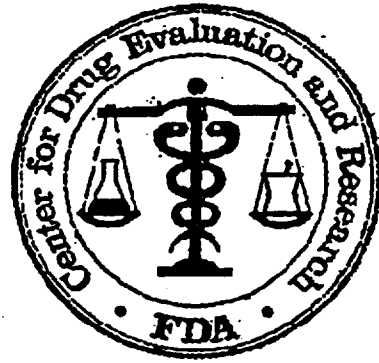
1. What are the prior qualifying therapies for patient # 702? Please provide the TCLT form for patient # 702.
2. For the following patients and agents, please provide the dates of administration (see below).

Patient	Agent	Dates of Administration
#704	Methotrexate	
#1761	Methotrexate	
	Nitrogen Mustard	
#694	Nitrogen Mustard	
#695	Nitrogen Mustard	
	PUVA	
#703	PUVA	
#743	UVB/UVA	
#871	Nitrogen Mustard	
	EBT	
#1711	PUVA	

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# FAX

FOOD AND DRUG ADMINISTRATION  
DIVISION OF ONCOLOGY DRUG PRODUCTS  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857



---

To: Howard Holden, Ligand Pharm

From: Amy Baird, CSO

---

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Phone: (301) 594-5771

---

Pages, including cover sheet: 2

Date: 5-8-00

---

**Re: NDA 21-056 Targretin (bexarotene) gel 1%.**

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## COMMENTS:

See the attached clinical comments. Please do not hesitate to call should you have any questions.

Thank you,

*AS*  
0

Amy Baird

APPEARS THIS WAY  
ON ORIGINAL

CC: Dig. NDA 21056  
HFD-150-1-Div. File  
HFD 130 / Baird

28. In the ACCESS database of Study -15, file DEMOG, there are 4 extra patients. Please explain.

29. For Study -25, it appears that the required histopathology reports and/or reviews have not been submitted for the cases below. Please clarify

PID	COMMENT
601	no reference review for pathology
832	Either the local or the reference pathology report is missing; the reading by Dr. Chalet is not conclusive.
1661	Either a reference pathology review is needed or a translation of the 2nd report is required.
1662	Either a reference pathology review is needed or a translation of the 2nd report is required.
1622	No pathology reports were submitted
1721	Either a reference pathology review is needed or a translation of the 2nd report is required
631	No reports for biopsies performed at baseline were submitted as required by the protocol.
805	No reports for biopsies performed at baseline were submitted as required by the protocol; the pathology reports submitted appear to be consultation reviews of slides from 1995; the ACCESS database [IC] indicates that the biopsy is from 11/97. Please clarify

30. In Study -25, biopsies were performed beyond the 30 day limit for the following cases: 622, 671, 701, 732, 741, and 851. This time limit was required by the protocol for a current biopsy at study entry. Please clarify.

31. From Study -25, please provide case report form CAPL logs for patients #622, #721, #871, and #1711.

32. From Study -25, please provide case report form CAPL logs & CMTL logs for #702.

33. Please provide photographs (indicators and globals) for patient #671 for weeks 8 & 12.

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ON ORIGINAL

# FAX



**FOOD AND DRUG ADMINISTRATION  
DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857

---

**To:** Howard Holden, Ligand Pharm

**From:** Amy Baird, CSO

---

**Fax:** 858-550-1827

**Fax:** (301) 594-0498

---

**Phone:** 858-550-7600

**Phone:** (301) 594-5771

---

**Pages, including cover sheet:** 2

**Date:** 4-11-00

---

**Re: NDA 21-056 Targretin (bexarotene) gel 1%.**

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**COMMENTS:**

See the attached clinical comments. Please do not hesitate to call should you have any questions.

Thank you,

^  
*ISI*  
Amy Baird

cc: Div. NDA 21-056  
HFD-150 / Div. File  
HFD-150 / Chapman

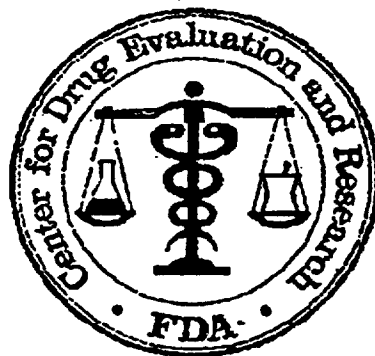


1. Please provide the monitoring report for site 14.
2. Please provide the case report forms for patient # 601.
3. In Ms. Shashlo's e-mail dated 3-21-00, statement is made that no patients were entered at site #54. However, in volume 1 of the NDA, Financial Disclosure, Dr. Elmets is included on the list of investigators who enrolled patients to Study -25. Please clarify.
4. Also, in the Financial Disclosure certification, there are at least 70 MD-investigators listed "who enrolled patients", who are not recorded in your list of investigators for the Study in volume 29 of the NDA, and who cannot be linked to any of the patients entered on the study. Please clarify.

