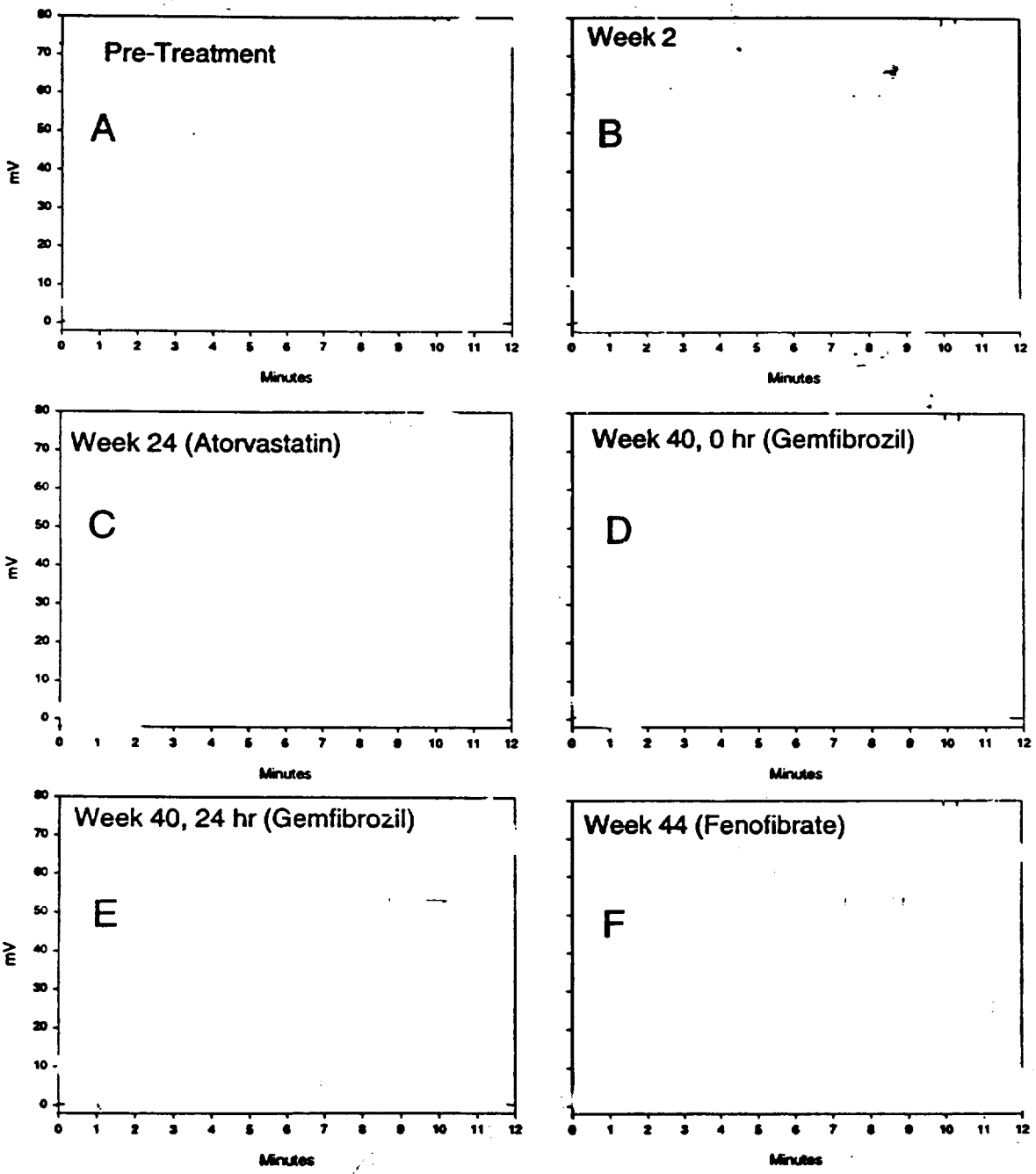
Figure 6.3-LL. [redacted] From Patient



[redacted] shown are from a pre-treatment plasma sample (Panel A), and from samples drawn after multiple oral doses of Targretin® capsules administered without concomitant Antilipemics (Panel B) or with concomitant atorvastatin (Panel C), gemfibrozil (Panels D, E) or fenofibrate (Panel F). Bexarotene elutes at 8 minutes and the assay internal standard at 10 minutes. The peaks eluting at approximately 2.5 and 3 minutes are believed to be oxidative metabolites of bexarotene.

Finally, for the evaluation of the effect of CYP3A4 inhibitors on orally administered bexarotene, all samples obtained during concomitant oral or systemic administration of an azole antifungal or a macrolide antibiotic were grouped. Data were available for patients ingesting concomitant clarithromycin, itraconazole, erythromycin, or fluconazole. The mean and median dose-normalized plasma bexarotene concentrations in patients receiving a concomitant CYP3A4 inhibitor were larger than respective values for the same patients when they were not administered a concomitant CYP3A4 inhibitor (**Table 6.3-RR**). However, dose-normalized plasma bexarotene concentrations for patients receiving concomitant CYP3A4 inhibitor were generally interspersed with dose-normalized concentrations in the same patients without a concomitant CYP3A4 inhibitor (**Figure 6.3-MM**).

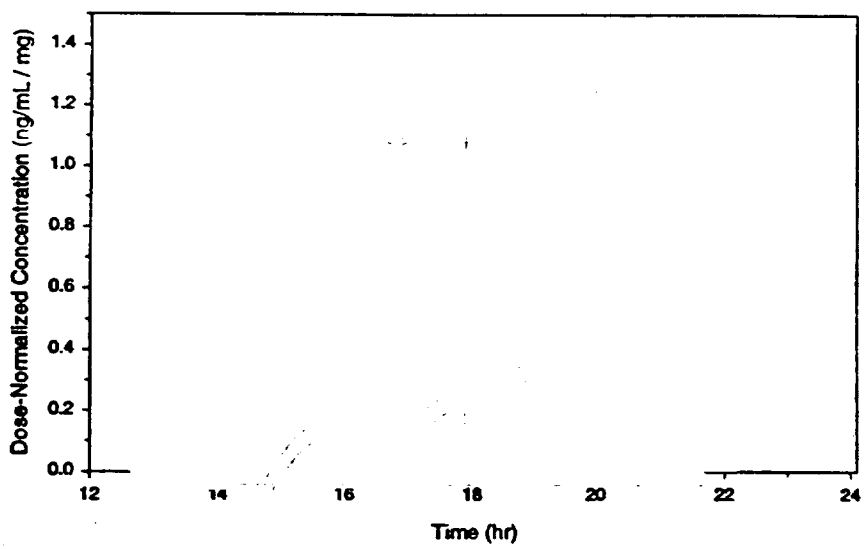
In addition, individual patient plasma bexarotene concentration data were not supportive of an association of higher dose-normalized plasma bexarotene concentrations with concomitant administration of a CYP3A4 inhibitor. Patients who had samples collected both with and without concomitant administration of a CYP3A4 inhibitor had no consistent difference in plasma bexarotene concentrations (**Figure 6.3-NN**). Most patients who only had samples collected during concomitant administration of a CYP3A4 inhibitor had some samples with relatively high dose-normalized plasma bexarotene concentrations. However, dose-normalized plasma bexarotene concentrations in these patients were variable. The lack of samples collected without concomitant administration of a CYP3A4 inhibitor for these patients prevents comparison between dose-normalized plasma bexarotene concentrations in samples collected with and without coadministration of a CYP3A4 inhibitor. Thus, while some patients receiving concomitant CYP3A4 inhibitors had high dose-normalized plasma bexarotene concentrations, a causal relationship could not be established.

Table 6.3-RR. Dose-Normalized Plasma Bexarotene Concentrations for Patients (N=10) After Administration of Targretin® Capsules With and Without Concomitant Clarithromycin, Erythromycin, Itraconazole, or Fluconazole for Samples Collected 12 to 24 Hours Postdose (Data from Studies L1069-23 and L1069-24)

	Dose-Normalized Plasma Bexarotene Concentrations (ng/mL/mg)	
	Targretin® Capsules Without Clarithromycin, Erythromycin, Itraconazole or Fluconazole	Targretin® Capsules With Clarithromycin, Erythromycin, Itraconazole or Fluconazole
N	25	23
Mean	0.152	0.331
SD	0.191	0.347
Median	0.073	0.206

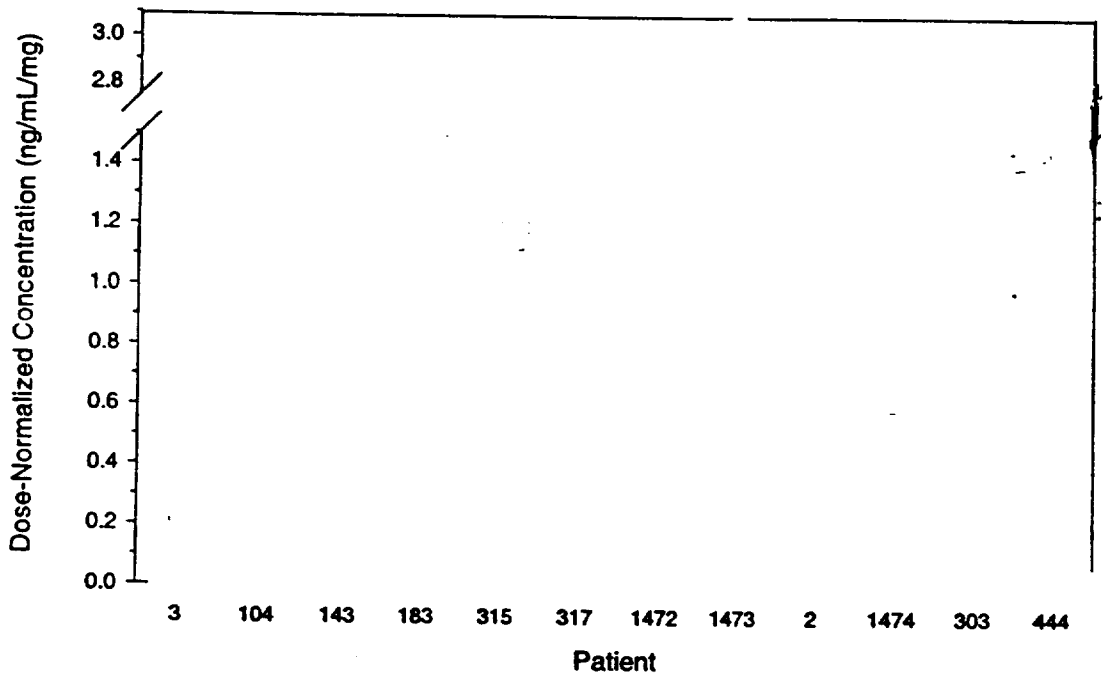
N = Number of Plasma samples.
SD = Standard deviation.
Excludes samples obtained during concomitant administration of gemfibrozil.

Figure 6.3-MM. Dose-Normalized Plasma Bexarotene Concentrations in Samples Collected 12 to 24 Hours After an Oral Dose of Targretin® Capsules Administered Daily To Patients (N=10) With Concomitant Clarithromycin (Filled Circles), Erythromycin (Filled Diamond), Itraconazole (Filled Down Triangles), Fluconazole (Filled Up Triangle) or Data From These Same Patients Without These Concomitant Medications (Open Squares) (Combined Data from Studies L1069-23 and L1069-24)



Excludes samples obtained during concomitant administration of gemfibrozil.

