GRADING OF LOCAL DERMAL IRRITATION

GRADE	DEFINING CLINICAL SIGNS
0 = No Reaction	None
1 = Mild	Definite pink to red coloration
2 = Moderate	Increased redness, possible edema
3 = Severe	Very red, with edema, with or without vesiculation
4 = Very Severe	Deep red, swelling and edema with or without signs of bullae formation and necrosis

Thirty-two patients or 64% of the patients were listed in ACCESS file TLT as having treatment-limiting toxicity. There were 94 events (#events:#pts: 1:9; 2:10; 3:3; 4:3; 5:1; 6:5; 8:1). Treatment-limiting toxicities were presumed limited to the skin; 22 event entries were blank (examination of the photographs was not helpful).

The Reasons for Discontinuation of Therapy

The primary reasons for termination from study included: progressive disease (5 pts), stable disease (5 pts), partial response (4 pts), clinical complete response (1 pt), withdrew consent (5 pts), lost to follow-up (1 pt), and adverse drug reaction (7 pts) (5 pts were terminated with adverse event as an additional reason for termination—3 of them were different than the primary ones).

The patients who withdrew consent were examined closer. Except for two patients, there was no further information suggestive of a reason a patient would withdraw consent in the adverse drug reaction and COMMENTS files in the ACCESS database. With regard to the two patients, one had died (2 months earlier patient had grade 3 elevations in LDH; alk phos, SGOT, and SGPT also elevated), and the other had grade 3 generalized rash and worsening of disease outside of index lesions.

All the patients who were terminated from the study because of an adverse event should have been listed in treatment-limiting toxicities and the grade of the toxicity should have been 3 or greater. The table below shows the discordance between termination due to an ADR and TLTL/grade of adverse event.

TERMINATED BECAUSE OF AN ADR PATIENT #	AE GRADE	ENTERED AS TLTL
631	2	YES
701	3	NO
704	2	NO
802	1	NO
891	3	YES
1621	1	NO

TERMINATED BECAUSE OF AN ADR PATIENT #	AE GRADE	ENTERED AS TLTL
1622	2	NO

SUPPORTIVE DATA

Targretin Capsules

The pivotal trials for the approved oral targretin capsules will contribute to the efficacy data of targretin. Targretin capsules were evaluted in 152 patients with advanced and early stage CTCL in two multicenter, open-label, historically-controlled clinical studies conducted in the US, Canada, Europe, and Australia.

Targretin capsules, a marketed product, were studied in a similar population as the patients in Study –25 for targretin gel. In the targretin capsules studies, patients with CTCL had the following characteristics with respect to prior therapy: intolerant, refractory, or reach a response plateau of 6 month. Patients were required to have at least two qualifying prior therapies (median 3.5 [range 2 to 12] [systemic, radiation, and/or topical]).

There were 90 patients with advanced CTCL and 62 CTCL patients with early stage disease. For each patients up to 5 index lesions were evaluated by the composite assessment response criteria.

Patients were treated with targretin capsules 300 mg/m2 PO QD.

The Efficacy Results

In the 62 patients with early stage CTCL, based on the CA assessment, the CCR was 1.6% (1/62); the partial response rate was 30% (19/62). The rate of relapse was 30% (6/20) over a median duration of observation of 21 weeks.

Safety

The safety data from the targretin capsules, a product with systemic activity, will not contribute directly to the safety data of targretin gel, a topical product. Below is a table with the most frequent toxicities in the targretin capsules studies.

ADVERSE EVENT WITH INCIDENCE ≥ 10%	300 MG/M2/DAY
Hyperlipidemia	79%
Hypercholesterolemia	32%
Hypothyroidism	29%
Headaches	30%
Asthenia	20%
Rash	17%

ADVERSE EVENT WITH INCIDENCE ≥ 10%	300 MG/M2/DAY
Dry skin	11%
Exfoliative dermatitis	10%
Leukopenia	17%

Moderate severe and severe toxicities included: headache (3.6% mod. sev.; 0% sev.), hyperlipidemia (19%; 7%); leukopenia (4%; 0%).

Phase I-II Program with Targretin Gel

Problems with the Phase I – II Program

The objective of the program initiated in 1994 was to gain experience with the newly-formulated topical Targretin® (bexarotene) gel in the treatment of cutaneous T-cell lymphoma, and to assess its activity and safety in this patient population when administered in different concentrations and at different frequencies of application. In order to eliminate the possibility of the vehicle's activity being interpreted as the activity of Targretin® gel, the protocols were amended in 1996 to include a provision (Option B) for new patients that at least two lesions should be treated with vehicle gel to provide comparative data with Targretin® gel. The frequency of application of the vehicle gel followed the frequency of application of the Targretin® gel. All the patients enrolled in Version 4 of the protocols were to have at least two lesions treated by vehicle gel.

The objectives of this Phase I-II program consisting of three similar studies were to evaluate the safety, dose tolerance, and potential efficacy of topical Targretin® gel (0.1%, 0.5%, and 1%) and later, by protocol amendment, the effect of vehicle gel in the treatment of early stage cutaneous T-cell lymphoma (mycosis fungoides).

The program was composed of three independent studies done at three different institutions. The regulatory background is below.

- Ligand had a [redacted] meeting with the Division of Oncology Drug Products on July 21, 1999; the purpose of the meeting was to discuss the targretin® gel in CTCL NDA. Statistical plans for the Phase III and Phase I-II clinical trial program were submitted to FDA in the pre-meeting package, along with selected data tables. At that meeting, the FDA expressed reservations about its previous agreement with Ligand that the Phase III study combined with the [redacted] clinical trial program (comprised of three nearly-identical single-center protocols) were sufficient to support an NDA. The reservations included the following:

a. The Phase 1-2 protocols were not designed as pivotal trials but as early "pilot" studies at the individual sites.

b. The pooling of data from the three protocols would not be desirable because of the differences among the protocols and changes in the protocols over time (e.g., treatment of all lesions, index lesions, non-index lesions, active treatment vs. vehicle treatment of 2 lesions, original treatment plan, new treatment plan)

c. There was no specific statistical plan in the original protocols. The plan that was included in the protocols changed over time. Originally, the principle evaluation visit for interpreting data was week 12; the current statistical proposal plans to use week 16.

d. Only of 18 of the 67 patients from the Phase 1-2 database were treated at the proposed dose of targretin gel; the response rate by PGA was 44%. Forty-seven patients were treated at a lower dose (1/10th the proposed dose); the response rate by PGA was 68%. If this data set is valid, one has to re-visit the rationale for choosing the proposed dose of targretin gel.

The above were not new issues. These were similar issues that the FDA discussed with Ligand prior to submission of the Panretin gel NDA. The FDA's opinion on the pooling of Phase 1-2 studies to comprise a second pivotal trial was made clear to Ligand in the past.

The Agency preferred a second, confirmatory, randomized Phase 3 trial. After further discussion, the FDA agreed to the data from the targretin capsules to contribute to the efficacy of targretin gel.

There were other review-related problems with the Phase 1-2 Program.

- The Physician's Global Assessment was the response criteria used for the primary endpoint. Only photographs of the index lesions were taken; the protocols did not provide for global photographs. Thus, the claimed PGA responses are not assessable by the FDA.