---

APPEARS THIS WAY  
ON ORIGINAL

# FAX



**FOOD AND DRUG ADMINISTRATION  
DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857

---

**To:** Howard Holden, Ligand Pharm

**From:** Amy Chapman, CSO

---

**Fax:** 858-550-1827

**Fax:** (301) 594-0498

---

**Phone:** 858-550-7600

**Phone:** (301) 594-5771

---

**Pages, including cover sheet:** -2

**Date:** 3-3-00

---

**Re: NDA 21-056 Targretin (bexarotene) gel 1%.**

---

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---

**COMMENTS:**

See the attached requests for clinical information. Please do not hesitate to call should you have any questions.

Thank you,

*AS*

Amy Chapman

CC: Orig. NDA 21-056  
HFD-150 / Div. FK  
HFD-150 / Chapman

1. For Study -25, please provide the detailed instructions for the photographs given to the investigators or identify where in the NDA can the information be found.
2. For Study -25, please clarify whether patient #622's best response to PUVA was stable disease?
3. Further query on patient #811 as a result of Ligand response dated 2-10-00 is indicated. The information in the CRF, with regard to this patient's lymph node status, does not appear to be consistent. In the protocol, section 7.4.5, the following statement is made, "Patients who have Stage IIA CTCL have clinically abnormal lymph nodes (1cm diameter) that will be evaluated at baseline (Day 1), every four weeks during treatment and again at follow-up". Patient #811 appears to have been staged as IIA, meaning abnormal lymph nodes (greater than or equal to 1cm diameter). Where is the follow-up of lymph nodes for this patient as indicated in the protocol?
4. In Study -25, patient #732 appears to have CTCL tumors at baseline. The baseline tumors were not recorded in the tumor assessment log and were not followed. Please clarify.
5. In Study -25, according to the protocol, monitoring visits took place at study sites throughout the study. Although the Investigator final written report may not be available at this time, please provide the monitoring reports for Heald, Martin, and Olsen. Also, from Study -11, please provide the monitoring reports.
6. In Study -25, patient #641, a decrease in performance status was the basis for intolerance to topical nitrogen mustard. What was the nadir of the performance status at the time of the intolerance?

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ON ORIGINAL



Redacted 1

pages of trade

secret and/or

confidential

commercial

information

# FAX

FOOD AND DRUG ADMINISTRATION  
DIVISION OF ONCOLOGY DRUG PRODUCTS  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857



---

To: Howard Holden, Ligand Pharm

From: Amy Chapman, CSO

---

Fax: 858-550-1827

Fax: (301) 594-0498

---

Phone: 858-550-7600

Phone: (301) 594-5771

---

Pages, including cover sheet: 2

Date: 2-1-00

---

Re: NDA 21-056 Targretin (bexarotene) gel 1%.

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**COMMENTS:**

See the attached requests for chemistry information. Please do not hesitate to call should you have any questions.

Thank you,

*/s/*  
Amy Chapman

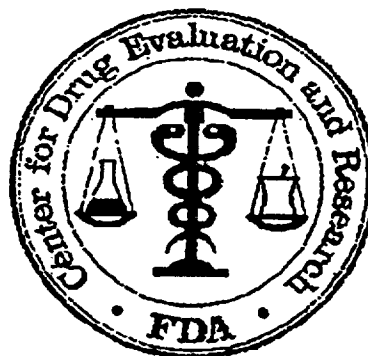
cc: Orig. NDA 21-056  
HFD-150 / Dw. File  
HFD-150 / Chapman

1. CMC information on drug substance, bexarotene, provided in NDA 21-056 should be updated according to the approved information on the drug substance in NDA 21-055 (e.g., specifications, etc.).
2. It is stated that the \_\_\_\_\_ will be discontinued. Please submit a letter stating the expected discontinuation data for \_\_\_\_\_. The letter should be written by the \_\_\_\_\_. In addition, please provide an estimate of the remaining projected months for the commercial supply for Targretin® gel using the \_\_\_\_\_ based on the discontinuation date stated in the letter.
3. \_\_\_\_\_
4. Information submitted on pages 234 and 236 (volume 2 of 133) are not legible. Please resubmit.
5. Executed batch records for all stability/clinical batches need to be submitted.

ON ORIGINAL

ON ORIGINAL

# FAX



**FOOD AND DRUG ADMINISTRATION**  
**DIVISION OF ONCOLOGY DRUG PRODUCTS**  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857

---

**To:** Howard Holden, Ligand Pharm

**From:** Amy Chapman, CSO

---

**Fax:** 858-550-1827

**Fax:** (301) 594-0498

---

**Phone:** 858-550-7600

**Phone:** (301) 594-5771

---

**Pages, including cover sheet:** 2

**Date:** 2-1-00

---

**Re: NDA 21-056 Targretin (bexarotene) gel 1%.**

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**COMMENTS:**

See the attached requests for clinical information. Please do not hesitate to call should you have any questions.