Figure 6.3-NN. Dose-Normalized Plasma Bexarotene Concentrations in Patients After an Oral Dose of Targretin® Capsules Administered Daily With (Solid Circles) or Without (Open Circles) Concomitant Clarithromycin (Patients 3, 104, 143, 183, 315, 317, 1472, and1473), Itraconazole (Patients 2 and1474), Erythromycin (Patient 444) or Fluconazole (Patient 303) (Combined Data from Studies L1069-23 and L1069-24)



Excludes samples obtained during concomitant administration of gemfibrozil.

6.3.7.3. Summary of Potential Drug Interactions with Bexarotene

Bexarotene is metabolized in humans to oxidative metabolites (6- and 7-hydroxy-bexarotene, and 6- and 7-oxo-bexarotene), and bexarotene acyl glucuronide. The oxidative metabolites are the major plasma metabolites of bexarotene, and their formation has been shown to be mediated by CYP3A4. Although no evidence for a drug interaction with CYP3A4 inhibitors has been observed during clinical studies of Targretin® capsules, a potential exists that a drug-drug interaction may occur between bexarotene and drugs that induce (e.g., rifampin, phenytoin, or phenobarbital) or inhibit (e.g., ketoconazole, itraconazole, or erythromycin) this enzyme. Besides the potential for interaction with CYP3A4

inducers or inhibitors, concomitant administration of gemfibrozil has also been shown to be associated with increased plasma bexarotene concentrations following oral administration of Targretin® capsules. Data from the clinical studies using Targretin® capsules have suggested that the observed interaction may be due to inhibition of the oxidative metabolism of bexarotene.

Based on the potential for interactions with CYP3A4 modulators and the observed interaction with gemfibrozil in studies of Targretin® capsules, orally administered gemfibrozil and other systemically administered concomitant CYP3A4 inducers or inhibitors of CYP3A4 have been evaluated for their potential to affect the pharmacokinetics of bexarotene. No formal drug interaction studies were conducted, but potential interactions were evaluated using data collected from clinical studies utilizing topically applied Targretin® gel and from studies utilizing orally administered Targretin® capsules. The results of these evaluations showed no significant effects of concomitantly administered CYP3A4 inducers or inhibitors on bexarotene following topical application of Targretin® gel. While no significant effect of gemfibrozil on topically applied bexarotene was found with population analysis, bexarotene concentrations were elevated in one patient on concomitant gemfibrozil, though concentrations were still relatively low in comparison to concentrations achieved following oral dosing. Thus, concomitant gemfibrozil may have the potential to increase bexarotene concentrations following application of Targretin® gel.

Following oral administration of Targretin® capsules, no significant effects of atorvastatin, levothyroxine, or CYP3A4 inhibitors (azole antifungals and macrolide antibiotics) were seen on bexarotene pharmacokinetics. However, concomitant gemfibrozil produced elevations in bexarotene concentrations.

377- 385 OR 171- 179

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Table 1. Concentration Monitoring During Studies With Targretin® Gel

Program	Route	Dose Form	Dose	Frequency	Study Number	Pts[1]	No. Samples[2]	Conclusion
Phase I-II KS	Topical	Gel	Targretin® Gel 0.1%, 0.5%, 1%	QD, BID, TID, QID	L1069-94-03T L1069T-07 L1069T-08 L1069T-13 L1069T-15	14 11 4 5 11	303 (Total for 5 Studies)	• Systemic exposure to bexarotene following application of Targretin® gel was low. Ninety-three percent of bexarotene concentrations in samples measured following application of the highest gel strength (1%) at frequencies of QOD to QID were below 5 ng/mL. • The highest bexarotene plasma concentrations tended to be observed within 12 hr of Targretin® gel application. • No appreciable accumulation of bexarotene was observed following long-term application for up to 135 weeks over up to 90% of BSA. • Increases in bexarotene plasma concentrations correlated with increasing surface area of treated lesions, increase in gel strength, and the application frequency of Targretin® gel. • Concomitant gemfibrozil caused a slight elevation in bexarotene concentrations in one patient. No other drug interactions were observed.
Phase I-II CTCL	Topical	Gel	Targretin® Gel 0.1%, 0.5%, 1%	QD, BID, TID	L1069-94-04T L1069T-11 L1069T-12	21 33 12	965 (Total for 3 Studies)	
Phase III CTCL	Topical	Gel	Targretin® Gel 1%	QOD, QD, BID, TID, QID	L1069T-25	38	301	

[1] Number of patients providing PK data.
[2] Number of blood samples collected.

Table 2. Distribution of Bexarotene Plasma Concentrations per Time Interval in Patients Participating in the Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12) for Targretin® Gel

Time post-dose	Number of Samples	N (%) Quantifiable Samples [1]	Bexarotene Concentration (ng/mL)		
			Mean ± SD	Median	Range
Pre-dose	62	0 (0.0%)	0	0	N/A
T < 4 hr	166	41 (24.7%)	1.02 ± 3.20	0	0 – 23.52
4 ≤ T < 8 hr	243	74 (30.5%)	1.10 ± 2.86	0	0 – 24.04
8 ≤ T < 12 hr	113	25 (22.1%)	1.19 ± 3.51	0	0 – 24.17
12 ≤ T < 16 hr	138	22 (15.9%)	0.514 ± 1.819	0	0 – 13.65
16 ≤ T < 20 hr	73	10 (13.7%)	0.256 ± 0.745	0	0 – 4.24
20 ≤ T < 24 hr	10	2 (20.0%)	0.894 ± 2.362	0	0 – 7.49
24 ≤ T < 48 hr	43	4 (9.3%)	0.567 ± 2.243	0	0 – 11.14
48 ≤ T < 72 hr	10	1 (10.0%)	0.713 ± 2.255	0	0 – 7.13
72 ≤ T < 96 hr	6	0 (0.0%)	0	0	N/A
T ≥ 96 hr	70	4 (5.7%)	0.494 ± 3.348	0	0 – 27.78
Total Post-dose	872	183 (21.0%)	0.842 ± 2.778	0	0 – 27.78

[1] Percentage based on the number of samples within each time interval.

Notes: Table entries are the number of samples collected within each time interval that have complete dosing and sampling information. Twenty-nine samples taken post-dose (after Week 1) did not have complete dosing and sampling information to calculate a post-dose time. Additionally, two samples that had insufficient volume for bexarotene determination are not included in this table.

Table 3. Distribution of Bexarotene Plasma Concentrations per Time Interval in Patients Participating in Study L1069T-25 for Targretin® Gel

Time post-dose	Number of Samples	N (%) Quantifiable Samples [1]	Bexarotene Concentration (ng/mL)		
			Mean ± SD	Median	Range
Pre-dose	34	6 (17.7%)	0.168 ± 0.399	0	0 – 1.460
T < 4 hr	90	55 (61.1%)	2.10 ± 3.59	0.865	0 – 21.600
4 ≤ T < 8 hr	41	28 (68.3%)	4.05 ± 9.07	1.15	0 – 54.900
8 ≤ T < 12 hr	20	17 (85.0%)	1.65 ± 1.61	1.10	0 – 6.150
12 ≤ T < 16 hr	28	24 (85.7%)	2.53 ± 3.17	1.39	0 – 11.983
16 ≤ T < 20 hr	9	4 (44.4%)	1.21 ± 1.55	0	0 – 3.794
20 ≤ T < 24 hr	7	3 (42.9%)	0.814 ± 1.099	0	0 – 2.504
24 ≤ T < 48 hr	29	18 (62.1%)	1.32 ± 1.92	0.739	0 – 8.985
48 ≤ T < 72 hr	3	2 (66.7%)	0.595 ± 0.582	0.621	0 – 1.164
72 ≤ T < 96 hr	2	0 (0.0%)	0	0	N/A
T ≥ 96 hr	11	5 (45.5%)	0.899 ± 1.256	0	0 – 4.004
Total Post-dose	240	156 (65.0%)	2.19 ± 4.64	0.899	0 – 54.900

[1] Percentage based on the number of samples (n) within each time interval.

Note: Table entries are the number of samples collected within each time interval that have complete dosing and sampling information.

Table 4. Distribution of Bexarotene Plasma Concentrations per Time Interval in Patients Participating in the Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15) for Targretin® Gel

Time post-dose	Number of Samples	N (%) Quantifiable Samples [1]	Bexarotene Concentration (ng/mL)		
			Mean ± SD	Median	Range
Pre-dose	0	0 (0.0%)	N/A	N/A	N/A
T < 4 hr	144	5 (3.5%)	0.106 ± 0.704	0	0 – 7.44
4 ≤ T < 8 hr	36	1 (2.8%)	0.0497 ± 0.298	0	0 – 1.79
8 ≤ T < 12 hr	39	0 (0.0%)	0	0	N/A
12 ≤ T < 16 hr	26	0 (0.0%)	0	0	N/A
16 ≤ T < 20 hr	18	0 (0.0%)	0	0	N/A
20 ≤ T < 24 hr	3	0 (0.0%)	0	0	N/A
24 ≤ T < 48 hr	1	0 (0.0%)	0	0	N/A
48 ≤ T < 72 hr	2	0 (0.0%)	0	0	N/A
72 ≤ T < 96 hr	4	0 (0.0%)	0	0	N/A
T ≥ 96 hr	11	0 (0.0%)	0	0	N/A
Total Post-dose	284	6 (2.1%)	0.0600 ± 0.5139	0	0 –

[1] Percentage based on the number of samples (n) within each time interval.

Note: Table entries are the number of samples collected within each time interval that have complete dosing and sampling information.

N/A – not applicable

ATTACHMENT 2

DRUG FORMULATION SUMMARY

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ATTACHMENT 3

ANALYTICAL METHODS TABULAR SUMMARY

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Appendix 5. Clinical Pharmacology/Biopharmaceutics review of Targretin® (bexarotene) capsules

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

Submission: NDA 21-055
Submission Date: June 22, 1999
Drug Name: Targretin® (bexarotene)
Dosage Form: 75 mg soft gelatin capsule
Applicant: Ligand Pharmaceuticals, Inc.
Submission Type:
Reviewer: Gene M. Williams, Ph.D.

This review is performed to determine if the Clinical Pharmacology and Biopharmaceutics data submitted in NDA 21-055 allows Targretin® to be dosed to provide effective and safe therapy.

Table of Contents

Table of Contents, Continued from p. 1

I. Synopsis and regulatory recommendations

I.A. Synopsis

The applicant seeks approval for Targretin® (bexarotene) 75 mg soft gealtin capsules for the treatment of patients with cutaneous T-cell lymphoma (CTCL IA-IVB).

There are no bioequivalence issues with this application. Release rate data (dissolution) has been included in the submission and the applicant proposes the following dissolution specification:

	Tier 1	Tier 2
Apparatus Type	Type 2	Type 2
Media		
Volume		
Speed of rotation		
Sampling Times		
Description of Analytical Method		
Recommended Dissolution Specification		

Since all lots of drug tested for dissolution in the past 3 years have passed the following specification at the time of manufacture, we recommend the following specification:

	Tier 1	Tier 2
Apparatus Type	Type 2	Type 2
Media		
Volume		
Speed of rotation		
Sampling Times		
Description of Analytical Metho		
Recommended Dissolution Specification		

The applicant has not performed Mass Balance, Dose Proportionality, Special Population or Drug Drug Interaction studies. Although the elimination of bexarotene is not well-described, the best available evidence suggests that the drug is a CYP 3A4 substrate and is eliminated and excreted through hepato-biliary mechanisms.

We are requesting the following Phase IV commitments of the applicant:

1

2.

We are also requesting significant alterations to the package insert -- see **I.B.** below.

We have made a number of recommendations for further study to the applicant -- see **I.C.** below.