- The composite assessment was not a response criteria used in this program. In the Phase 1 – 2 Program, investigators did evaluate scaling, erythema, and plaque elevation; percent body surface area of involvement with CTCL was also collected. In Study –25, the Composite Assessment included hypo/hyperpigmentation and index lesion area. The response data from the Phase 1 – 2 Program was not evaluated in the same manner as Study –25 and cannot be used to contribute to the efficacy data from Study –25.

- Up to a total of 195 patients with early stage CTCL were planned to be treated with either Targretin® gel only or both Targretin® gel and vehicle gel (applied on separate skin lesions). Up to 65 patients in each protocol could be enrolled; a combined total

of only 67 patients were enrolled and analyzed in all 3 protocols. There were 33, 13 and 21 patients accrued to Protocols L1069T-11, L1069T-12, and L1069-94-04T.

- According to Ligand , response to vehicle was not interpretable because there were fewer than 15 of 67 patients with vehicle gel-treated lesions at any study visit after baseline. This is important because the vehicle gel response rate would have confirmed or refuted Ligand's claim in Study –25 that the spontaneous response rate in CTCL is less than 5%.

- In Study –25, there were only 3 Stage II patients and no Stage II responders. In the Phase 1 – 2 Program there were 6 Stage II patients and two Stage II PGA responders--#622 & #627. These two patients do not provided sufficient evidence: 1. there were no global photographs; 2 there was no evaluation by Composite Assessment; 3. for #622, although the prior therapies included IM steroids, topical steroids, PUVA, UVB, local irradiation, there was no indication of intolerance or refractoriness; 4. For #627, there were no prior therapies. The Phase 1 – 2 Program does not support the proposed label indication for CTCL Stage IIA patients who have not tolerated other therapies or who have refractory or persistent disease.

- The same problems with poor quality data in Study –25 was also the case for the Phase 1 – 2 Program. The table below illustrates the protocol deviations.

Protocol Deviations by Protocol and Category of Deviation

Category of Deviation[1]	L1069T-11 (N=33) n (%)[2]	L1069T-12 (N=13) n (%)[2]	L1069-94-04T (N=21) n (%)[2]	Total (N=67) n (%)[2]
Total Number of Deviations[3]	17	3	22	42
Total Number of Patients with at Least One Deviation	16 (48)	3 (23)	21 (100)	40 (60)
Deviation From Inclusion Criteria	0	0	2 (10)	2 (3)
Deviation From Exclusion Criteria	1 (3)	0	0	1 (1)
Received Prohibited Drug/Therapy	16 (48)	3 (23)	20 (95)	39 (58)

[1] Patients are counted only once in each category, even if the patient had multiple deviations in each given category.

[2] Percentage of total number with a least one deviation.

[3] Patients may contribute multiple deviations in any given category and deviations from multiple categories.

The most common category of protocol deviation was use of a prohibited drug or therapy. A total of 58% of patients (39/67) had at least one deviation in this category; 48% (16/33), 23% (3/13), and 95% (20/21) of patients in Centers L1069T-11, L1069T-12, and L1069-94-04T, respectively.

The narrative that follows is Ligand's analysis of the protocol deviations (page 75 of Final Report).

"There were 14 patients who had taken corticosteroid preparations during the study period. Most of the medications administered were topical steroids, and

eight of the 14 patients started their first dose after Day 150. For the remaining six patients, four had incomplete data (Patients 304, 312, 313 and 319 from Study L1069-94-04T). One patient (607 from Center L1069T-11) was on a tapering dose of oral steroid (Day 79 to Day 119), and one patient (601 from Study L1069T-12) was on two 5-day courses of oral steroid (Days 46 to 50 & Days 103 to 107). Both the patients were prescribed steroids for indications other than CTCL. For these six patients, there was a possibility that these prohibited medications might have affected the response evaluations. However, since only two of the patients were responders, the response rate or the efficacy endpoints would not change significantly whether the data were included or not. There were two patients who received systemic anti-CTCL therapy (Patients 607 and 614 from Center L1069T-11) during the study period, starting on Days 91 and 95, respectively. One patient was already included in the violation group above for oral steroid use; and the other (Patient 614) had a response status of Stable Disease throughout the course of the study.

Other categories of protocol deviations included deviation from inclusion criteria or exclusion criteria. There were two patients (3%, 2/67), both enrolled in Protocol L1069-94-04T, with deviations from inclusion criteria: Patient 303 did not have histologically confirmed diagnosis of CTCL; and Patient 311 did not have clinically adequate function of all organ systems meeting the minimal criteria. One patient (Patient 633 in Study L1069T-11) had a deviation in the exclusion criteria category who had prohibited systemic therapy during the preceding four weeks before entering the study. Further information on the type of therapy she received was not collected."

The Patient Population Studied

Sixty-seven patients were enrolled in the three studies. Demographic data is shown below. The three populations were similar.

Baseline Demographic Variables by Study Center

Demographic Variables		L1069T-11 (N=33)	L1069T-12 (N=13)	L1069-94-04T (N=21)
Age (years)	Mean (SE)	58.5 (2.3)	57.7 (3.2)	56.8 (3.1)
	Median	61	58	63
	Range	(30, 87)	(34, 79)	(33, 77)
Gender	Male	17 (52%)	9 (69%)	11 (52%)
	Female	16 (48%)	4 (31%)	10 (48%)
Race	White	29 (88%)	11 (85%)	17 (81%)
	Black	4 (12%)	2 (15%)	2 (10%)
	Hispanic	0	0	2 (10%)

In contrast to the Study –25 about 22% of the patients (n = 15) enrolled received no prior anti-CTCL therapy. Most of the patients had received a topical/local therapy; about a

quarter of the patients had received prior systemic therapy. The data is shown in the table below.

Baseline Patient Characteristics: Prior Anti-CTCL Therapies by Dose Group

Prior Anti-CTCL Therapies[1]	Patients Who Reached 1% (N=58) n (%)[2]	All Patients (N=67) n (%)[2]
None	14 (24)	15 (22)
Any Systemic Agent/Therapy	15 (26)	18 (27)
Any Topical/Local Therapy	44 (76)	52 (78)
Both Systemic and Topical/Local Therapy	15 (26)	18 (27)

[1] Multiple courses of the same topical/local therapy for a patient are counted only once.
[2] Percent based on number of patients in each dose group.

Efficacy

Using the Physician's Global Assessment, the response for patients, who reached a targretin gel concentration of 1%, was 64%. No global photographs were submitted to the NDA for these three studies. The FDA is unable to confirm the responses with the information available. Ligand's response data is in the table below.

Physician's Global Assessment Response Rate by Dose Group

Response[1]	Patients Who Reached 1% (N=58) n (%)	All Patients (N=67) n (%)
CCR + PR[2] 95% CI[3]	37 (64) (50, 76)	42 (63) (50, 74)
CCR	14 (24)	14 (21)
PR	23 (40)	28 (42)
SD[4]	13 (22)	14 (21)
PD[5]	8 (14)	11 (16)

[1] Required confirmation over at least 4 study weeks.
[2] Includes Completely Cleared, Almost Cleared, and Marked Improvement.
[3] Confidence intervals obtained using Exact method.
[4] Includes the patients without any confirmed response or progression of disease.
[5] Includes condition worsened.

According the PGA, the earliest a response occurred was in 29 days; the latest for a response to occur was 601 days. The median time to onset of response was 141 days. The results are shown below.

