

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21055

ADMINISTRATIVE DOCUMENTS

Re-Consult of #731 and #732(HFD-150)

PANRETIN and
TARGRETIN

9-cis-retinoic acid
LGD 1069

Kim
~~JUN 18 1998~~
Feb 18/98

The concern of the Committee in the original consult was over the use of the USAN stem syllable "retin" in the proposed trademarks. The Committee's concern has undergone revision due to a shift in our interpretation of 21CFR299.4. We used to object to any use of USAN stems since it made USAN's job more difficult to find unconflicting names for compounds in the same class. USAN specifically discourages this practice in their handbook and dictionary.

However, we have no statutory authority to implement the recommendations of a non-regulatory program (that is, the USAN council). Therefore, we encourage sponsors' to respect the USAN council's recommendation to keep USAN stems out of trademarks, but will object to the use of USAN stems in a trademark only when they are false, misleading, or present a health or safety concern.

Therefore, we are no longer in opposition to PANRETIN and TARGRETIN on the basis of their USAN stem inclusion. However, PANRETIN is too similar to the International Nonproprietary Name of pelretin listed in the USAN dictionary. But, we also have no indication that pelretin is under development in the U.S. It may be an INN for a compound that didn't work out or it may be in development abroad. If the division is concerned about pelretin, please ask Ligand to determine the status of the compound and submit documentation that a conflict will not occur.

Also, even though we find TARGRETIN acceptable, we have not seen the labeling and are concerned that the mechanism may be listed as unknown. We see it as misleading if the name indicates the compound "targets retinoid receptors" but the labeling says the mechanism is unknown.

Overall, we find the two proposed proprietary names acceptable with some concerns as listed.

6/18/98, Chair
CDER Labeling and Nomenclature Committee

NDA 21-055 CMC Preliminary Review for 45 Day Fileability Meeting:

REVIEWER: Sung K. Kim, Ph.D.
DOCUMENT DATE: June 22, 1999

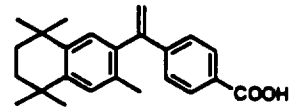
REVIEW DATE: August 3, 1999
CDER DATE: June 23, 1999

AUG - 3 1999

NAME AND ADDRESS OF APPLICANT: Ligand Pharmaceuticals Inc.
10275 Science Center Drive
San Diego, CA 92121-1117

DRUG PRODUCT NAME:

Proprietary: Targretin® Soft Gelatin Capsule
Nonproprietary/USAN: Bexarotene
Code Name and Number: LGD1069, LG100069
CAS: 153559-49-0
Chemical Name/Structure: 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)vinyl]benzenecarboxylic acid



DOSAGE FORM: Soft Gelatin Capsule
STRENGTH: 75mg/Capsule
ROUTE OF ADMINISTRATION: Oral
PHARMACOL. CATEGORY/INDICATION: Cutaneous T-cell lymphoma (CTCL)

RELATED IND: []

COMMENTS:

EERs for []

Under IND [] with a request from Ligand, Targretin was consulted to the Labeling Committee on 1/16/97. Targretin was initially denied in the Labeling Committee's recommendation dated 3/4/97 and subsequently Targretin was found to be acceptable as a trademark (recommended by the Labeling Committee on 2/18/98).

CONCLUSION & RECOMMENDATIONS:

The initial preliminary review is completed
issues, the submission is fileable.

With respect to CMC

 |S|
Review Chemist, HFD-150

cc:
Original NDA # 21-055
HFD-150/Div. File
HFD-150/AChapman
HFD-150/SKim
HFD-150/RWood
R/D Init. by: []

 |S|
8-3-99

13. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG
IN ACCORDANCE WITH 21 U.S.C. §355(b)

<u>Owner</u>	<u>Patent No.</u>	<u>Expiration Date</u>	<u>Type</u>
Ligand Pharmaceuticals Inc.	5,780,676	July 14, 20015	Drug Product Method of Use
SRI International The Burnham Institute (Exclusively Licensed to Ligand Pharmaceuticals Inc.)	5,466,861	Nov. 14, 2012	Drug Drug Product

In the opinion of and to the best knowledge of the undersigned representative of Ligand Pharmaceuticals Incorporated, the patents listed above cover the formulation, composition, and/or method of use of bexarotene. This product is the subject of this application for which approval is being sought.

By William L. Respass
William L. Respass

Title: Senior Vice President, General
Counsel, Government Affairs

Date: 05/17/99

14. PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG IN ACCORDANCE WITH 21 U.S.C. §355(b)(2) OR §355 (i)(2)(A)

No certification is necessary because this application is for a drug for which investigations described in 21 U.S.C. §355(b)(1)(A) and relied upon by the applicant for approval of this application *were* conducted by or for the applicant, and this application is not an abbreviated application for a new drug.