I.B. Package insert alterations

Clinical Pharmacology -- Pharmacokinetics -- Absorption/Dose Proportionality:

Absorption/Dose Proportionality

DRAFT LABELING

Clinical Pharmacology -- Pharmacokinetics -- Metabolism

Metabolism

DRAFT LABELING

Clinical Pharmacology -- Pharmacokinetics -- Excretion

Excretion

DRAFT LABELING

5-8

4 pages redacted from this section of the approval package consisted of draft labeling

I.D. Approval/non-approval recommendation

Although the submission has met the current absolute minimum requirements of the Office of Clinical Pharmacology and Biopharmaceutics, it does not provide dosing guidelines for patients receiving certain concomittant therapies. The Office of Clinical Pharmacology and Biopharmaceutics finds the application approvable if the dissolution specification is changed as recommended, the applicant agrees to perform the studies listed under Phase IV commitments, and the recommended package insert alterations are made.

/S/

Gene M, Williams, Ph. D.
Pharmacokinetic Reviewer
Division of Pharmaceutical Evaluation I

/S/

N.A.M. Atiqur Rahman, Ph.D.
Team Leader, Oncology
Division of Pharmaceutical Evaluation I

Clinical Pharmacology and Biopharmaceutics Briefing: December 16, 1999.

cc: NDA 21,055(original file)
HFD-150/Division File
HFD-150/ AChapman
HFD-150/ JJohnson, OOdujinrin
HFD-850/LLesko
HFD-860/ MMehta, ARahman
CDRBiopharm

II. Background

II.A. What is the indication?

Answer: *Targretin® (bexarotene) capsules are indicated for the treatment of patients with all clinical stages of cutaneous T-cell lymphoma (CTCL IA-IIB) in the following categories: patients with early stage CTCL who have not tolerated other therapies, patients with refractory or persistent early stage CTCL, and patients with refractory advanced stage CTCL.*

II.B. Are there drugs on the market for this indication?

Answer: *There are a number of enteral and parenteral therapies used to treat CTCL.*

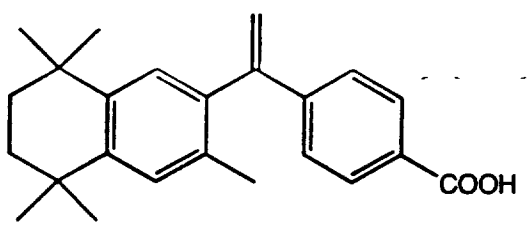
II.C. Are there any unique regulatory agreements or issues for this application (ex.: did we request filing?, FDAMA date)?

Answer: *There are no unique regulatory agreements. The applicant was made aware of our General Recommendations for NDA Item 6 over 3 years ago and was reminded of these Recommendations throughout the development process.*

The indication sought by the sponsor has Orphan Drug status.

II.D. What is the structure of the drug and what is the formulation?

Answer: *The chemical name is 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)vinyl]benzenecarboxylic acid, and the structural formula is*



Bexarotene is an off-white to white powder with a molecular weight of 348.48 and a molecular formula of $C_{24}H_{28}O_2$. It is insoluble in water and slightly soluble in vegetable oils and ethanol, USP.

Targretin® capsules are supplied as 75-mg off-white soft gelatin capsules for oral administration. Each capsule contains the following inactIle ingredients: polyethylene glycol 400, NF, polysorbate 20, NF, povidone, USP, and butylated hydroxyanisole, NF. The capsule shell contains gelatin, NF, sorbitol special-glycerin blend, and titanium dioxide, USP.

II.E. What chemical entities appear to be responsible for efficacy and toxicity following bexarotene dosing?

Discussion: *Mass balance accounting of drug-related species in plasma was not performed. Mass balance of drug-related species in excreta was also not performed. Four bexarotene metabolites have been elucidated: 6-OH-bexarotene, 6-oxo-bexarotene, 7-OH-bexarotene and 7-oxo-bexarotene. Testing of these metabolites in in vIIo animal models was not performed and the animal toxicity studies performed with parent drug did not attempt to estimate the contribution of metabolites to toxicity. In retinoid receptor transactIlation assays (the putative mechanism of action of bexarotene is retinoid receptor activation), metabolites were 4 - 20-fold less potent than bexarotene.*

The plasma concentration-time profiles of these 4 metabolites were not assessed using a each metabolite by using for each metabolite. Instead, an bexarotene and included only bexarotene reference standards was used. Using this method, 2 metabolite peaks were measured -- one thought to be 6 and 7-OH-bexarotene and the other believed to be 6 and 7-oxo-bexarotene. It appears that the measurements are from a single patient who received 230 mg/m^2/day; the measurements were made after the first dose and again after dosing on Day 16. If these peaks are interpreted using the assumption that sensitivity of the to metabolites is equal to sensitivity to bexarotene, the $AUC_{0\text{-}6hrs}$ for 6/7-oxo-bexarotene approximates that of bexarotene, while the $AUC_{0\text{-}6hrs}$ of 6/7-OH-bexarotene is approximately double that of bexarotene.

Answer: *Because mass balance accounting of drug-related species was not performed, there may be unknown efficacious or toxic species present. The known metabolites appear to be 4 - 20 fold less potent than bexarotene in receptor assays thought to be predictive of efficacy; the toxicity of the metabolites was not assessed. The concentration of the metabolites in plasma and tissues is unknown, but is best estimated as being greater than bexarotene within plasma. In total, insufficient data is available to make conclusions regarding the contribution of metabolites to the efficacy and safety profile of the drug.*

III Non-package-insert items

III.A. Does this product have an appropriate release rate specification?

Discussion: *No studies comparing bioavailability between oral capsule formulations were performed. The applicant seeks the following dissolution rate specification:*

	Tier 1	Tier 2
Apparatus Type		
Media		
Volume		
Speed of rotation		
Sampling Times		
Description of Analytical Method		
Recommended Dissolution Specification		

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Answer: *The applicant's recommended specification is insufficiently rigorous to assure appropriate quality control. We recommend the following specification:*

	Tier 1	Tier 2
Apparatus Type		
Media		
Volume		
Speed of rotation		
Sampling Times		
Description of Analytical Method		
Recommended Dissolution Specification		

As can be seen by examining the previous table, all lots tested since October of 1996 have met this specification.

Appendix 2, p.1 shows

III.B. Are there bioequivalence issues with this application?

Discussion: *Formulation development is summarized in Appendix 2, p.2.*

The pivotal safety and efficacy studies (L1069-23 and L1069-24) used formulations

Answer: *There are no bioequivalence issues.*

15-29

16 pages redacted from this section of the approval package consisted of draft labeling

MEMORANDUM

Date: May 30, 2000

From: Paul A. Andrews, Ph.D.
Pharmacology Team Leader, HFD-150 F.O.D. 5/30/2000

To: Files for NDA# 21-056, Targretin® Gel

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 Gel for topical treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL). CTCL is an indolent disease and to treat this disease patients might apply Targretin Gel to their skin daily for many years. The pharmacology and toxicology studies submitted to this NDA for Targretin Gel and previously to the NDA for Targretin Capsules have been 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 oral studies in rats and single dose, 91 day, and 6 month oral 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. In addition, a 28 day study of topically administered Targretin Gel was conducted in rats. Carcinogenicity studies are not necessary to support approval for the intended indication and were not submitted. 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.

A detailed labeling review was provided by Dr. Ahn and I agree with the requested changes. A key issue for extrapolating animal findings to humans with regards to labeling statements is the systemic exposure to bexarotene following topical administration of Targretin Gel. The human pharmacokinetic data provided was not sufficient to calculate AUCs. Also, the dose administered is highly variable- some patients covered up to 90% of their body surface area with the gel. Many plasma samples collected had undetectable bexarotene levels. The mean C_{max} was ~5 ng/ml but some patients had concentrations as a high as [redacted]. Assessments of the risk to pregnancy from Targretin Gel use were based on the worst case scenario presented by the [redacted] value.

I wish to highlight the following from Dr. Ahn's reviews of NDAs 21-055 and 21-056:

- Toxicology studies in both species showed that chronic administration of bexarotene causes lens opacities and cataracts. Although this has not yet been demonstrated clinically, a precaution was included in the label for Targretin Capsules. This statement should be included in the label for Targretin Gel since there is measurable systemic exposure to [redacted]

bexarotene.

- 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. This precaution was placed in the label for Targretin Capsules and is particularly relevant to Targretin Gel which is likely to cause much higher concentrations of bexarotene in light-exposed skin. A precaution regarding the potential for photosensitization should also be placed in the Targretin Gel label.
- Dr. Ahn practiced use of the Draft Pregnancy Risk Integration Guidance to assess the concern for human reproductive and developmental toxicity from Targretin Gel (pp. 11-14 of review). His analysis indicates significant concern for humans for the endpoints of fertility, developmental mortality, dysmorphogenesis, and alterations to growth (net adjustments +5 to +6). In particular, he notes that in some patients the C_{max} was within ten-fold of the C_{max} associated with developmental toxicity in rats. This indicates a significant risk to human pregnancy following topical administration. Since Targretin Gel is indicated for treatment of cutaneous lesions and has no known affect on long-term survival, we concluded that a Category X designation was appropriate, *i.e.*, the benefits do not outweigh the risk to pregnancy and treatment should be terminated if pregnancy arises or is planned.
- A topical toxicology study was conducted in rats using bexarotene formulated in DEET, an insect repellant present in many over-the-counter products. Although terminated early due to premature deaths, the study clearly demonstrated that bexarotene enhanced the toxicities of DEET. A precaution regarding this interaction was put in the Targretin Capsule label and is even more relevant to the Targretin Gel label because simultaneous application of the gel and a DEET-containing repellant would directly mimic the conditions of the rat study.

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

Original NDA
cc: Div File
HFD-150
/CAhn
/ABaird
/PAndrews
/RWhite

Division of Oncology Drug Products, HFD-150

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Review No. 2 (Labeling Review)

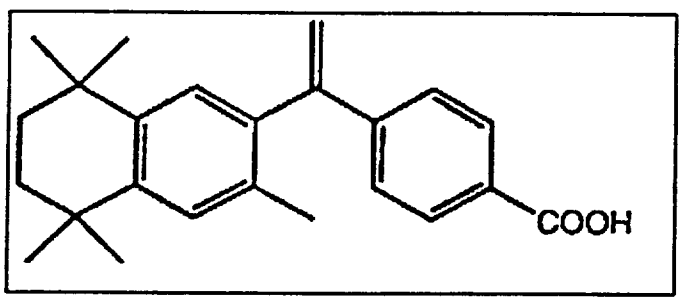
Keywords: Targretin gel, bexarotene, RXR agonist, CTCL, NDA

NDA #: 21-056
Serial #: 000 **Type:** NDA **Letter Dated:** 12/9/99 **Received by CDR:** 12/9/99

Information to be conveyed to the sponsor: Yes
Reviewer: Chang H. Ahn, Ph.D.
Review Completion Date: May 23, 2000
Sponsor: Ligand Pharmaceuticals Inc. San Diego, CA
Manufacturer:
Drug:

Code Name: LG100069, LGD1069
Generic Name: bexarotene
Trade Name: Targretin® gel 1% Topical
Secondary therapies: none
Chemical Name: 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthaleneyl)vinyl] benzene carboxylic acid
CAS Registry Number: 153559-49-0
Molecular formula/weight: $C_{24}H_{28}O_2$ (348.48)

Structure:



Related INDs, NDAs, DMFs: NDA 21055
Drug Class: Antineoplastic agent (retinoid analogue with RXR selectivity)
Indication: The topical treatment of cutaneous lesions patients with CTCL (stage 1A, 1B and IIA) who have not tolerated other therapies or who have refractory or persistent disease.