Time to Onset of First and Best Response According to the Physician's Global Assessment by Dose Group

Response Category	Total Number of Patients	Number of Responding Patients		Time to Response (Days)[1,2,3]				
	N	n	%	Min	25th pctl	Median	75th pctl	Max
All Patients								
First Response	67	42	62.7	29	85	141	335	601
Best Response	67	42	62.7	29	92	183	390	1135
Patients Who Reached 1%								
First Response	58	37	63.8	29	80	141	335	390
Best Response	58	37	63.8	29	112	183	344	1135

[1] Time to response is defined as (Date of onset of response – Date of first dose of study medication) + 1 day.

[2] Median, 25th, and 75th percentiles are obtained from the Kaplan-Meier Method.

[3] Min and Max represent the range of time to response for those patients who responded.

Below is a table with the results of the Overall Severity Assessment of index lesion. Unlike the Composite Assessment used in Study –25, the Overall Severity Assessment used only scaling, erythema, and plaque elevation; index lesion area and hyper/hypopigmentation were not included in the criteria.

Clinically Significant Response According to Overall Severity by Center

	L1069T-11 (N=33) n (%)	L1069T-12 (N=13) n (%)	L1069-94-04T (N=21) n (%)
Number of Patients With Clinically Significant Response[1]	21 (64)	6 (46)	7 (33)
95% CI[2]	(45, 80)	(19, 75)	(15, 57)

[1] Response is defined as at least one-grade decrease in overall severity (the average of erythema, scaling, and plaque elevation) by Week 16 of treatment or earlier compared with Baseline.

(2) Confidence intervals obtained using Exact method.

Safety

Approximately 70% of the patients were exposed to targretin gel for 24 or more weeks as shown in the table below.

Duration of Drug Exposure by Treatment Group

Duration of Therapy	Patients Who Reached 1% (N=58)	All Patients (N=67)
1-3 Weeks	0	1 (1)
4-7 Weeks	1 (2)	2 (3)
8-11 Weeks	3 (5)	4 (6)
12-15 Weeks	5 (9)	5 (7)
16-23 Weeks	7 (12)	10 (15)
≥24 Weeks	42 (72)	45 (67)
Duration of Therapy (days)		
N	58	67
Mean (SE)	455.0 (48.14)	435.6 (45.15)
Median	325.5	315.0
Range	43, 1203	12, 1203

However, only 3% of patients reached the maximum concentration of 1% and the maximum frequency of QID. Most of the patients achieved at targretin gel 1% at a frequency of BID or TID.

Maximum Level and Last Level of Drug Exposure by Treatment Group

Level of Drug Exposure		Patients Who Reached 1% (N=58)		All (N=67)	
		Maximum Level	Last Level	Maximum Level	Last Level
Targretin® Gel 0.1%	QD	-	1 (2)	2 (3)	4 (6)
	BID	-	1 (2)	1 (1)	2 (3)
Targretin® Gel 0.5%	QD	-	5 (9)	3 (4)	8 (12)
	BID	-	1 (2)	3 (4)	3 (4)
Targretin® Gel 1%	QOD	3 (5)	6 (10)	3 (4)	6 (9)
	QD	12 (21)	15 (26)	12 (18)	15 (22)
	BID	25 (43)	24 (41)	25 (37)	24 (36)
	TID	16 (28)	4 (7)	16 (24)	4 (6)
	QID	2 (3)	1 (2)	2 (3)	1 (1)

Note: Last level is defined as the last prescribed dose level.

The table below illustrates that the predominant toxicity of targretin gel occurs at the application site. The major toxicities included: rash (80%), pruritus (40%), skin disorder (16%), and acne (16%); pain was 40% and infection was 28%.

Incidence of All AEs Occurring in at Least 5% of the Patients by Treatment Group, Body System, and Preferred Term[1]

Body System Preferred Term[2,3]	Patients Who Reached 1% (N = 58) n(%)	All Patients (N = 67) n(%)
Patients with Any AE	57 (98)	65 (97)
Skin and Appendages	55 (95)	60 (90)
Acne	9 (16)	9 (13)
Carcinoma Skin	3 (5)	3 (4)
Dermatitis Fungal	4 (7)	5 (7)
Skin Hypertrophy	3 (5)	3 (4)
Pruritus	23 (40)	27 (40)
Rash	47 (81)	52 (78)
Rash Vesiculobullous	4 (7)	4 (6)
Seborrhea	4 (7)	4 (6)
Skin Disorder	9 (16)	9 (13)
Dry Skin	3 (5)	3 (4)
Body As A Whole	42 (72)	46 (69)
Allergic Reaction	3 (5)	3 (4)
Fever	4 (7)	4 (6)
Flu Syndrome	4 (7)	4 (6)
Headache	7 (12)	7 (10)
Infection	16 (28)	17 (25)
Bacterial Infection	3 (5)	5 (7)
Accidental Injury	3 (5)	3 (4)
Pain	23 (40)	27 (40)
Pain Abdomen	3 (5)	3 (4)
Back Pain	6 (10)	7 (10)
Digestive System	18 (31)	22 (33)
Diarrhea	5 (9)	5 (7)
Liver Function Abnormal	3 (5)	4 (6)
Nausea	3 (5)	3 (4)
Respiratory System	15 (26)	18 (27)
Bronchitis	4 (7)	5 (7)
Cough Increased	3 (5)	3 (4)
Pharyngitis	4 (7)	4 (6)
Rhinitis	3 (5)	4 (6)
Sinusitis	4 (7)	5 (7)
Urogenital	8 (14)	10 (15)
Urinary Tract Infection	2 (3)	4 (6)

(1) Preferred Term coded according to LIGAND modified COSTART 5 Dictionary.

(2) Patients were counted only once for each body system and each preferred term.

(3) Adverse events recorded on the AE CRFs or the Dermatological Observations CRF are included.

As shown in the table below, severe toxicities were infrequent. Application site had the most frequent toxicities of pruritis (9%) and rash (5%).

Incidence of Severe Adverse Events by Body System, Preferred Term,[1] and Treatment Group

Body System Preferred Term[2,3]	Patients Who Reached 1% (N = 58) n (%)	All Patients (N= 67) n (%)
Patients with Any Severe AE	16 (28)	19 (28)
Skin and Appendages	10 (17)	12 (18)
Pruritis	5 (9)	7 (10)
Rash	3 (5)	3 (4)
Rash Vesiculobullous	2 (3)	2 (3)
Body As A Whole	6 (10)	7 (10)
Headache	1 (2)	1 (1)
Bacterial Infection	0	1 (1)
Accidental Injury	1 (2)	1 (1)
Pain	2 (3)	3 (4)
Pain Abdominal	1 (2)	1 (1)
Radiation Injury	1 (2)	1 (1)
Cardiovascular System	1 (2)	1 (1)
Myocardial Infarction	1 (2)	1 (1)
Digestive System	2 (3)	2 (3)
Abscess Periodontal	1 (2)	1 (1)
Diarrhea	1 (2)	1 (1)
Nervous System	1 (2)	1 (1)
Neuralgia	1 (2)	1 (1)
Respiratory System	1 (2)	2 (3)
Asthma	0	1 (1)
Pneumonia	1 (2)	1 (1)
Urogenital	1 (2)	1 (1)
Urine Impaired	1 (2)	1 (1)
Urinary Retention	1 (2)	1 (1)

(1) Preferred Term coded according to LIGAND modified COSTART 5 Dictionary.