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 21-055 SUPPL # _____

Trade Name Dargentin capsules Generic Name Dexarotone

Applicant Name Ligand Pharmaceuticals HFD # 150

Approval Date If Known 12-29-99

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES /X/ NO / /

b) Is it an effectiveness supplement? _____
YES / / NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")
YES /X/ NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES / ___ / ! NO / ___ / Explain: _____
! _____

Investigation #2 !

IND # _____ YES / ___ / ! NO / ___ / Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES / ___ / Explain _____ ! NO / ___ / Explain _____
! _____

Investigation #2 !

YES / ___ / Explain _____ ! NO / ___ / Explain _____
! _____
! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/

NO /__/

If yes, explain: _____

ISI 12-20-99

Signature Date

Title: Consumer Safety Officer

ISI

12-23-99

Signature of Office/ Date
Division Director

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>21055</u>	Trade Name:	<u>TARGRETIN (BEXAROTENE) 75MG CAPS</u>
Supplement Number:		Generic Name:	<u>BEXAROTENE</u>
Supplement Type:		Dosage Form:	<u>CAP</u>
Regulatory Action:	<u>AP</u>	Proposed Indication:	<u>Targretin (bexarotene) capsules are indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Does Not Apply
Formulation Status
Studies Needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Targretin capsules received an orphan designation, therefore, pediatric studies are not applicable.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, AMY CHAPMAN

Signature js/

12-29-99
Date

DEBARMENT CERTIFICATION

In compliance with the Generic Drug Enforcement Act of 1992, Section 306(k)(1) of the act (21 U.S.C. 335a(k)(1)), we, Ligand Pharmaceuticals Inc., state the following with respect to this new drug application:

Ligand Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Howard T. Holden

Howard T. Holden, Ph.D.
Vice President
Regulatory Affairs and Compliance
Ligand Pharmaceuticals Inc.
San Diego, California

10 June 1999
Date

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

*

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Gian Aliprandi	TITLE Vice President, Senior Corporate Controller
FIRM/ORGANIZATION Ligand Pharmaceuticals Inc.	
SIGNATURE <i>G. Aliprandi</i>	DATE 6/10/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address in the right.

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

* With respect to the equity ownership certification, please refer to Attachments A and B.

Memorandum

Date: 22 December 1999

From: David E. Morse, Ph.D.
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III
Acting Asc. Director (Pharm./Tox.), Office of Review Management

To: Robert Temple, M.D.
Director, Office of Drug Evaluation I

Cc: Richard Pazdur, M.D., Dir., DODP (HFD-150)
Paul Andrews, Ph.D., TL Pharm./Tox., DODP (HFD-150)
Chang H. Ahn, Ph.D., Pharm./Tox., DODP (HFD-150)

Subject: NDA 21-055
TARGRETIN® Capsules (Bexarotene)
Review of Pharm./Tox. Information and Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Review of NDA 21-055, dated 10 Dec. 1999, written by Chang H. Ahn, Ph.D.
2. TL Memorandum for NDA 21-055, dated 17 Dec. 1999, written by Paul Andrews, Ph.D.
3. NDA 21-055 Approval Package with Draft Product Labeling (dated 21 Dec. 1999).

II. Background

The sponsor (Ligand Pharmaceuticals) is seeking approval of TARGRETIN® for the treatment of the cutaneous manifestations of cutaneous T-cell lymphoma (CTCL). CTCL is frequently a slowly progressive or "indolent" disease, such that patients may receive daily TARGRETIN® for multiple years.

III. Comments and Conclusions

1. A review of the action package for NDA 21-055, TARGRETIN®, suggests that the product has been adequately evaluated in multiple non-clinical safety studies (up to six months repeat-dose administration in rats and dogs) for approval for extended use in the treatment of the cutaneous lesions associated with CTCL (in patients who have failed to respond to one or more other treatments for CTCL). The proposed product labeling adequately reflects the toxicological findings for bexarotene regarding carcinogenesis, mutagenesis, fertility, pregnancy and overdose.
2. Specific comments related to the product label follow:
 - It is recommended that the "Boxed Warning" for TARGRETIN® include statements pertaining to: a) the use of contraceptive methods before, during and for 1 month following the use of TARGRETIN®, and b) the need for periodic laboratory monitoring of pregnancy status for women of reproductive potential. Inclusion of the recommended statements within the "Boxed Warning" for TARGRETIN® will provide consistency of labeling with two additional systemically administered

retinoids (i.e., ACCUTANE® for the treatment of severe nodular acne, and VESANOID® for the treatment of acute promyelocytic leukemia).