Clinical Formulation:

Ingredient	Amount (% w/w in bulk gel)
Bexarotene	
Dehydrated alcohol, USP	
PEG 400, NF	
Butylated hydroxytoluene, NF	
Hydroxypropyl cellulose, NF	

Dosage and administration: Targretin® gel is topically applied two to four times per day to cutaneous lesions

2-5

4 pages redacted from this section of the approval package consisted of draft labeling

Division of Oncology Drug Products, HFD-150

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Review No. 1

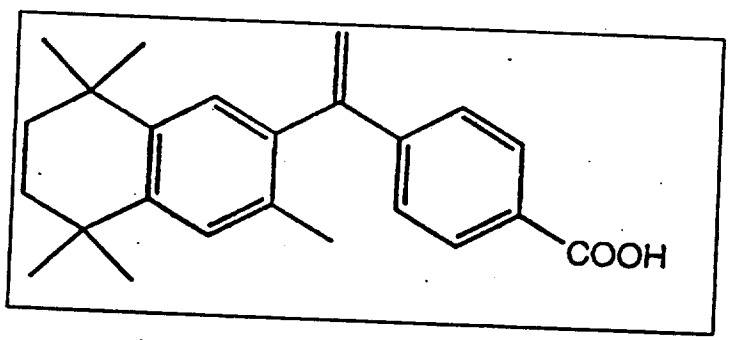
Keywords: Targretin gel, bexarotene, RXR agonist, CTCL, NDA

NDA #: 21-056
Serial #: 000 **Type:** NDA **Letter Dated:** 12/9/99 **Received by CDR:** 12/9/99

Information to be conveyed to the sponsor: Yes
Reviewer: Chang H. Ahn, Ph.D.
Review Completion Date: May 24, 2000
Sponsor: Ligand Pharmaceuticals Inc. San Diego, CA
Manufacturer: [redacted]
Drug:

Code Name: LG100069, LGD1069
Generic Name: bexarotene
Trade Name: Targretin® gel 1% Topical
Secondary therapies: none
Chemical Name: 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthaleneyl)vinyl]benzene carboxylic acid
CAS Registry Number: 153559-49-0
Molecular formula/weight: $C_{24}H_{28}O_2$ (348.48)

Structure:



Related INDs, NDAs, DMFs: [redacted] NDA 21055
Drug Class: Antineoplastic agent (retinoid analogue with RXR selectivity)
Indication: The topical treatment of cutaneous lesions in patients with CTCL (stage 1A, 1B and IIA) who have not tolerated other therapies or who have refractory or persistent disease.

Clinical Formulation:

Ingredient	Amount (% w/w in bulk gel)
Bexarotene	
Dehydrated alcohol, USP	
PEG 400, NF	
Butylated hydroxytoluene, NF	
Hydroxypropyl cellulose, NF	
[redacted]	

Dosage and administration: Targretin® gel is topically applied two to four times per day to cutaneous lesions

Studies Reviewed within this submission:

Toxicology

1. 28-Day dermal toxicity study in rats (0.1% and 1% gel containing DEET) (vol. 1.38, pp2-36, RR-815-98-005a)

Pharmacology

1. Antikeratinizing activities in the rhino mouse (vol. 1.11, pp 146-159, RR-740-93-002)

pharmacokinetics

1. Topical pharmacokinetics in rats and humans (vol. 1.48 (rat), 167- , RR-845-94-008a; vol. 1.7 (human), pp2- and vol. 1.13, pp 1- , RR-885-99-004/007)

Studies Not Reviewed within this submission: none

Studies Previously Reviewed: The following studies were reviewed in [redacted] NDA 21055.

A. Studies reviewed in [redacted]

Pharmacokinetics

1. Pharmacokinetics in rats (vol. 1.3, RR-845-94-008)
2. Pharmacokinetics from 28-day dermal toxicity study in rats (vol. 1.4, RR-815-94-008)

Toxicology

1. Guinea pig primary skin irritation study (vol. 1.4, RR-815-94-010)
2. In vitro human skin penetration study (vol. 1.3, RR-845-94-006)
3. 28-Day repeated dose dermal toxicity study in rats (vol. 1.4, RR-815-94-008)
4. Dermal sensitization study in guinea pigs (vol. 1.5, RR-815-94-009)

B. Studies reviewed in [redacted]

Pharmacology

1. Transcriptional activation (vol. 1.4, RR-750-93-004)
2. Retinoic acid receptor binding profile (vol 1.4, RR-750-93-013)
3. Effects on human leukemia cells, Kaposi's sarcoma, cervical carcinoma cells, head and neck squamous carcinoma and breast carcinoma cells (vol. 1.4, RR-750-93-008/-012; vol. 1.5, RR-750-93-007/-013)
4. Effects on human head and neck squamous cell carcinoma xenografts in nude mice (vol. 1.5, RR-740-93-014)
5. Effects on human cervical carcinoma xenografts in nude mice (vol. 1.5, RR-740-93-015)
6. Effects on cardiovascular and central nervous systems (vol. 1.5, RR-740-93-006/-007)

Pharmacokinetics

1. Toxicokinetics in rats (vol. 1.7, RR-845-93-021)
2. Toxicokinetics in dogs (vol. 1.6, RR-845-93-023)
3. Bioavailability in rats (vol. 1.6, RR-845-93-018)
4. Bioavailability and metabolism in dogs (vol. 1.6/1.7, RR-845-93-022/-024)
5. Tissue distribution and metabolism in mice (vol. 1.7, RR-845-93-017)
6. Metabolism in rats (vol. 1.7, RR-945-93-020)
7. Plasma protein binding (vol. 1.7, RR-845-93-025)

Toxicology

1. Acute oral toxicity study in rats (vol. 1.13, RR-815-93-020/-021)
2. Acute oral toxicity study in dogs (vol. 1.13, RR-815-93-015)
3. 28-Day repeat dose oral toxicity study in rats (vol. 1.14, RR-815-93-022)

4. 28-Day repeat dose oral toxicity study in rats (interim report, vol. 1.16, RR-815-94-013)
5. 28-Day repeat dose oral toxicity study in dogs (vol. 1.12, RR-815-93-016)

C. Studies reviewed in NDA 21055
Toxicology
1. 28-Day oral toxicity study in rats (vol. 1.16, pp 2-409, RR-815-94-013,
2. 91-Day oral toxicity study in dogs (vol. 1.30, pp 105, to vol.1.32, RR-815-95-003,
3. 6-Month oral toxicity study in rats (vol. 1. 21, pp 2-, to vol. 1.27, RR-815-98-004, ,
4. 6-Month oral toxicity study in dogs (vol. 1.33,pp 2- to vol. 1.36, RR-815-98-003a)

Pharmacology
Mechanism of Action
1. Transcriptional activation and receptor binding profile (vol. 1.10, pp276-341, RR-750-93-013/-004/011)
2. Repression of AP-1 activity (vol. 1.10, pp 390-397, RR-750-93-011)
3. Regulation of Fas-ligand expression and activation-induced T-cell apoptosis (vol. 1.11, pp 2-21, RR-750-98-002)

In vitro efficacy studies
1. Growth inhibitory effects on carcinoma cells of breast, head/neck and on primary tumor samples (vol. 1.10, pp398, to 1.11, pp38-80, RR-750-98-009/014, 93-013)
2. Induction of cell cycle arrest and differentiation in NB4 APL cells (vol. 1.11, pp 22-37, RR-750-98-003)

In vivo/Ex vivo studies
1. Effects on growth of human head and neck carcinoma xenografts in nude mice (vol. 1.11, pp 95-108, 132-145, 255-271, RR-740-94-007a, 93-014a, 750-98-005)
2. Effects on mammary carcinoma in the NMU-induced rat mammary tumor model (vol. 1.11, pp 160-223, RR-750-98-001/004/010)
3. Antikeratinizing activities in the rhino mouse (vol. 1.11, pp 146-159, RR-740-93-002)

Safety Pharmacology
1. Summary table of safety pharmacology (vol. 1.12, pp 1-261, RR-740-93-002/006/007/009/013/016/017)

Pharmacokinetics
1. Relative bioavailability of micronized LGD 1069 in sesame oil and in 10% PEG/Aqueous formulation in male rats (vol. 1.43, pp 207- , RR-845-96-003a)
2. Single oral pharmacokinetics study in rats (vol. 1.44, pp 2- , RR-815-98-013)
3. Single and repeat dose oral pharmacokinetics in rats (vol. 1.45, pp2-33, RR-845-98-007)
4. Three-way crossover oral bioequivalence study of two clinical formulations in dogs (vol. 1.46, pp83-163, RR-845-94-011)
5. Five-way crossover oral study in female beagle dogs (vol. 1.46, pp 205-315, RR-845-98-014)
6. Tissue distribution of [^{14}C]LGD 1069 in rats (vol. 1.47, pp 188- , RR-845-97-002b)
7. Effects on hepatic microsomal cytochrome P450 and in vitro metabolism (vol. 1.48, pp 2-20, RR-845-98-009)
8. Metabolic fate in rats (vol. 1.48, pp 42-79, RR-845-98-001)
9. Binding to human plasma protein (vol. 1.57, pp 135-136, RR-845-99-002)

Reproductive Toxicology
1. Oral developmental toxicity study in rats (vol.1.38, pp 134- , RR-815-97-003b)
2. Oral dose-range development toxicity study in rats (vol. 1.39, pp 2-260, RR-915-97-004a)

Genetic Toxicology
1. Salmonella/E. coli mutation assays (vol. 1.39, pp262- /1.40, pp 2-65, RR-815-95-005/RR-815-95-004)
2. CHO chromosome aberration assay (vol. 1.40, pp 66-141, RR-815-97-008)
3. L5178Y mouse lymphoma cell tk+/tk- gene mutation assay (vol 1.40, pp 142- , RR-815-97-009)
4. In vivo bone marrow micronucleus assay in mice (vol. 1.41, pp 2-163, RR-815-97-010)

Phototoxicity
1. In vitro phototoxicity studies (summary; vol 1.41, pp165-243, RR-815-98-006)

Note: Portions of this review were excerpted directly from the sponsor's submission.

INTRODUCTION AND DRUG HISTORY

Targretin is a synthetic retinoid analogue that is claimed to selectively activate retinoid X receptors. Targretin is the first RXR-specific retinoid to be approved for marketing. RAR-specific retinoids (e.g., all-trans retinoic acid, 13-cis-retinoic acid) and pan-RAR/RXR agonist (e.g., 9-cis-retinoic acid) are either NDA-approved or in clinical trials for oncologic indications. Targretin has demonstrated its antitumor activity against squamous cell carcinoma xenografts in nude mice and carcinogen-induced mammary tumors in rats. It has also shown antikeratinizing activity in rhino mice. The NDA (#21055) for Targretin® capsules was approved for the treatment of patients with cutaneous manifestations of refractory or persistent early and refractory advanced stage CTCL on December 28, 1999.

The sponsor conducted a Phase III safety and efficacy trial and three combined Phase I-II trials of Targretin® Gel in patients with CTCL. Based on the results of these studies, the sponsor seeks approval of Targretin® Gel for the topical treatment of cutaneous lesions in patients with CTCL (stage 1A, 1B and IIA) who have not tolerated other therapies or who have refractory or persistent disease.