(2) Patients were counted only once for each body system and each preferred term.

(3) Adverse events recorded on the AE CRFs or the Dermatological Observations CRF are included.

120 DAY SAFETY UPDATE

The Safety Update covers patients treated in targretin gel trials through February 4, 2000. The safety update includes information on 117 patients from the Study –25 (n = 50) and the Phase I - II program (n = 67). These numbers are identical to those submitted to the NDA; no new patients were entered.

The Safety Update provides additional follow up of patients from Study –25 (n = 22) and the Phase I – II Program (n = 26). The number of patients ongoing as of the cutoff date of 2/4/2000 is 26 (11 in Study –25 and 15 in the Phase I – II Program). The incidence of the adverse events is similar to the information provided in the NDA submission and does not appear different than the already reviewed safety profile for targretin gel. The information in the Safety Update does not reveal any new kinds of adverse events when compared to the data reviewed in the NDA.

FINANCIAL DISCLOSURE FOR CLINICAL INVESTIGATORS

Study -25

In compliance with 21 CFR part 54.2, Financial Disclosure for Clinical Investigators, Ligand requested and provided statements of financial interests and arrangements from investigators in Study -25. Ligand provided certification that neither investigators who enrolled patients in the study, nor their spouses nor dependent children, had an equity interest (i..e., stock ownership) in Ligand that exceeds $50,000 based on current market value. All principal investigators responded to the request for information except investigator site #310 contributed two patients to Study –25; there were no CA responders.

Also, in Ligand's NDA Financial Disclosure certification, there were at least 70 MD-investigators listed "who enrolled patients", who were not recorded in the list of investigators for the Study –25 in volume 29 of the NDA, and who could not be linked to any of the patients entered on the study. According to Ligand, these MD-investigators were subinvestigators. Ligand identified 14 principal investigators/investigator sites who received drug but did enroll any patients; no financial disclosure information was provided on these individuals.

Phase I – II Program (Studies –04, -11, -12)

Financial disclosure information was not provided in the NDA for the Phase 1 – II program. The FDA requested this information on 1/18/2000.

On 1/24/2000, Ligand provided certification that neither investigators who enrolled patients in the study, nor their spouses nor dependent children, had an equity interest (i.e., stock ownership) in Ligand that exceeds $50,000 based on current market value. All principal investigators responded to the request for information except the principal investigator at the Ligand indicated that the reason information was not obtained was because "Follow-up in progress." site contributed 21 patients to Study –04; there were seven PGA responders.

On 6/1/2000, FDA requested further follow-up on financial disclosure. According to Ms. Amy Baird, on 6/2/2000, Ligand claimed that spouse may have owned greater than $50,000 of Ligand stock but the stock had been sold. On 6/6/2000, Ligand's written response claimed that spouse purchased a total of worth of Ligand stock on October 19 and on November 8, 1999. Ligand further stated that "This purchase was made independent of knowledge. When became aware that this could potentially be perceived as a conflict of interest for sold the shares (February 2000)". The arrow in the graphic below is indicating a conservative stock price estimate for the month of February. There would be a large difference in the sale price depending on when in February the sale occurred.

The ODAC meeting for targretin capsules took place on December 13, 1999. [redacted] was a consultant for Ligand and made a presentation at the ODAC meeting. The targretin capsules NDA was approved on December 29, 1999. See graphic below.

In the Financial Disclosure information received by FDA on 12/9/99 in the targretin gel NDA, Ligand has certified, with regard to Study –25, that [redacted] and [redacted] spouse did not have a greater than $50,000 equity interest in Ligand. On 6/5/2000, Ligand has updated this with the information reported above. Also, the [redacted] investigator site was not audited by DSI for the targretin gel NDA. The site was audited for the targretin capsule NDA.

Review of the financial disclosure statements for the targretin capsules NDA shows that Ligand certified that [redacted] and [redacted] spouse did not have a greater than $50,000 equity in Ligand.

COMMENT

Financial Disclosure information appears satisfactory for Study –25 except for the [redacted] site. However, [redacted] enrolled only one known patient in that study. In the Phase I – II Program for targretin gel, [redacted] spouse had financial interests in Ligand equity that exceeded acceptable limits when bought; [redacted] site enrolled 31% of patients enrolled into the Phase 1 – 2 Program. Thirty-three percent (n = 7) of 21 patients at the [redacted] site responded. Also, since the efficacy and safety from the targretin capsules NDA was to be supportive of the targretin gel NDA, it is noted that the equity interest in Ligand, which was held by [redacted] was bought 1 – 2 months before the

targretin capsules NDA was presented at the Oncology Drugs Advisory Committee meeting on December 1999.

On June 7, 2000, an internal FDA meeting was held to discuss the issues above. In attendance at the meeting was Dr. Robert Temple, Dr. Rachel Behrman, Ms. Linda Carter, Dr. John Johnson, Dr. Oluwole Odujinrin (medical reviewer for targretin capsules), Ms. Amy Baird, and Dr. Robert White (medical reviewer for targretin gel). Based on the discussion, the approval would move forward. [redacted] had only one patient on Study –25 and this patient was not a responder. Most of [redacted] data from the Phase 1 – 2 Program had been submitted to Ligand prior to the above financial transaction and [redacted] results were not importantly different than the other investigators. [redacted] data from targretin capsules was submitted well before the above financial transaction.

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ONCOLOGY DRUGS ADVISORY COMMITTEE

The data to support the safety and efficacy of the targretin gel NDA were not presented before an advisory committee at the request of Ligand.

On January 24, 2000, Ligand questioned the necessity of taking targretin gel to an advisory committee. Basis for this was:

- Many or most of the issues that might be presented have been addressed in the ODAC meeting for the targretin capsules
- Targretin gel is not a new chemical entity but a new formulation.
- Efficacy of the molecule has been demonstrated with the targretin capsules in CTCL.
- Targretin capsules give higher blood levels than targretin gel.
- Systemic safety issues have been defined with the capsules.
- Safety concerns regarding targretin gel at the application site are less.

The FDA agrees with Ligand that presentation of this NDA to the ODAC is not necessary.

APPEARS THIS WAY
ON ORIGINAL

LABELING

Labeling revisions were made during a multidiscipline FDA review team meeting. Please see approved labeling which is a separate document.

MEDICAL OFFICER DISCUSSION

Decrease in Number of Planned Study Patients (Study-25)

Evaluable patients (FDA) versus Intent-to-Treat patients (Ligand)

There were multiple protocol violations committed in carrying out the study. At a Ligand/FDA meeting in August 1996, Ligand proposed a 30 CTCL-patient study to support their NDA for targretin gel. FDA stated that at a minimum of at 60 evaluable patients study should be performed. In the SYNOPSIS OF PROTOCOL section of the protocol submitted in the NDA, it stipulates that "Up to a total of 72 patients will be enrolled to provide for a total of 60 evaluable patients." At a Ligand/FDA meeting in December 1997, Ligand stated based on their projections that 45 evaluable patients would be enrolled and not the originally targeted 60 evaluable patients. FDA told Ligand that the originally targeted number of 60 evaluable patients was required. After further discussion , the FDA stated that 45 patients may be acceptable depending on the results. At a Ligand/FDA meeting in October 1998, Ligand proposed 45 patients for the "Phase III" study; FDA re-iterated their prior agreement to 60 evaluable patients but FDA was agreeable to 45 patients depending on the results.