- It is recommended that TARGRETIN® be designated Pregnancy Category "X". Designation of TARGRETIN® as Pregnancy Category "X" may be based on: a) retinoid analogues having previously demonstrated significant teratogenic potential in humans, and b) use of the drug during pregnancy being potentially not necessary for the benefit and/or maintenance of maternal health. Designation of TARGRETIN® as Pregnancy Category "X" would then be consistent with the designation for ACCUTANE®, which is also indicated for the treatment of a not imminently life-threatening condition.
- Under the heading of "Warnings," it is suggested that the product label include a statement that a significant dose related incidence (up to 80%) of lens opacities and cataracts was seen in multiple species (rat and dog) treated with bexarotene for 6 months.
- It is suggested that a description of the alterations in coagulation responses (PT and APTT) as demonstrated in multiple animal species after high dose short-term (3-4 doses) bexarotene administration be included in the "Overdosage" section of the product label.

IV. Summary

A review of the action package for NDA 21-055, TARGRETIN®, suggests that the product has been adequately evaluated in multiple non-clinical safety studies for approval. The proposed product label, with possible revision as suggested in the preceding section of this memorandum, adequately reflects the safety data for this product.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

Date: December 17, 1999

From: Paul A. Andrews, Ph.D.
Pharmacology Team Leader, HFD-150

P.A.A. 12/17/99

To: Files for NDA# 21-055, Targretin®

Re: Approvability for Pharmacology and Toxicology

Targretin (bexarotene) is a retinoid analog that selectively binds the RXR receptor at concentrations much lower than those that affect the RAR receptor. Ligand Pharmaceuticals seeks approval of Targretin for treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL). CTCL is an indolent disease and patients might receive daily Targretin for many years. The extensive pharmacology and toxicology studies submitted to this NDA for Targretin have been thoroughly and thoughtfully reviewed by Dr. Chang Ahn who has considered them adequate to support approval for the intended indication. I concur with his recommendation. The non-clinical studies in the NDA covered the core expectations for a chronically administered drug in HFD-150. The package included single dose, 28 day, and 6 month studies in rats and single dose, 91 day, and 6 month studies in dogs. The 6 month study in dogs was accepted in lieu of 9 months since CTCL can be a life threatening disease, the retinoids are a well studied class, and clinical experience with chronic dosing adequately demonstrated the safety in humans. Carcinogenicity studies are not necessary to support approval for the intended indication and were not submitted. A detailed labeling review was provided by Dr. Ahn in his original review and I agree with the requested changes. I wish to highlight the following from his review:

- Toxicology studies in both species showed that chronic administration of bexarotene causes lens opacities and cataracts. This has not yet been demonstrated clinically, but a precaution should be noted in the label.
- A panel of genetic toxicity studies demonstrated no potential for genetic toxicity. Results from the chromosome aberration assay in CHO cells were not included in the label because the highest concentration used in the absence of S9 activation was not considered adequate according to ICH criteria.
- *In vitro* testing indicated that bexarotene has the potential for photosensitization and this precaution is presented in the label.
- A single ICH Stage C-D developmental toxicity study (in rats) was accepted to support the NDA because the indication is for patients with cancer and the study confirmed the expected developmental toxicity of a retinoid. Of particular note, Dr. Ahn used the Draft Pregnancy Risk Integration Guidance to assess the concern for human reproductive and developmental toxicity from Targretin (pp. 24-25 of review). His analysis indicates significant concern for humans for the endpoints of developmental mortality and dysmorphogenesis (net adjustments +6).
- Good pharmacokinetic data was provided, including from pregnant rats, and comparisons of preclinical doses to human doses in the label are made based on AUC ratios. Doses in acute studies, however, were well above the range where the pharmacokinetics were known to be linear, so dose comparisons in the OVERDOSAGE section were based on mg/m^2 .

Recommendations: The pharmacology and toxicology data supports approval of this NDA. There are no outstanding issues.

Original NDA
cc: Div File
HFD-150

/CAhn
/AChapman
/PAndrews

Div. Files

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 29, 1999

FROM: Robert L. Justice, M.D. **IS**
Acting Director
Division of Oncology Drug Products, HFD-150

TO: Director, Division of Scientific
Investigations, HFD-340

SUBJECT: Request for Clinical Inspections for NDA 21-055
Targretin (bexarotene) capsules, 75mg
PDUFA goal date is December 20, 1999
Indication: Treatment of patients with all clinical stages (IA-IVB) of cutaneous
T-cell lymphoma (CTCL) in the following categories: patients with early stage
CTCL who have not tolerated other therapies, patients with refractory or
persistant early stage CTCL, and patients with refractory advanced stage CTCL.

We have identified the attached studies as being pivotal to the approval of this application.
Attached is the list of studies with their sites.

We request that the inspections be performed and the Inspection Summary Results be provided
by November 5, 1999. We intend to make a regulatory decision on this application by
November 20, 1999.

Should you require any additional information please contact:

Angeline K. Shashlo
Director, U.S. Regulatory Affairs and Compliance
Phone: 858-550-7600
Fax: 858-550-1827

The reviewing medical officer for this application is Wole Odujinrin at 594-5757.

The project manager for this application is Amy Chapman at 594-5771.

The division's action goal date is November 20, 1999.