PHARMACOLOGY

1. Antikeratinizing activities in the rhino mouse (vol. 1.11, pp 146-159, RR-740-93-002)

method- Hairless female rhino mice (18 g, 6-8 weeks old) were administered topical daily doses of 0, 0.05, 0.1 or 0.5% LG1069 (in ethanol:propylene glycol =70:30 v/v, 0.1 ml) (or 0.01, 0.05 and 0.1% ATRA) or received daily oral doses of 0, 10, 30 or 100 mg/kg/day LG1069 (or 1, 10 and 30 mg/kg/day ATRA) (in super refined sesame oil) by gavage (5 ml/kg) for 3 weeks. Mice were sacrificed 72h after the last dose and dosal trunk skin was removed and place into 0.5% acetic acid for 24-36h at 4°C. An area of skin (2x 5 cm) was partitioned and the epidermis was carefully peeled off. The epidermis was placed on a glass slide with the dermal side facing up, cleared in alcohol/xylene, and coverslipped with Permount for microscopic evaluation. For each mount the diameters of 10 utriculi in 5 random fields were measured with an Optomax Image Analysis System and mean utriculi diameter was calculated for each treatment group.

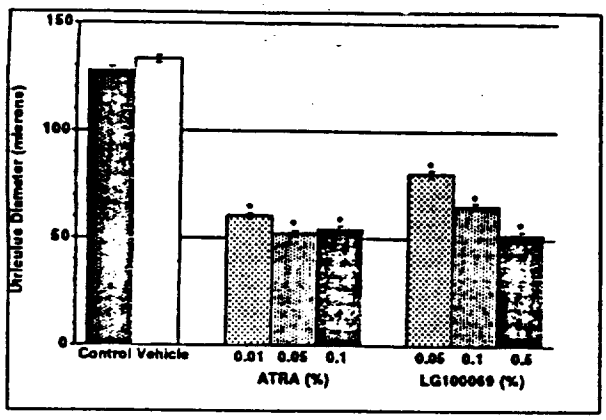
GLP statement- No

Results- Topical administration- LG1069 produced dose-related decreases in utriculus diameter from 40% at 0.05% LG1069 to 61% at 0.5% LG1069 (vs. 0.01-0.1% ATRA which were almost equally efficacious with approximately 60% decrease).

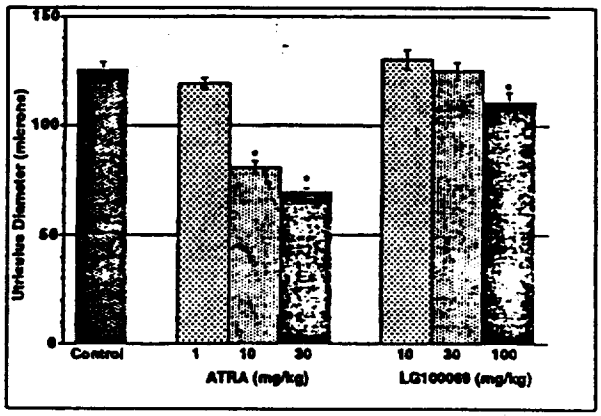
Oral administration- 100 mg/kg/day LG1069 produced only 13% decrease in utriculus diameter and 10 and 30 mg/kg doses were inactive. ATRA produced dose-dependent decreases with 6, 36 and 44% at 1,

10 and 30 mg/kg/day. These results suggest that LG1069 may be an effective antikeratinizing agent when administered topically, but is not an active agent following oral administration at the dose used.

Topical Administration



Oral Administration



Summary of Pharmacology: Antikeratinizing effect in rhino mice was observed by LG 1069 when administered topically (0.05 – 0.5%), but not when administered orally at dose up to 100 mg/kg/day.

PHARMACOKINETICS AND TOXICOKINETICS

1. Topical pharmacokinetics in rats and humans (vol. 1.48 (rat), 167-207, RR-845-94-008a; vol. 1.7 (human), pp2- and vol. 1.13, pp 1- , RR-885-99-004/007)

method- Rat- A dose of 0.5 ml of 1% LG1069 gel (lot # LG 100069-000Z008; in ethanol/PEG 400/hydroxypropyl cellulose/butylated hydroxyanisole/butylated hydroxy toluene/ascorbic acid = 1370:600:30:1:1:1; Formulation 2LG-89A) was applied to skin clipped free of hair on the dorsal surface (about 10% body surface) of SD rats (6/sex, M- approx. 250 g, F- approx. 200g) for 7 consecutive days. The dosing solution was spiked with [^{3}H] LG 1069 (sp. activity = 58.9 uCi/mmol, ~25.4 uCi/0.5 ml topical solution) for d1 and d7 applications. Blood samples were collected at 0, 1, 3, 12 and 24 h postdose on d1 and d7. LG1069 content was extracted from plasma, feces and urine and quantified by [redacted]

Human- In Phase I-II trials (studies L1069-94-04T, L1069T-11 and L1069T-12; 65 patients) and a Phase III trial (study L1069T-25; 38 patients) in patients with CTCL, 1.0% Targretin® gel was topically applied to the lesions with qod, qd, bid, tid and/or qid schedule and blood samples were collected pre-dose and every 2-4 weeks until week 24 and every 4 weeks thereafter. Plasma LG1069 concentrations were measured up to 96h.

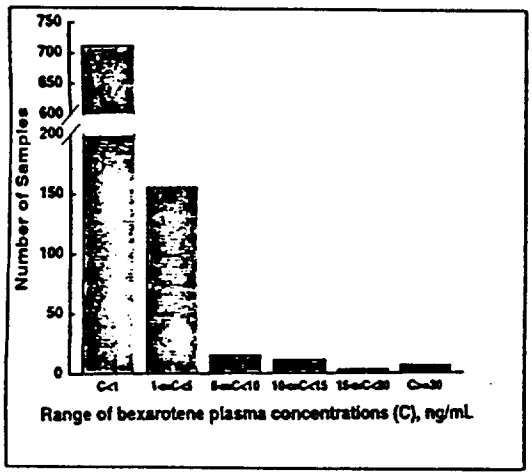
GLP statement- No

Results- Topically applied LG1069 to rats and human patients appears to be systemically absorbed. In rats, males exhibited greater exposure and Cmax than females. In humans, at least one post-dose plasma concentrations of LG 1069 could be measured from 42 of 65 patients in phase I/II studies, although 79% of 901 blood samples collected had LG 1069 concentration below the limit of quantification (<1 ng/ml). Blood samples from 35 of the 38 patients in a phase III study had at least one LG 1069 concentration quantifiable. Of the 267 post-dose blood samples, 38% had concentrations below the limit of quantification and 62% were quantifiable. In humans, the sponsor did not provide exposure information.

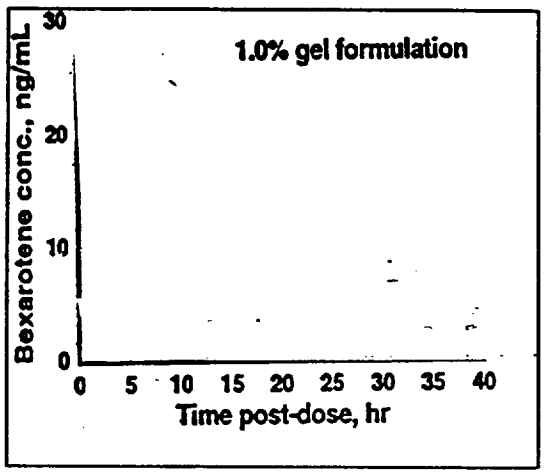
Species	Rat Male	Rat Female	Human- Phase I-II	Human Phase III
Dose, 1% gel	~ 120 mg/m2	~ 150 mg/m2		
Route	Topical	Topical	Topical	Topical
Cmax, ng/ml	332	55.7	1.19 ± 3.51	4.05 ± 9.07
Tmax, h	3.83	8.67	8-12	4-8
T1/2, h	-	-	-	-
AUC_{0-24h}, ng.h/ml	3450	846	-	-

Human Phase I-II

i) Distribution of plasma concentrations

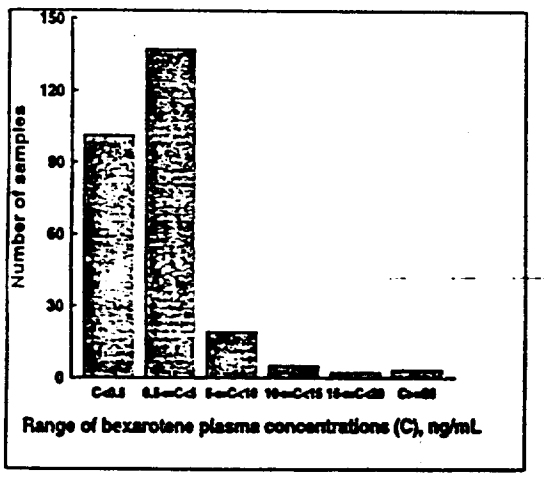


ii) Distribution of samples with >1 ng/ml as a function of time post-dose

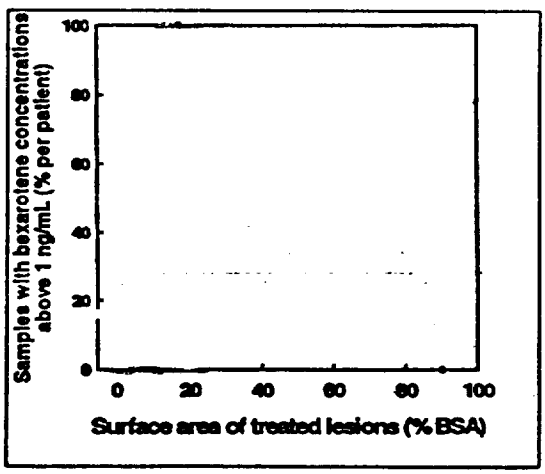


Human Phase III

i) Distribution of plasma concentrations



ii) Distribution of samples with >1 ng/ml as a function of surface area of treated lesions



Summary of Pharmacokinetics: Topically applied LG 1069 was systemically absorbed both in rats and humans. Due to the limited human exposure (or due to the lack of human exposure data), extensive interspecies comparisons of pharmacokinetics between animals and humans could not be made. When compared to orally administrated LG1069 in rats, topically applied LG 1069 produced almost same levels of AUC and approximately 1/3 of Cmax in males, whereas it produced approximately 8.5-fold less AUC and 27-fold lower Cmax in females (see following table). The significant gender difference in exposure apparently did not result in differential toxic effects in the 28-day repeated dermal toxicity study (study # RR-815-94-008). It is unknown whether this difference could be due to differences in grooming/licking habits in males that increased oral intake.

Gender	Male		Female	
Dose, mg/m2	600	120	600	150
Route	Po	Topical	Po	topical
AUC, ug.h/ml	15.5	3.4	28.6	0.84
Cmax, ug/ml	5.43	0.33	5.88	0.055
Per 100 mg/m2 Basis				
AUC, ug.h/ml	2.58	2.83	4.76	0.56
Cmax, ug/ml	0.90	0.27	0.98	0.036

TOXICOLOGY

1. 28-Day dermal toxicity study in rats (0.1% and 1% gel containing DEET) (vol. 1.38, pp2-36, RR-815-98-005a)

animal- SD rats (10/sex/group, additional 4/sex for PK (high-dose group only), BW: M- 224.2-225.6g, F- 172.7-174.8g, 5-7 weeks old)

dose/schedule/duration- animals received a once daily topical doses (0.5 ml/day) of 0, 0.1% and 1.0 % LG1069 (lot #- LG100069-000Z008, in mixture (w/w) of DEET, PEG400, PEG3350, butylated hydroxytoluene, butylated hydroxyanisole, and ascorbic acid) onto the fur-clipped dorsal area that is approximately 10% of total body area for a 6-h exposure period a day for 28 days. The following is percent composition of the topical ointment formulations applied to the animals:

Component	Ointment (%w/w)		
	0	0.1	1
LG 1069			
PEG 3550			
PEG 400			
DEET			
Laureth 4			
BHT			
BHA			
Ascorbic acid			

Observation- 14-d recovery; clinical signs/dermal irritation- daily, body weights/food consumption- weekly, clinical pathology/necropsy- d28 and at the end of recovery, pharmacokinetics- d1/d28 (blood collection times not specified).