The "Phase III" study in the NDA has 50 CTCL patients enrolled. According to Ligand's evaluation, only 16 are evaluable. An intent-to-treat analysis is performed on the 50 enrolled patients; the term intent-to-treat was not used in the protocol (Ligand response to FDA query, dated 5/17/2000). **This is not what the FDA believed they would receive in the NDA. The FDA expected 50 evaluable patients out of 60 to 70 intent-to-treat patients.**

Study Conduct: Protocol Violations and Data Quality

A total of 34 (68%) patients from the ITT population did not satisfy all of the protocol-specified evaluable patient criteria, and so the evaluable patient population was comprised of the remaining 16 patients. According to Ligand's analysis, the reasons inevaluable patients were not evaluable patients were: receiving prohibited medication (25 patients), skin biopsy early or late (18 patients), did not meet other inclusion/exclusion criteria (3 patients), had not been treated with targretin gel for at least 8 weeks (2 patients), insufficient pathological confirmation (1 patient), and insufficient qualifying therapy (1 patient). Many patients were excluded for more than one reason. **According to the FDA analysis, only 13 (26%) of the 50 patients provided in this pivotal trial are evaluable.** The two analyses are shown in the table below.

REASON NON-EVALUABLE	FDA ANALYSIS # OF PATIENTS (%)	LIGAND'S ANALYSIS # OF PATIENTS (%)
prohibited medication	26 (52%)	25 (50%)
insufficient pathological confirmation	3 (6%)	1 (2%)
skin biopsy early or late	19 (38%)	18 (36%)
did not meet other inclusion/exclusion criteria	3 (6%)	3 (6%)
had not been treated for at least 8 weeks	2 (4%)	2 (4%)
insufficient qualifying therapy	6 (12%)	1 (2%)
TOTAL # OF PATIENTS WITH AT LEAST ONE OF ABOVE CRITERIA	37[30] (74%)	34 (68%)
# CA RESPONDERS not evaluable	12	10

Prohibited topical medications were the most common reason for non-evaluablity. Most of the prohibited topical medications received by patients were corticosteroids which could be expected to have some anti-CTCL activity and could potentially influence the evaluation of some of the efficacy endpoints in this study. Some suppression of local inflammation and itching would likewise be predicted. According to the protocol (Prohibitions and Restrictions section), topical corticosteroids were prohibited during study and may not be administered to patients being treated on this protocol. The prescription of topical corticosteroids could disqualify or decrease the duration of the response.

Response Criteria for Topical Agents in CTCL

There are no standardized, widely-accepted, or uniform criteria for evaluating response to therapy in patients with CTCL. The PGA has been a useful measure for CTCL as well as psoriasis and AIDS-related Kaposi's sarcoma, as it permits the physician, who by training and experience has the greatest expertise with the disease, to evaluate the full range of clinical changes for the patient. Also, a Composite Assessment of Index Lesion Disease Severity was generated by a summation of the grades for each index lesion erythema, scaling, plaque elevation, hypopigmentation or hyperpigmentation, and area of involvement. It appears that a response criteria suited for benign dermatological conditions was used. In benign conditions, the expected outcome of therapy is complete

[30] Patient #703 was not qualified because of receipt of PUVA one year before the histopathological diagnosis of CTCL was made; there were two other QPTs.

clearing of disease. In the case of CTCL, acceptability of the outcome of therapy (i.e., partial responses) is determined by oncologic standards.

The CA response rates with topical targretin gel topical are not comparable to the response rates produced with systemic therapy for a number of reasons.

- For topical therapy, only a maximum of 5 lesions was required as index lesions. The NDA has complete information on only the index lesions in each patient, although other lesions could be treated if desired.

- With systemic therapy, the appearance of new lesions often prevents a response from being declared, confirmed, or prolonged. New lesions are not considered progressive disease with topical therapy and in this NDA information on new lesions was not collected. In Study –25, in the total population of patients accrued, 14 patients (28 %) developed new lesions since baseline. For the targretin CA responders, at least 6 developed new lesions during the trial. In contrast, in trials with systemic therapy, new lesions would have interfered with the declaration, confirmation, or prolongation of a response.

- By composite assessment (CA) progressive disease was scored only in the treated index lesions for targretin gel.

Overall, the response rates for targretin topical therapy are inflated when compared to the response rates for systemic therapy.

Photographs

The five (5) designated index lesions were to be serially photographed. On Day 1 (baseline), every four (4) weeks thereafter for the duration of treatment, and again at the follow-up visit, these five index lesions were be photographed. **Global photographs (half-body fields, anterior and posterior) of each patient's CTCL disease were to be** obtained on Day 1 (baseline), every four (4) weeks during treatment and again at the patient's follow-up visit. All index lesion and global areas, which were photographed at baseline, must have been re-photographed every four (4) weeks, even if the lesions have cleared, until the patient completed the follow-up study visit.

There were two problems with the photographs as submitted to the NDA:

First, the procedures for the taking of the photographs submitted in the NDA was different than described in the protocol. **No global photographs as described in the protocol were taken.** Instead of true global photographs, as described above, wider-view photographs of the index lesions were submitted. Ligand called these photographs global. There was no amendment to the protocol, indicating this change and there was ample opportunity to make that change (Versions of Protocol: OCT 7, 1996, NOV 25, 1996, FEB 25, 1997, 08 APR 97, 30 JULY 1997, and 8 JAN 1998). Because there

were no global photographs, FDA was unable to assess the status non-index lesions that the patient may have treated and to assess Ligand's claim regarding the Physician's Global Assessment.

Second, among the 17 composite assessment responders claimed by Ligand from Study - 25, 11 patients had photographs missing or the wrong area was photographed (as indicated on the hard-copies of the photographs: "Shift in Target Area Photographed"). In the case of investigator site #167, when an index lesion completely regressed, the investigator followed a different lesion (this is according to the DSI audit of this site). It is not known whether this was an isolated practice or whether other investigators also shifted to a different lesion.

Efficacy

The following table summarizes the efficacy results for targretin gel in the pivotal trial.

Summary of the Analyses of Response–Study –25

The shaded row represents the final FDA response rate.

RESPONSE	RESULTS % (# of responders/50[31]) 95% CI
LIGAND CA INTENT-TO-TREAT	34% (17/50) 21%, 47%
LIGAND CA EVALUABLE	44% (7/16) 19%, 68%
FDA REVIEW OF CA LISTINGS ITT	32% (16/50) 19%, 45%
FDA calculation of CA response[32] ITT	30% (15/50) 17%, 43%

[31] The number evaluable patients will be much lower.

RESPONSE	RESULTS % (# of responders/50[31]) 95% CI
FDA evaluation of response by area of index lesions ITT	26% (13/50) 14%, 38%
FDA response by BSA ITT	24% (12/50) 12%, 36%
FDA evaluation of photographs for response ITT	28% (14/50) 16%, 40%
FDA CA response minus disqualified responders[32,33,34] ITT	24% (12/50) 12%, 36%
FDA response evaluation of evaluable	39% (5/13) 12%, 65%
FDA Median time to CA response ITT time to CCR	87.5 days range (36 – 154) 174 days

The supportive efficacy results from the approved targretin capsules follows.