Thank you,

^ /S/

0  
Amy Chapman

cc: Orig. NDA 21-056  
HFD-150 / Div. File  
HFD-150 / Chapman



1. In study -25, does patient #811 have clinically abnormal lymph nodes?
2. Study 25: a. According to the protocol, each patient's histopathology specimens were to be sent to a reference dermatopathologist. Where in the NDA are the results of all these evaluations? b. If this reference dermatopathologist concluded that the specimens were neither diagnostic or nor consistent with CTCL, the specimens were to be sent to a second reference dermatopathologist. Where in the NDA are the results of all these evaluations?
3. From study -25, please provide the Investigator final written reports for the following investigators: Heald, Martin and Olsen. Also, from study -11, please provide the Investigator final written report.
4. For study -25, where in the ACCESS database and/or in the NDA is the number of non-index lesions treated recorded?
5. For study -25, where in the ACCESS database and/or in the NDA is the number of new lesions from baseline recorded?
6. For study -25, please send on a disk the merged files CENTLABR/CENTLABH. The instructions sent in your 1-24-00 response were not satisfactory and the data is not usable.

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

NDA 21-056

Ligand Pharmaceuticals  
Attention: Howard T. Holden, Ph.D.  
Vice President, Regulatory Affairs and Compliance  
10275 Science Center Drive  
San Diego, California 92121-1117

FEB 1 2000

Dear Dr. Holden:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Targretin® (bexarotene) gel 1%

Therapeutic Classification: Priority (P)

Date of Application: December 8, 1999

Date of Receipt: December 9, 1999

Our Reference Number: NDA 21-056

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 6, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 9, 2000.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
Attention: Division Document Room HFD-150  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
Attention: Division Document Room HFD-150  
1451 Rockville Pike  
Rockville, Maryland 20852-1420

If you have any questions, call Amy Chapman, Project Manager, at (301) 594-5771.

Sincerely,

*TSI*  
*for 2-1-00*  
Dotti Pease  
Chief, Project Management Staff  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc:

Archival NDA 21-056  
HFD-150/Div. Files  
HFD-150/A.Chapman  
HFD-150/Johnson/White/GChen/Rothmann/Wood/Kim/Andrews/Kim/Rahman/GeneWilliams

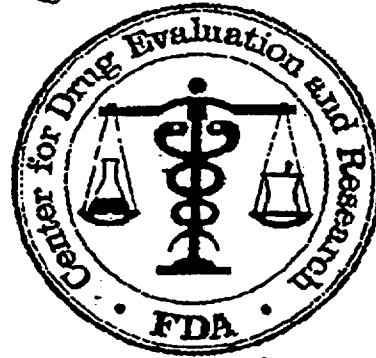
DISTRICT OFFICE

F/T by: Chapman-2-1-00

**ACKNOWLEDGEMENT (AC)**

# FAX

FOOD AND DRUG ADMINISTRATION  
DIVISION OF ONCOLOGY DRUG PRODUCTS  
Center for Drug Evaluation and Research, HFD-150  
5600 Fishers Lane, Rockville, MD 20857



---

To: Howard Holden, Ligand Pharm

From: Amy Chapman, CSO

---

Fax: 858-550-1827

Fax: (301) 594-0498

---

Phone: 858-550-7600

Phone: (301) 594-5771

---

Pages, including cover sheet: 2

Date: 1-18-00

---

Re: NDA 21-056 Targretin (bexarotene) gel 1%.

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---

## COMMENTS:

See the attached requests for clinical information. Please do not hesitate to call should you have any questions.

Thank you,

/S/

U  
Amy Chapman

cc: Orig. NDA 21-056  
HFD-150 / Div. File  
HFD-150 / Chapman

1. From Study 25, the following appear to be missing from the ACCESS database:  
  
CENTLABR: PID and visit columns  
LNBR: no data  
SAE\_CASE: no data  
SAECASE: no data
2. From Study 04, the following appear to be missing from the ACCESS database:  
  
HISTORY: no data
3. From Study 11, the following appear to be missing from the ACCESS database:  
  
No data in: ADDIT, CD, CONTIN, DEATHS, DEO, KARNOFSK, KSHAGENT, KSHDIS, LOCATION, MEASUR, RANDOM, RESP, TERM, UNSCHED
4. From Study 12, the following appear to be missing from the ACCESS database:  
  
No data in: DEATH, SERAE, T6912
5. Where is the annotated CRF's for Study 04 (both electronically and hard copy)?
6. Where is the financial disclosure documentation for Studies 04, 11, and 12?
7. At the advisory committee open hearing, prior to the Targretin Capsules presentation, Ms. Nancy Borcharding made a presentation. Please provide her patient identification numbers from the targretin gel and targretin capsules studies she participated in.

APPEARS THIS WAY  
ON ORIGINAL