GLP statement- Yes

Results: Due to signs of debilitation observed in majority of the treated animals in control and 1% gel groups, the study was terminated on day 20. Premature deaths occurred in vehicle group (1 F) and 1% gel group (14M/9F), but none in 0.1% group.

Dose, 0.5 ml/day	Control- vehicle only	0.1%	1 %
Mortality	1F (d8)	none	14M (d8), 9/14 F (d14) – early termination due to pain severe distress, lethargy and debilitation
Clinical sign	M/F	M/F	M/F
Debilitation	Some animals	UR	All animals
Black discharge- eyes	Some animals	Some animals	Some animals
Scaling/fissuring	All animals	All animals (less severe than animals in the control group)	All animals

Body weight gain, g D7 D14	M/F 24.1/12/3 32.2/15.2	M/F 28.8/17.2 37.6/17.5	M/F 14.9/1.2 -/26.6 (5/14 survived only)
Food consumption, g, d7	M/F 189.5/153.4	M/F 199.6/163.2	M/F 181.3/143.1
Hematology	No data submitted		
Clinical chemistry	No data submitted		
Gross pathology Tan crust on the adm. site	No data submitted	No Data submitted	10M/7F
Histopathology	No data submitted		
Pharmacokinetics	No data submitted		

Additional Information on DEET

DEET (N,N-diethyl-m-toluamide; $C_{12}H_{17}NO$, M.W. 191.3; CAS No. 134-62-3)

1. Pharmacopoeias- in US
2. Therapeutic category- insect repellent
3. Products- Numerous insect repellent (containing 6.65% to 100% DEET)
4. Toxicity- primarily neurologic (encephalopathy, seizures, movement disorders, coma), which may occur via oral or dermal exposure, most commonly in children.
   a. Non-human Toxicity (sources: Hazardous Substances Data Bank and MEDITEXT®)
   LD_{50} male and female rats- 3000 and 2000 mg/kg po, respectively, and
   LD50 rats- 5 gm/kg dermal (RTECS)
   LD_{50} rabbit dermal- 3180 mg/kg
   Teratogenicity- Not teratogenic at oral doses up to 725 mg/kg/day in rats on days 6 to 15 of gestation, and up to 325 mg/kg/day in rabbits on days 6 to 18 (Schoenig GP et al. Fundam Appl Toxicol 23:63-69, 1994). Offspring of male rats that received DEET 0.3 or 0.73 ml/kg/day subcutaneously 5 days/week for 9 weeks did not show evidence of teratogenic effects (Wright DM et al. Fundam Appl Toxicol 19:33-42, 1992).
   b. Neurologic toxicity- encephalopathy, seizures, and coma after ingestion or excessive dermal application of DEET (Tenenbein M JAMA 258:1509-1511, 1987; Edwards DL and Johnson CE Clin Pharm 6:496-498, 1987; Roland EN et al Canad Med Assoc J 132:155-156, 1985; Zadikoff MB J Pediatr 95:140-142, 1979)
   c. Dermatology- bullous eruption (and urticaria and contact dermatitis) after topical use of 50-70% DEET preparations (Lamberg SI and Mulrennan JA Arch Dermatol 100:582-586, 1069)
   d. Manic reaction- acute manic psychosis with paranoid and grandiose delusions and flight of ideas in 30-yr old man after 2 weeks of daily application of a 70% DEET preparation to treat a skin rash (Snyder JW et al. Clin Toxicol 24:429-439, 1986).

Summery of toxicology: The incidence of irritation at the administration site was higher in the high-DEET (25%) groups. The symptoms observed in animals treated with high DEET formulations are consistent with the known toxicities of DEET. The lethality of DEET in this study (0.5 ml x 25% = 0.125 g= 125 mg) was higher than published for rats (i.e., ~300 mg iv and ~ 750 mg dermal). The presence of 1% LG1069 appeared to enhance the toxicity of DEET in this study (1/20 death in the vehicle control group vs 23/28 death in 1% gel group). Readily available over-the-counter high strength insect repellants can contain up to 100% DEET. The results of this study are thus relevant to the human use of LG1069 gel formulation and the precaution in the label under Drug Interaction regarding concurrent use of DEET is appropriate.

Labeling: Precaution Section

Drug Interaction – Dermal toxicity study in rats with Targretin gel showed synergistic toxic effects with DEET, which is used as an insect repellant. Therefore, the concurrent use of Targretin gel with DEET-containing dermal products is discouraged.

OVERALL SUMMARY AND EVALUATION (of current and earlier reviews)

I. Pharmacology

A. Interaction with retinoid receptors

LG1069 interacts with retinoid X receptor subtypes (RXRα, RXRβ, and RXRγ), but not with retinoic acid receptor (RAR). LG1069 is capable of inhibiting AP-1 activity, inducing apoptosis, cell cycle arrest and differentiation, and inhibiting growth of tumor cells, through interaction with RXRs (and potentially with RAR at concentrations ≥ 1 uM) that function as ligand-dependent transcription co-factors and thus modulate expression of target genes. The following table shows binding affinity and transcriptional activator function of LG1069:

Receptor	Transactivation EC_{50} (nM)	Saturation Binding Kd (nM)
RARα	>10,000	6298
RARβ	>10,000	>10,000
RARγ	>10,000	4804
RXRα	25	30
RXRβ	27	14
RXRγ	19	15

A. Effects on cancer cells

Cancer Cell Line		Inhibition of Proliferation
Breast	T47D, SK-BR-3, MCR-7 Primary tumor samples	IC_{50}= 0.1-1 uM No inhibition with 0.1 uM LG1069
Cervix	ME-180 Primary tumor samples	IC_{50}= 0.5 uM No inhibition with 0.1 uM LG1069
Colon	Primary tumor samples	No inhibition at 0.1 uM LG1069
Head and Neck	1483, SCC25, SqCC/Y1	10-30% inhibition with 1 uM LG1069
Kaposi's sarcoma-derived cells		40% inhibition by 1 uM and 75% by 10 uM LG1069
Leukemia	Primary AML cells	0-50% inhibition with 0.1 uM LG1069
Melanoma	Primary tumor samples	No inhibition with 0.1 uM LG1069
Ovary	Primary tumor samples	10-50% inhibition with 0.1 uM LG1069

A. In vivo tumor models

Head and Neck cancer xenograft in nude mice- LG1069 (60 mg/kg/day, po) induced complete regression of HN9N and HN21P-xenografted tumors by day 49 and day 37, respectively. The complete regressions were maintained up to 68 days post-implantation of tumor cells. No growth inhibitory effects on 1483-xenografted tumors were observed.

NMU-induced rat mammary tumor- Dose-dependent effects of LG1069 were observed on complete response, tumor burden and number of tumors per animal. LG1069 at 100 mg/kg/day resulted in complete regression in 72% of primary tumors, 81% decrease in tumor burden, and significant decrease in number of tumors/animal (0.69 vs 3.63 in control).

B. Epidermal effects

Retinoids are known to inhibit the conversion of squamous cells to keratinocytes, suggesting retinoids as a potentially important therapeutic agent for treatment of skin disorders of keratinization (e.g., acne vulgaris, psoriasis). In an in vivo model study to examine antikeratinization activity of LG1069, hairless rhino mice received daily oral doses of LG1069. Antikeratinizing effect was not observed at doses up to 100 mg/kg/day. However, when administered topically (0.05 – 0.5%), antikeratinizing effect was observed.

II. Pharmacokinetics

A. Preclinical and clinical pharmacokinetics

Topically applied LG 1069 was systemically absorbed both in rats and humans. Due to the limited human exposure (or due to the lack of human exposure data), extensive interspecies comparisons of pharmacokinetics between animals and humans could not be made. When compared to orally administrated LG1069 in rats, topically applied LG 1069 produced almost equal levels of AUC and approximately 1/3 of Cmax in male rats, whereas it produced approximately 8.5-fold less AUC and 27-fold lower Cmax in female rats. The significant gender difference in exposure did not result in differential toxic effects in the 28-day repeated dermal toxicity study (study # RR-815-94-008). It is unknown whether this difference could be due to differences in grooming/licking habits in males that increased oral intake.

Pharmacokinetics	Rat			Human	
Dose, mg/m2 mg/kg	120 20	150 25	600, multiple dose 100	0.1-0.5% QD, BID, TID, QID	1% QOD, QD, BID, TID,QID
Route	Topical (Male)	Topical (Female)	PO (Male/Female)	Topical (phase I/II)	Topical (phase III)
Cmax, ug/ml	5.43	0.055	5.43/5.88	1.19 ± 3.51	4.05 ± 9.07
Tmax, h	3.83	8.67	3.2/2.1	8 - 12	4 - 8
T1/2, h	-	-	4.4/5.0	-	
$AUC_{0-\infty}$, ug.h/ml	3.4	0.84	15.5/28.6	-	
Per 100 mg/m2					
Cmax, ug/ml	00.27	0.055	5.43/5.88		
$AUC_{0-\infty}$, ug.h/ml	2.83	0.84	15.5/28.6		
Protein binding	-	-	-	>99.8 (5-5000 ng/ml)	
Metabolism	CYP2B, CYP3A and/or CYP4A-mediated oxidation: 6-hydroxy LG1069, 7-hydroxy LG1069, 6-oxo-LG1069, 7-oxo-LG1069 Glucuronidation: acyl glucuronide, ether glucuronide Conjugation: taurine conjugate, 7-sulfate conjugate				

*human pharmacokinetic parameters from vol. 1.6 (pp207-262)

III. Toxicology

Toxicity Study	Treatment	Toxicity Targets and Toxic Effects	Toxic Levels
Rat 28-Day Dermal Toxicity Study	0.01%, 0.1% or 1% LG1069 gel (0.5 ml/day, 2LG89A formulation) applied to skin area of approximately 10% of the body surface for 20 consecutive days.	- gr. 1 erythema, scabbing and epidermal scaling in all treated groups. - Increases in alkaline phosphatase (all treated groups), ALT (1% group), AST (1% group), cholesterol (0.1 and 1% groups),and triglyceride (1% group).	HNSTD= 1% TDL= 0.01%
Rat 28-Day Dermal Toxicity study RR-815-98-005a,	0.1% and 1% LG 1069 gel containing DEET, onto the fur-clipped dorsal area that is approximately 10% of total body area for a 6-h exposure period a day for 28 days.	- Due to signs of debilitation observed in majority of the treated animals in control and 1% gel groups, the study was terminated on day 20. Premature deaths occurred in vehicle group (1 F) and 1% gel group (14M/9F), but none in 0.1% group. DEET in formulations applied to animals in vehicle control and 1% gel groups and to animals in 0.1% group were 25% (w/w) and 2.5% (w/w), respectively. - Due to the synergistic toxic effects with DEET, which is used as an insect repellant, the concurrent use of Targretin gel with DEET-containing dermal products is discouraged.	LD_{50} = 1% (in formulation containing 25% DEET)
Guinea Pig Skin Irritation	30 mg/treatment site LG1069, covering 1-2 cm, bud x 7 d on dorsal area. A 7-point scoring scale (0- none to 6- necrosis) for erythema and edema was used.	time-dependent increases in the irritation by 1.0% alcoholic gel formulation, 0.45% PEG formulation or 0.35% petroleum ointment. Following 6-day treatment, irritation scores ranged from 2.9 to 4.0 in all formulations (i.e., moderate to severe irritation).	