The Efficacy Results for Targretin Capsules

Based on the CA assessment, the CCR was 1.6% (1/62); the partial response rate was 30% (19/62). The rate of relapse was 30% (6/20) over a median duration of observation of 21 weeks.

[32] Patients #841 & #1711 were disqualified as responders because of missing data.
[33] patients #691, #741, & #743 disqualified as responders because of a prohibited medication (i.e., topical steroids)
[34] No patients were disqualified as responders based on photographs although 3 claimed responders could not be confirmed by photographs.

Quality of Life—Study -25

The QOL evaluation did not provide the results the FDA expected. In Study –25, QOL scores were essentially normal at baseline. As a result of the questionnaires used demonstrated that most scores generally were unchanged at Week 16 or had changed (improved or deteriorated) to a very small extent. Interestingly, in response to two global questions the majority of patients reported improvement in their overall CTCL status and were satisfied with treatment.

Ligand claimed the disease to be worse than their study found, raising the FDA's expectation that this study would provide valuable QOL information.

> "CTCL is a devastating, highly-symptomatic, chronic malignancy characterized by years of deforming symptomatic skin lesions that often culminate in ulceration with secondary infection and visceral tumor invasion. Nearly all patients have symptoms relating to skin lesions, that may itch and cause pain, bleeding, infection, or disfigurement" (Vol. 1; p. 60)

Safety

The following tables summarize the safety results in Study -25 and the Phase 1 – 2 Program.

Study -25

The incidence of all adverse events* and application site adverse events with incidence ≥5% for all application frequencies of targretin® gel in the Phase III CTCL Study is shown below.

	All Adverse Events	Application Site Adverse Events
COSTART 5 Body System/Preferred Term	N = 50 n (%)	N = 50 n (%)
Patients with AE	49 (98)	39 (78)
Skin and Appendages		
Contact Dermatitis[1]	7 (14)	4 (8)
Exfoliative Dermatitis	3 (6)	0
Pruritus[2]	18 (36)	9 (18)
Rash[3]	36 (72)	28 (56)
Maculopapular Rash	3 (6)	0
Skin Disorder (NOS)[4]	13 (26)	9 (18)
Sweat	3 (6)	0
Body as a Whole		
Asthenia	3 (6)	0
Headache	7 (14)	0
Infection	9 (18)	0
Pain	15 (30)	9 (18)
Cardiovascular		

	All Adverse Events	Application Site Adverse Events
COSTART 5 Body System/Preferred Term	N = 50 n (%)	N = 50 n (%)
Edema	5 (10)	0
Edema Peripheral	3 (6)	0
Hemic and Lymphatic		
Leukopenia	3 (6)	0
Lymphadenopathy	3 (6)	0
WBC Abnormal	3 (6)	0
Metabolic and Nutritional		
Hyperlipemia	5 (10)	0
Nervous		
Paresthesia	3 (6)	3 (6)
Respiratory		
Cough Increased	3 (6)	0
Pharyngitis	3 (6)	0

* Regardless of association with treatment

Includes Investigator Terms Such As:

[1]Contact dermatitis, irritant contact dermatitis, irritant dermatitis

[2]Pruritus, itching, itching of lesion

[3]Erythema, scaling, irritation, redness, rash, dermatitis

[4]Skin inflammation, excoriation, sticky or tacky sensation of skin; NOS = Not Otherwise Specified

Treatment-Limiting Toxicity

Treatment-Limiting Toxicity (TLT) is defined as any treatment-related Grade 3 or higher local dermal irritation. Thirty-two patients or 64% of the patients were listed in ACCESS file TLT as having treatment-limiting toxicity. There were 94 events (#events:#pts: 1:9; 2:10; 3:3; 4:3; 5:1; 6:5; 8:1). Treatment-limiting toxicities were presumed limited to the skin; 22 event entries were blank (examination of the photographs was not helpful).

APPEARS THIS WAY
ON ORIGINAL

Incidence of All AEs Occurring in at Least 5% of the Patients by Treatment Group, Body System, and Preferred Term[1]

Body System Preferred Term[2,3]	Patients Who Reached 1% (N = 58) n(%)	All Patients (N = 67) n(%)
Patients with Any AE	57 (98)	65 (97)
Skin and Appendages	55 (95)	60 (90)
Acne	9 (16)	9 (13)
Carcinoma Skin	3 (5)	3 (4)
Dermatitis Fungal	4 (7)	5 (7)
Skin Hypertrophy	3 (5)	3 (4)
Pruritus	23 (40)	27 (40)
Rash	47 (81)	52 (78)
Rash Vesiculobullous	4 (7)	4 (6)
Seborrhea	4 (7)	4 (6)
Skin Disorder	9 (16)	9 (13)
Dry Skin	3 (5)	3 (4)
Body As A Whole	42 (72)	46 (69)
Allergic Reaction	3 (5)	3 (4)
Fever	4 (7)	4 (6)
Flu Syndrome	4 (7)	4 (6)
Headache	7 (12)	7 (10)
Infection	16 (28)	17 (25)
Bacterial Infection	3 (5)	5 (7)
Accidental Injury	3 (5)	3 (4)
Pain	23 (40)	27 (40)
Pain Abdomen	3 (5)	3 (4)
Back Pain	6 (10)	7 (10)
Digestive System	18 (31)	22 (33)
Diarrhea	5 (9)	5 (7)
Liver Function Abnormal	3 (5)	4 (6)
Nausea	3 (5)	3 (4)
Respiratory System	15 (26)	18 (27)
Bronchitis	4 (7)	5 (7)
Cough Increased	3 (5)	3 (4)
Pharyngitis	4 (7)	4 (6)
Rhinitis	3 (5)	4 (6)
Sinusitis	4 (7)	5 (7)
Urogenital	8 (14)	10 (15)
Urinary Tract Infection	2 (3)	4 (6)

(1) Preferred Term coded according to LIGAND modified COSTART 5 Dictionary.

(2) Patients were counted only once for each body system and each preferred term.

(3) Adverse events recorded on the AE CRFs or the Dermatological Observations CRF are included.

RECOMMENDATION

A single arm non-randomized trial demonstrated the efficacy and safety of Targretin gel (1%) for topical treatment of cutaneous lesions in patients with CTCL (Stage IA & IB) who have not tolerated other therapies or who have refractory or persistent disease after prior therapies. Sufficient data was not provided to support the safety and efficacy of this product in Stage II patients. Supportive efficacy data was derived from the approved targretin capsules. Supportive safety data was derived from the Phase 1 – 2 Program of targretin gel. Based on this review, NDA 21-056 is clinically approvable for topical treatment of cutaneous lesions in patients with CTCL (Stage IA & IB) who have not tolerated other therapies or who have refractory or persistent disease after prior therapies. The claimed tumor response rate may exaggerate the benefit of the drug. For example, the response rate based on the Composite Assessment of Index Lesion Disease Severity focused only on the CTCL index lesions treated and ignored other treated lesions, new lesions, and progression in non-index treated lesions. Approval is also conditional on satisfactory resolution of Chemistry and Manufacturing Deficiencies and satisfactory resolution of labeling issues from chemistry, pharmacology/toxicology, biopharmaceutics, biometrics, and medical disciplines.

/S/

ROBERT M. WHITE, JR, MD, FACP
June 7, 2000

/S/ 6-7-00

cc:
NDA #21-056
HFD-150/DIV FILE
HFD-150/RWHITE
HFD-150/A BAIRD CSO
HFD-340
HFD-150

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-056

CHEMISTRY REVIEW

DIVISION OF ONCOLOGY DRUG PRODUCTS
Original NDA Review of Chemistry, Manufacturing, and Controls

NDA #: 21-056 CHEMISTRY. REVIEW #: 2 REVIEW DATE: June 7, 2000

SUBMISSION TYPE	DOC. DATE	CDER DATE	ASSIGNED DATE
Original	December 8, 1999	December 9, 1999	December 16, 1999
Amendment (BC)	May 26, 2000	May 30, 2000	May 30, 2000
Amendment (BC)	June 6, 2000	June 6, 2000 (facsimile)	June 7, 2000

NAME & ADDRESS OF APPLICANT:

Ligand Pharmaceuticals Inc.
10275 Science Center Drive
San Diego, CA 92121-1117

DRUG PRODUCT NAME:

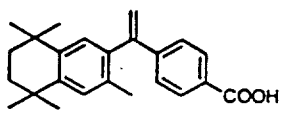
Proprietary: Targretin® Gel 1.0 %
Nonproprietary/USAN: Bexarotene (This name was adopted by the USAN Council, correspondence of 3/25/98)
Code Name/Number: LGD1069, LG100069
Chem. Type/Ther. Class: ~~1~~ 3P

PHARMACOL. CATEGORY/INDICATION: Activation of three retinoid X receptors (RXRα, β, γ)/ Cutaneous T-cell lymphoma (CTCL)

DOSAGE FORM: Topical Gel
STRENGTHS: 1.0 % (60gram size)
ROUTE OF ADMINISTRATION: Topical
DISPENSED: _x_ Rx ____ OTC
SPECIAL PRODUCTS: Yes ___ No _X_
(if yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

CAS Name: 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid (see attached USAN publication)
Other Chemical Name: p-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl 2-naphthyl)vinyl]-benzoic acid
Common Name: Not available
CAS Number: 153559-49-0
Code Number: LGD1069, LG100069
M.F.: $C_{24}H_{28}O_2$
M.W.: 348.48



SUPPORTING DOCUMENTS:

INDs:
NDAs: NDA 21-055
DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
DMF		6/23/99 (page 232, v2 of 133)		Withdrawn (amendment of 3/10/00)		
DMF		11/6/98 (page 231, v2 of 133)		Adequate	1/23/95 (HFD-643), 4/15/96 (HFD-170)	

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
						with 21CFR 177.1520
DMF		2/11/98 (page 230, v2 of 133)		Adequate	3/22/95 and 10/4/96 (HFD-540)	complies with 21CFR 175.300
DMF		11/9/99 (amendment of 3/10/00)		Adequate	5/25/00 (HFD-150)	
DMF		LOA dated 12/11/98				

*Several chemistry reviews on bottles for a solid oral dosage form have been noted and the reviews found acceptable.

CONSULTS:

EER

Submitted to OC on 1/30/00; Overall acceptable OC recommendation on 5/22/00 (see attached report).

Trademark consultation **was requested under on 1/16/97.** ***Targretin® was found acceptable on 2/18/98.***

Micro consultation, **not applicable**

Environmental assessment, ***Exemption is requested. Granted.***

Stability data consultation, **Not needed. A twenty-four months expiration dating period is granted based on provided long-term stability data (store at 25°C).**

Method validation, **Pending for initiation.**

REMARKS/COMMENTS:

See Review Notes.

CONCLUSIONS & RECOMMENDATIONS:

All CMC deficiencies have been resolved. CMC information on the manufacture, controls and package of Targretin 1% Gel are adequately provided. Approval of this NDA 21-056 is recommended from the CMC viewpoints.

/S/

Sung K. Kim, Ph.D.,
Review Chemist, HFD-150

cc:
Orig. NDA 21-056
HFD-150/Division File
HFD-150/ABaird
HFD-150/SKim
HFD-150/RWood
HFD-810/HPatel
HFD-810/JSimmons
R/D Init. by: /S/ 6-7-00

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21056/000
Stamp: 09-DEC-1999 Regulatory Due: 09-JUN-2000
Applicant: LIGAND
10275 SCIENCE CENTER DR
SAN DIEGO, CA 921211117

Priority: 3P Org Code: 150
Action Goal: District Goal: 10-APR-2000
Brand Name: TARGRETIN (BEXAROTENE) GEL 1%
Established Name:
Generic Name: BEXAROTENE
Dosage Form: GEL (GEL)
Strength: 1%

FDA Contacts:			
	A. CHAPMAN	(HFD-150)	301-594-2473 , Project Manager
	S. KIM	(HFD-150)	301-827-1522 , Review Chemist
	R. WOOD	(HFD-150)	301-594-2473 , Team Leader

Overall Recommendation:

ACCEPTABLE on 22-MAY-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 24-JAN-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment: [redacted]
DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-JAN-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment: [redacted]
DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-JAN-2000
Decision: ACCEPTABLE

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Reason: **BASED ON PROFILE**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CRU** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **31-JAN-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MICRONIZER**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **24-JAN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
DRUG SUBSTANCE RELEASE TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **24-JAN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **OIN** OAI Status: **NONE**

Responsibilities: **FINISHED DOSAGE**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date **22-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

MANUFACTURER
FINISHED DOSAGE PACKAGER

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **29-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE RELEASE TESTER**
FINISHED DOSAGE STABILITY TESTER
FINISHED DOSAGE STERILITY TESTER

APPEARS THIS WAY
ON ORIGINAL

LIGAND PHARMACEUTICALS

FACSIMILE TRANSMISSION

DATE:	June 6, 2000
TO:	Amy Baird Project Manager, CSO
COMPANY:	Food and Drug Administration Division of Oncology Drug Products, HFD-150
PHONE: FAX:	(301) 594-5771 (301) 827-4590
FROM:	Ray Lubecki, R.Ph. Associate Director, Regulatory Affairs and Compliance
PHONE: FAX:	(858) 550-7600 (858) 550-1827
Pages including cover:	2

Please call Elizabeth Borst at (858) 550-7765 if this transmission is unclear or incomplete.

Subject: NDA 21-056 for Targretin® (bexarotene) gel 1%
Response to FDA Request for Chemistry, Manufacturing and Controls Information of 6/6/00

Regarding the above subject, attached please find Ligand's response.

Should you have any questions concerning this submission or NDA 21-056, please contact the undersigned or Howard T. Holden, Ph.D., at 858-550-7600 (facsimile 858-550-1827).

Sincerely,

Ray Lubecki, R.Ph.

/emb

LIGAND PHARMACEUTICALS

Regulatory Affairs and Compliance

June 6, 2000

RE: NDA 21-056
Targretin® (bexarotene) gel 1%

General Correspondence:
Response to FDA 6/6/00 Request for Chemistry, Manufacturing and Controls Information

Richard Pazdur, M.D.
Food and Drug Administration
CDER/Oncology HFD-150
Attention: Document Control Room
1451 Rockville Pike
Rockville, Maryland 20852

Dear Dr. Pazdur:

Reference is made to NDA 21-056 for Targretin® gel 1% (submitted on December 8, 1999), and to Dr. Sung Kim's request today regarding the need to provide [redacted] in Targretin® gel 1%.