Guinea Pig Dermal Sensitization	0.01 and 1.0 % LG1069 gel (0.5 ml/application) applied to skin area- 6 h once weekly for 3 weeks for the induction and 6 h once for the challenge phase. Dermal sensitization potential (Buehler's technique) and dermal irritation (erythema and edema) by Draize scale were measured.	- observed with erythema, scabbing, fissuring and necrosis, but no edema or inflammation, suggesting dermal irritation, but not dermal sensitization. - Erythema shown at challenge phase was grade 1 with or without epidermal scaling, indicating that 1.0% LG 1069 formulation may not be a sensitizer of the guinea pig skin.	NOAEL for skin sensitization = 1.0 %
In vitro human skin penetration	10 mg/cm^2 of 1% [^{14}C]LG 1069 in 1.0% alcoholic gel formulation, 0.45% PEG formulation or 0.35% petroleum ointment were applied to the skin chamber which were placed excised human cadaver skin (3 cm^2) with 200-300 um thickness. Dermis and epidermis of the skin were separated and counted in a scintillation counter.	- The 24-h cumulative penetration of the formulation was 0.1-0.22% except the alcoholic gel formulation which was less than 0.1%. - Percent recovery revealed that the order of the recovery was epidermis (4.1-20.9%) >> stratum corneum (1.4-5.7%) > dermis (0.2-2.5%)	
Rat 28-Day Oral Tox.	3, 10, 30 or 100 mkd, po, for 28 days	- Blood (hemorrhage in many tissues, prolongation of PT and aPTT, increased levels of fibrinogen), liver (hepatocellular necrosis), pancreas (acinar cell necrosis), heart(cardiomyopathy), bone (tibial osteopathy), skin (dermatopathy), lymphoid organs (lymphoid depletion in spleen, lymph nodes and thymus)	LD_{10}= 10 mkd HNSTD= 3 mkd

• mkd- mg/kg/day; * increased incidence of gavage-related deaths at 300 mkd

IV. Genetic Toxicology

LG1069 is not mutagenic in bacterial (Salmonella and E.coli) or mammalian cell (mouse lymphoma L5178Y tk$^{-/+}$) mutation assays, or clastogenic in vitro (CHO cells) or in vivo (micronucleus test in mice). Note that the CHO cell assay in the absence of S9 was not an adequate test due to the absence of cytotoxicity at the highest concentration tested. This result should therefore not be included in the label.

V. Reproductive Toxicology

Reproductive risk integration for Targretin: Oral developmental toxicity studies with bexarotene were conducted in rats with doses ranging from 1 mg/kg/day to 65 mg/kg/day. Since these studies confirmed the expected positive findings for a retinoid, one species was accepted as sufficient to support an NDA for CTCL patients. Although the study was oral, it was considered relevant to topical use, because there is measurable systemic exposure following topical administration. Positive signals were seen in fertility, development mortality, dysmorphogenesis and alterations to growth endpoints.

Practicing the reproductive risk analysis according to the draft 'Reproductive and Development Toxicity Integration tool', there is significant concern for adverse effects of Targretin on human fertility, fetal survival, morphogenesis and fetal growth. Concern is increased for all positive signals after considering the 'Signal Strength II', 'Pharmacodynamics', 'Concordance between Test Species and Humans, 'Relative exposures' and 'Class Alert' factors in the tool. Consideration of adjustments to overall concern based on the 'Signal Strength I' factor is discussed with the individual positive endpoints below.

Factors for Assessment	Reproductive Toxicity	Developmental Toxicities		
	Fertility	Development Mortality	Dysmorphogenesis	Alteration to Growth
Signal Strength I	0	+1	+1	+1
Cross-species concordance	-	-	-	-
Multiplicity of effects	-	↑	↑	↑
Adverse effects as function of time	-	↑	-	↑
Signal Strength II	+1	+1	+1	+1
Maternal toxicity/paternal toxicity	↑	-	-	-
Dose response	-	↑	↑	↑
Rare events	-	-	-	-
Pharmacodynamics	+1	+1	+1	+1
Therapeutic index	↑	↑	↑	↑
Comparison of biomarker benchmarks	-	↑	↑	↑
Similarity pharmacological and toxic mechanism	↑	-	-	-
Concordance between Test Species and Humans	+1	+1	+1	+1
Metabolism	↑	↑	↑	↑
General toxicity profiles	↑	↑	↑	↑
Biomarker profiles	-	-	-	-
Relative Exposure	+1	+1	+1	+1
Class Alerts	+1	+1	+1	+1
Total Score	+5	+6	+6	+6

Factors applying equally to all positive endpoints

Signal Strength II:

a. Maternal toxicity- Doses causing developmental toxicity, ≥ 24 mg/m2/day, were also maternally toxic (e.g., reduced body weight gain during the treatment period, $p<0.05$). Since these effects cannot be convincingly attributed to the reduced weight gain, the concern is unchanged. In contrast, no other findings at doses causing testicular degeneration were noted in male dogs and thus concern is increased for the fertility endpoint.

b. Dose-response relationship- There was a dose-response relationship for the testicular degeneration in the 91-day toxicity study in dogs, but not in the 6-month study. Therefore, the concern is unchanged. The body weight gains in dams was reduced in a dose-dependent manner. The incidence and severity of embryo/feto-toxicity (e.g., reduced embryo/fetal viability, reduced fetal body weights) and dysmorphogenesis (increased fetal incidences of variations and malformations such as cleft palate, depressed eye bulges, microphthalmia and incomplete or no ossifications) by LG1069 increased in a dose-dependent manner. Concern is enhanced.

c. Rare events- No rare events observed.

After considering all contributory elements for the Signal Strength II factor, concern was increased for all positive endpoints.

Pharmacodynamics: Endpoints with a positive signal were analyzed with respect to 2 contributory elements: the therapeutic index and the similarity between the pharmacological and toxicological mechanisms. Due to the lack of supporting data, the comparative biomarker index was not analyzed.

a. Therapeutic Index (TI)- as shown in the following table, TI is well below 5 for all the comparisons made and thus concern is enhanced.

Estimation Basis	TI	Remarks
(Dose of rat dysmorphogenesis)/ (human recommended dose)	0.08	(24 mg/m2/day)/ (300 mg/m2/day) = 0.08, i.e., $TI_{10/90}$ is <5 and thus the level of concern is enhanced.
(Dose of dog testicular degeneration)/ (human recommended dose)	0.1	(30 mg/m2/day)/ (300 mg/m2/day) = 0.1, i.e., $TI_{10/90}$ is <5 and thus the level of concern is enhanced

(Dose of rat dysmorphogenesis)/ (in vivo tumor efficacy in nude mice)	0.13	(24 mg/m2/day)/ (180 mg/m2/day) = 0.13, i.e., $TI_{10/90}$ is <5 and thus the level of concern is enhanced

b. Similarity between the pharmacological and toxicological mechanisms- LG1069 selectively binds and activates nuclear receptors of RARs and/or RXRs. RXRs can form heterodimers with various nuclear receptor partners (e.g., RARs, vitamin D receptor, thyroid receptor and peroxisome proliferator activator receptors). Once activated, these receptors function as transcription factors that regulate the expression of genes that control cellular proliferation and differentiation. Toxicities such as effects on the skin and bones are believed to be due to activation of retinoid receptors, the intended pharmacological target. Teratogenic effects of LG1069 may also result from these receptor interactions. Therefore, concern is enhanced.

After considering all contributory elements for the Pharmacodynamics factor, concern was increased for all positive endpoints listed above.

Concordance between Test Species and Humans:

a. Metabolic and drug distribution profiles- In human plasma and rat liver slices/liver microsomes, LG1069 underwent oxidative metabolism mediated by cytochrome P450 (mainly CYP 3A4). Its identified metabolites include 6- and 7-hydroxy LG1069 and 6- and 7- oxo-LG1069. LG 1069 (and its metabolites) is thought to be eliminated primarily through the hepatobiliary system in rats and humans and renal elimination of parent and its metabolites was minimal. Distribution profile in human is not available and thus differences between animals and humans could not be analyzed. Concern is enhanced.
b. General toxicity profiles- The overall toxicity profile of LG1069 in rats is similar to that in humans (e.g., lipid abnormalities, liver function abnormalities and cataract formation). Concern is enhanced.
c. Biomarker profiles- No data are available to assess the concordance of biomarker profiles.

After considering all contributory elements for the Concordance factor, concern was increased for all positive endpoints listed above.

Relative Exposure:

a. Kinetic comparison of relative exposure- as shown in the following table, relative exposure is well below 10 for all the comparisons made and thus concern is enhanced.

Estimation Basis	TI	Remarks
(Cmax of rat dysmorphogenesis)/ (Cmax* of human dose from the pivotal study)	8.37	(459.9 /54.9 ng/ml)= 8.3, i.e., the relative exposure is ≤ 10 and thus the level of concern is enhanced
(Cmax of dog testicular degeneration)/ (Cmax of human recommended dose)	2.35	(129.5 ng/ml /54.9 ng/ml)= 2.35, i.e., the relative exposure is ≤ 10 and thus the level of concern is enhanced

* Cmax of highest human values

b. biomarker as a measure of relative exposure- No data are available to assess this concern.

After considering all contributory elements for the Relative Exposure factor, concern was increased for all positive endpoints listed above.

Class Alerts: Retinoids as a class have demonstrated their capability of inducing teratogenic effects in animals and humans. Concern is increased.

Assessment of concern based on the Signal Strength I for individual positive endpoints

Fertility: Testicular effects were only seen in dogs. There was no temporal effect and no findings within other endpoints in this category. Concern was thus unchanged for the cross-species concordance, multiplicity of effects, adverse effects as function of time elements. Concern for the Signal Strength I factor was unchanged.

Developmental Mortality: Cross-species concordance could not be assessed because the reproductive toxicity studies were conducted in only one species. Concern is enhanced for the multiplicity of effects (e.g., developmental mortality, structural alterations and growth alterations) within the developmental toxicity category and adverse effects as function of time (e.g., early and late resorptions). Concern for the Signal Strength I factor was increased.

Dysmorphogenesis: Gross external (at 96 mg/m2/day), visceral (at 96 mg/m2/day) and skeletal (24 mg/m2/day) alterations were observed: external alterations- cleft palate, depressed eyes and small ears ; visceral alterations- cleft palate and microphthalmia of eye; and skeletal alterations- incomplete and/or no ossification in palate of skull, tympanic rings, sphenoid, squamosal, sterna centra and pelvis, 7th cervical rib and unilateral ossification of thoracic vertebrae.

Concern for the multiplicity of effects is enhanced because mortality and growth alterations as well as structural alterations were observed. Concern for the cross-species concordance and adverse effects as a function of time were not adjusted since studies were conducted in only one species and there was only one sacrifice time, respectively. Concern for the Signal Strength I factor was increased.

Alteration to Growth: Concern for the cross-species concordance was unchanged due to studies only in one species. Concern for the multiplicity of effects was enhanced, since mortality and structural alterations as well as growth alterations were observed. Concern for the adverse effects as function of time was enhanced because LG1069 effects on fetal weight and skeletal ossification might reflect adverse effects over a period of time. Concern for the Signal Strength I factor was increased.