By way of this correspondence, Ligand commits to provide [redacted] certificate of analysis or the drug product manufacturer's certificate of analysis for future production (post-validation) batches of Targretin® gel 1%.

We trust that this information will meet the Agency's immediate needs. Please contact the undersigned or Howard T. Holden, Ph.D., at 858-550-7600 (facsimile 858-550-1827) in the event you have any questions concerning the enclosed information.

Sincerely,

Ray Lubecki

Ray Lubecki, R.P.h.
Associate Director
Regulatory Affairs and Compliance

REL/emb

Daira

MAY 25 2000

DIVISION OF ONCOLOGY DRUG PRODUCTS
Original NDA Review of Chemistry, Manufacturing, and Controls

NDA #: 21-056 CHEMISTRY. REVIEW #: 1 REVIEW DATE: May 23, 2000

SUBMISSION TYPE	DOC. DATE	CDER DATE	ASSIGNED DATE
Original	December 8, 1999	December 9, 1999	December 16, 1999
Amendment (NC)	December 14, 1999	December 17, 1999	December 23, 1999
Amendment (BC)	December 22, 1999	December 23, 1999	January 5, 2000
Amendment (BL)	February 4, 2000	February 7, 2000	February 7, 2000
Amendment (BC)	February 15, 2000	February 16, 2000	February 17, 2000
Amendment (BC)	March 9, 2000	March 10, 2000	March 23, 2000
Amendment (NC)	March 10, 2000	March 13, 2000	March 23, 2000
Amendment (NC)	March 14, 2000	March 16, 2000	March 23, 2000
Amendment (BL)	May 9, 2000	May 9,2000 (fax)	May 9, 2000

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

DRUG PRODUCT NAME:

Proprietary: Targretin® Gel 1.0 %

Nonproprietary/USAN: Bexarotene (This name was adopted by the USAN Council, correspondence of 3/25/98)

Code Name/Number: LGD1069, LG100069

Chem. Type/Ther. Class: #30

PHARMACOL. CATEGORY/INDICATION: Activation of three retinoid X receptors (RXRα, β, γ)/ Cutaneous T-cell lymphoma (CTCL)

DOSAGE FORM: Topical Gel

STRENGTHS: 1.0 % (60gram size)

ROUTE OF ADMINISTRATION: Topical

DISPENSED: x Rx ____ OTC

SPECIAL PRODUCTS: Yes ____ No X

(if yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

CAS Name: 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid (see attached USAN publication)

Other Chemical Name: p-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl 2-naphthyl)vinyl]-benzoic acid

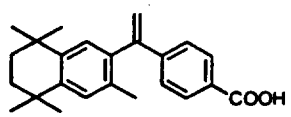
Common Name: Not available

CAS Number: 153559-49-0

Code Number: LGD1069, LG100069

M.F.: $C_{24}H_{28}O_2$

M.W.: 348.48



SUPPORTING DOCUMENTS:

INDs: [redacted]

NDAs: NDA 21-055

DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
DMF [redacted]	[redacted]	6/23/99 (page 232, v2 of 133)	[redacted]	withdrawn (amendment of 3/10/00)		

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
DMF		11/6/98 (page 231, v2 of 233)		Adequate	1/23/95 (HFD-643), 4/15/96 (HFD-170)	is compliant with 21CFR 177.1520
DMF		2/11/98 (page 230, v2 of 133)		Adequate	3/22/95 and 10/4/96 (HFD-540)	complies with 21CFR 175.300
DMF	Co.	11/9/99 (amendment of 3/10/00)		Adequate pending for TL signature	—— (HFD-150)	
		LOA dated 12/11/98				

*Several chemistry reviews on bottles for a solid oral dosage form have been noted and the reviews found acceptable.

CONSULTS:

EER for

Submitted to OC on 1/30/00; Pending for final approval

Trademark consultation **was requested under on 1/16/97.** ***Targretin® was found acceptable on 2/18/98.***

Micro consultation, **not applicable**

Environmental assessment, ***Exemption is requested. Granted.***

Stability data consultation, **Not needed.**

Method validation, **Pending for initiation.**

REMARKS/COMMENTS:

See Review Notes.

CONCLUSIONS & RECOMMENDATIONS:

CMC deficiencies were noted. Approvable pending for satisfactory response to our comments described in the daft letter.

/S/

Sung K. Kim, Ph.D.,
Review Chemist, HFD-150

cc:
Orig. NDA 21-056
HFD-150/Division File
HFD-150/ABaird
HFD-150/SKim
HFD-150/RWood
HFD-810/HPatel
HFD-810/JSimmons
R/D Init. by: /S/ 5-25-00

1st draft on 5/17/00

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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21056/000
Stamp: 09-DEC-1999 Regulatory Due: 09-JUN-2000
Applicant: LIGAND
10275 SCIENCE CENTER DR
SAN DIEGO, CA 921211117

Priority: 3P Org Code: 150
Action Goal: District Goal: 10-APR-2000
Brand Name: TARGRETIN (BEXAROTENE) GEL 1%
Established Name:
Generic Name: BEXAROTENE
Dosage Form: GEL (GEL)
Strength: 1%

FDA Contacts:			
	A. CHAPMAN	(HFD-150)	301-594-2473 , Project Manager
	S. KIM	(HFD-150)	301-827-1522 , Review Chemist
	R. WOOD	(HFD-150)	301-594-2473 , Team Leader

Overall Recommendation:

ACCEPTABLE on 22-MAY-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 24-JAN-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-JAN-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-JAN-2000
Decision: ACCEPTABLE

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Reason: **BASED ON PROFILE**

Establishment: [redacted]

DMF No:
AADA No:

Profile: CRU
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 31-JAN-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE MICRONIZER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 24-JAN-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 24-JAN-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: [redacted]

DMF No:
AADA No:

Profile: OIN
OAI Status: NONE

Responsibilities: FINISHED DOSAGE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

MANUFACTURER
FINISHED DOSAGE PACKAGER

Last Milestone: **OC RECOMMENDATION**
Milestone Date **22-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **29-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE RELEASE TESTER**
FINISHED DOSAGE STABILITY TESTER
FINISHED DOSAGE STERILITY TESTER

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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: Ray Lubecki/Ligand Pharm.	**From:** Amy Baird, CSO
Fax: 858-550-1827	**Fax:** (301) 594-0498
Phone: 858-550-7889	**Phone:** (301) 594-5771
Pages, including cover sheet: 2	**Date:** 5-19-00

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

COMMENTS:

See the attached chemistry comments and please respond as soon as possible. Please do not hesitate to call should you have any questions.

Thank you,

/S/

Amy Baird

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

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

JUN 18 1998

Feb 18/98

[redacted] and TARGRETIN

9-cis-retinoic acid
LGD 1069

The concern of the Committee in the original consult was over the use of the USAN stem syllable "retin" in the proposed trademarks. The Committees 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 councils 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 [redacted] TARGRETIN on the basis of their USAN stem inclusion. However, [redacted] is too similar to the International Nonproprietary Name of [redacted] listed in the USAN dictionary. But, we also have no indication that [redacted] 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 [redacted] 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.

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