Endpoints not studied

Studies were not conducted to assess effects of LG1069 on parturition, lactation or functional toxicities. The label should state that there were no observed effects on the endpoints because studies were not conducted, however positive signals were seen for related reproductive and developmental endpoints, which suggests some human risk.

Overall conclusion

The score of reproductive and developmental concerns ranged from +5 to +6, indicating a significant degree of concern in humans for impaired fertility, developmental mortality, dysmorphogenesis and altered fetal growth from exposure to LG1069. Plasma bexarotene concentrations in patients with CTCL applying Targretin® gel 1% were generally1/100 the Cmax associated with dysmorphogenesis in rats, although some patients had Cmax levels that were only approximately 1/8 the concentration associated with dysmorphogenesis in rats.

VI. Safety Pharmacology

Study	Model	Effects
Cardiovascular Assay	Normotensive male SD rats received daily oral doses of 0, 10, 30 and 60 mg/kg/day LG 1069 by gavage. Mean arterial blood pressure and heart rate (plus clinical pathology) were measured.	1. No effects on mean arterial blood pressure and heart rate. 2. 23% and 20% Increases in aPTT in 30 ($p<0.01$) and 60 mg/kg ($p<0.01$) groups, respectively.

Blood Coagulation	Male SD rats received daily oral doses of 0, 10 or 100 mg/kg/day LG1069, admixed with powdered feed, for 29 days. When PT and aPTT increased 2-fold, animals received 10 mg/kg vitamin K_1 by ip (d17/18) or sc (d19/20).	1. aPTT increased 3-fold in 10 mg/kg group and 4-fold in 100 mg/kg group over control at week 3. PT also increased 2-fold in 100 mg/kg group. Vitamin K restored PTs and aTPTTs to control levels after 4 days of treatment. 2. Due to bleeding disorders, 6/8 animals in 100 mg/kg group died. The bleeding disorders were fully reversed when vitamin K was co-administered.
Hepatocyte Proliferation	Female SD rats received daily oral doses of 100 mg/kg/day by gavage for 1, 2, 4, or 12 days. Two h prior to sacrifice, rats were injected with 50 uCi [^{3}H]thymidine by ip. At necropsy, livers were excised, homogenized and analyzed for [^{3}H]thymidine incorporation and DNA contents.	3. absolute liver weight increased significantly following 4 or 12 days dosing (8.4 g vs. 5.1 g control). 4. Increased rate of [^{3}H]thymidine incorporation into liver occurred during LG1069 administration and was reversible over a 5-day recovery period. 5. liver concentrations of protein, DNA and glycogen from LG1069-treated groups were not significantly different from control group.
Plasma Lipids	Male rabbits received oral daily doses of 0, 1, 10 or 100 mg/kg/day LG1069 by gavage for 4 days. Blood for evaluation of lipids was collected at termination.	1. increases in plasma cholesterol (3-fold) and triglycerides (10-fold) in 100 mg/kg group. LDL and HDL were not affected.
Neuro-pharmacology	Male SD rats received daily oral doses of 0, 10, 30 or 100 mg/kg/day LG1069 by gavage for 4 days. Ataxia, convulsions, alertness and spontaneous motor activity were measured.	2. No treatment-related effects on ataxia, convulsions, alertness, spontaneous motor activity, or body temperature were observed.

VII. Phototoxicity

LG1069 was photoreactive in in vitro assays which indicates a photosensitizing potential (photo-irritation or photo-allergy).

Phototoxic Assay	Results
MatTEK phototoxicity test	Not photoreactive
Hemoglobin oxidation and photohemolysis	Photoreactive
Histidine Assay	Photoreactive
Protein photobinding assay	The stoichiometry of photobinding was 1 molecule of LG1069 to 9.05 molecules of albumin (i.e., (albumin/LG1069) = 16.2 uM/1.79 uM = 9.05). These results suggest that LG1069 is a potential photosensitizer.

VIII. Overall Summary of Labeling Issues

A. Pharmacological and Toxicological Effects

Retinoids are an integral part of regulating mechanisms of cell proliferation and differentiation via control of the expression of the genes for many cytokines (e.g., TGFβ, TGFα, FGF, IGF, IL-1, IL-2, IL-8, IFNγ, NGF and PDGF), their receptors (e.g., TGFβ-R, EGFR, PDGF-R, IL-6R, and NGF-R) and oncogenes (e.g., jun, fos, fgr (src TK family)). Retinoids interact with retinoid receptors that are classified as retinoic acid receptor (RAR) and retinoid X receptor (RXR) subtypes. Retinoid receptors act as transcription factors by forming homodimers (RAR-RAR and RXR-RXR) or heterodimers (RAR-RXR). RXR also forms complexes with many transcriptional factors (e.g., vitamin D receptor, thyroid hormone receptor, PPARs, etc) for subsequent regulation of gene transcription. LG1069 is a RXR-specific agonist that interacts with RXR subtypes with Kd (affinity) ranging from 14 nM to 30 nM and with EC_{50} (transactivation) ranging from 19 nM to 27 nM.

LG1069 inhibits proliferation of cancer cells of breast, head and neck, ovary and Kaposi's sarcoma, and of AML cells with IC_{50} of ≥ 0.1 uM. Oral LG1069 did not inhibit the conversion of squamous cells to keratinocytes.

In the 28-day dermal toxicity study in rats, skin irritation study in guinea pigs and dermal sensitization study in guinea pigs, topically applied LG1069 (up to 1 %) produced erythema, scabbing, fissuring and necrosis, but no edema or inflammation, suggesting it as a dermal irritant, but not a sensitizer. In addition to the effects on the skin, topical LG1069 also increased liver enzymes (e.g., ALT and AST), cholesterol, triglyceride and HDL in rats, suggesting significant systemic exposure following topical application of LG1069.

Following oral administration in animals, LG1069 also produced liver toxicities (hepatocellular necrosis, hypertrophy, ↑AST/ALT). Other LG1069-induced toxicities after oral administration included blood (hemorrhage in many tissues, ↓hemoglobin and RBC prolongation of PT and aPTT, increased levels of fibrinogen), bone (tibial osteopathy), eye (cataract), heart (cardiomyopathy), pancreas (acinar cell necrosis), skin (dermatopathy, acanthosis), lymphoid organs (lymphoid depletion in spleen, lymph nodes and thymus), stomach (acanthosis, hyperkeratosis), and testes (tubular degeneration).

Assays (e.g., MatTEKskin model assay, hemoglobin oxidation/photohemolysis, histidine assay and protein photobinding assay) conducted to assess phototoxic potential of LG1069 suggest that LG1069 is a phototoxin and photoallergen.

B. Carcinogenicity, Mutagenicity, and Impairment of Fertility

Carcinogenicity- Long-term studies in animals to assess the carcinogenic potential of LG1069 have not been conducted.

Mutagenicity- LG1069 was not genotoxic in a bacterial (Salmonella and E.coli) mutation assay, mammalian cell (mouse lymphoma L5178Y $tk^{-/+}$) mutation assay, chromosome aberration assay (CHO cell) or an *in vivo* micronucleus test in mouse bone marrow. The CHO cell assay in the absence of S9 activation was not an adequate test for genetic toxicity.

Impairment of Fertility- LG1069 induces testicular degeneration in dogs (1.5 mg/kg/day).

C. Pregnancy Category

Pregnancy Category- X

Retinoids, as a class, have demonstrated their capability of inducing teratogenic effects in animals and humans. LG1069 is maternally toxic in rats when given orally at 4 mg/kg/day (8.3-fold the highest human Cmax obtained from the clinical trials). LG1069 is fetotoxic (≥ 10 mg/kg/day, 13.8-fold the highest human Cmax obtained from the clinical trials) and teratogenic (≥ 4 mg/kg/day, 8.3-fold the highest human Cmax). In the analysis according to the draft Reproductive and Developmental Toxicity Integration Tool, the score of reproductive and developmental concerns ranged from +5 to +6, indicating a significant degree of concern in humans for impaired fertility, developmental mortality, dysmorphogenesis and altered fetal growth from exposure to LG1069.

Topically applied LG1069 appears to be systemically absorbed in rats and humans. However, due to the limited human exposure data and/or to the limited human exposure, the interspecies comparisons could not be made. The half-life in rats appears to be similar to that in humans (e.g., 8.67 h in rats and 8-12 or 4-8 h in humans). In rats, a significant gender difference was observed. Male animals showed greater exposure and Cmax than female animals. When compared to the oral administration, after topical application of LG1069 and per unit mg/m2 basis, males produced almost same levels of AUC and approximately one third the Cmax, whereas females produced approximately 8.5-fold and 27-fold lower levels in AUC and Cmax, respectively.

Gender	Male		Female	
Dose, mg/m2	600	120	600	150
Route	Po	Topical	Po	topical
AUC, ug.h/ml	15.5	3.4	28.6	0.84
Cmax, ug/ml	5.43	0.33	5.88	0.055
Per 100 mg/m2 Basis				
AUC, ug.h/ml	2.58	2.83	4.76	0.56
Cmax, ug/ml	0.90	0.27	0.98	0.036

However, differential toxic effects based on gender were not observed in the 28-day repeated dose dermal toxicity study.

In humans, the sponsor provided only Cmax plasma levels, but not AUC exposure information. Some patients had covered up to 90% of their body surface with the Targretin gel. The submitted data showed that at least one post-dose plasma concentrations of LG 1069 could be measured from 42 of 65 patients in phase I/II studies, although 79% of 901 blood samples collected had LG 1069 concentration below the limit of quantification (<1 ng/ml). Blood samples from 35 of the 38 patients in a phase III study had at least one LG 1069 concentration quantifiable. Of the 267 post-dose blood samples, 38% had concentrations below the limit of quantification and 62% were quantifiable. These results suggest that dermal absorption in humans appears to be very low to undetectable. Human Cmax levels were approximately 1/100 the Cmax associated with dysmorphogenesis in rats, although some patients had higher levels such that the ratio was approximately 1/8. Since the human exposure (based on Cmax) is within 10-fold of the Cmax associated with developmental toxicity, there appears to be a significant risk of fetal harm in pregnant women using Targretin gel.

Considering the long lifespan of patients, the availability of alternative treatments and no effect on long-term survival, the benefit of Targretin gel use does not clearly out-weigh the risk to pregnancy. Targretin gel should thus be classified as Pregnancy Category X.

D. Cataract Formation

Cataract development has been reported in association with the oral administration of LG1069 at 3 mg/kg/day in rats (1/17th the recommended oral clinical dose on a mg/m2 basis) and 3 mg/kg/day in dogs (1/5th the recommended oral clinical dose on a mg/m2 basis). The mechanism of LG1069-induced cataracts was not known.

E. Drug Interaction

Dermal toxicity study in rats with Targretin gel showed synergistic toxic effects with DEET, which is used as an insect repellant. Therefore, the concurrent use of Targretin gel with DEET-containing dermal products is discouraged.

G. Phototoxicity

Retinoids as a class have been associated with photosensitivity. LG1069 was phototoxic in in vitro phototoxicity assays and showed a photosensitizing potential in the protein photobinding assay.

RECOMMENDATION

1. The pharmacology/toxicology data submitted supports approval of Targretin gel for the treatment of cutaneous manifestations of CTCL.
2. Revise labeling as recommended in a separate labeling review.

/S/ 5/30/00

Chang H. Ahn, Ph.D.
Expert Pharmacologist

Original NDA 21-056
c.c. /Division File
/PAndrews
/RWhite/ABaird
/CAhn

/S/ 5/30/00

Unbinding