CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-056

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

Submission: NDA 21-056
Submission Date: December 9, 1999
Drug Name: Targretin® (bexarotene) gel 1%
Dosage Form: topical gel
Applicant: Ligand Pharmaceuticals, Inc.
Submission Type:
Reviewer: Gene M. Williams, Ph.D.

Table of Contents

Appendix 1. **Reviewer's package insert modifcation recommendations.**

Appendix 2. **Applicant's Non-Annotated Package Insert**

Appendix 3. **Applicant's Human Pharmacokinetic and Bioavailability Technical Summary**

Appendix 4. **Current package insert for Targretin® (bexarotene) capsules**

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

APPEARS THIS WAY
ON ORIGINAL

I. Synopsis and regulatory recommendations

I.A. Synopsis

The applicant seeks approval for Targretin® (bexarotene) gel 1% for the treatment of patients with all clinical stages of CTCL (IA-IVB) 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. Targretin® (bexarotene) capsule, 75 mg for oral administration (recommended initial dose: 300 mg/m^2), was recently approved for a similar indication.

The pharmacokinetic database for CTCL patients receiving 1% gel was 841 plasma concentration-time samples which were obtained from 92 patients. Of these 841 samples, only two (both from the same individual) had bexarotene concentrations above 30 ng/mL: one was 55 ng/mL, the other 47 ng/mL. Mean bexarotene Cmax following oral administration of Targretin® (bexarotene) capsule (300 mg/m^2) is > 1100 ng/mL (see Appendix 5. Clinical Pharmacology/Biopharmaceutics review of Targretin® (bexarotene) capsules). However, only two patients with intense dosing (> 40% body surface area with lesions and QID dosing) were sampled for pharmacokinetics.

The to-be-marketed formulation and only the to-be-marketed formulation was studied in the single efficacy and safety study (Study L1069T-25). Thirty-eight of the patients in this study were sampled for pharmacokinetics (total number entered in study = 50); these 38 patients produced 301 plasma samples.

The Applicant has not submitted release rate testing for this product.

APPEARS THIS WAY
ON ORIGINAL

I.B. Recommendations

1. Because only two patients with > 40% body surface area lesioned and QID dosing were sampled for pharmacokinetics, we recommend~~ation~~ that the language in the package insert be qualified so that it is understood that conclusions can only be drawn for patients at the lower end of the recommended dosing range.

2. Because patients with intense dosing regimens (> 40% BSA lesioned, QID dosing) were largely not studied for pharmcokinetics, the impact of patient characteristics on pharmacokinetics following intense dosing is largely unknown. For this reason, we recommend that the Special Population section of the package insert be modified and that the language indicating that there are not concentration differences between Special Population and non-Special Population patients be eliminated.

/S/ 6/6/00

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

/S/ 6/6/00

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

Clinical Pharmacology and Biopharmaceutics Briefing: June x, 2000.

cc: NDA 21-056(original file)
HFD-150/Division File
HFD-150/ ABaird
HFD-150/ JJohnson, RWhite
HFD-850/LLesko
HFD-860/ MMehta, ARahman
CDRBiopharm

II. Background

II.A. What is the indication?

Answer: The applicant seeks approval for the topical treatment of cutaneous lesions in patients with CTCL (Stage IA and IB) who have not tolerated other therapies or who have refractory or persistent disease.

Targretin® (bexarotene) capsules were recently approved for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.

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, including Targretin® (bexarotene) oral capsules.

II.C. Are there any unique regulatory agreements or issues for this?

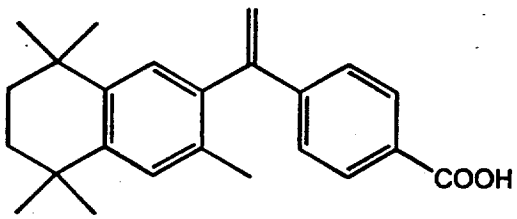
Answer: There are no unique regulatory agreements.

The indication sought by the applicant has Orphan Drug status.

APPEARS THIS WAY
ON ORIGINAL

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® gel is a clear gelled solution containing 1.0% (w/w) bexarotene in a base of dehydrated alcohol, USP, polyethylene glycol 400, NF, hydroxypropyl cellulose, NF, and butylated hydroxytoluene, NF.

III. Question-based review

III.A. Is bexarotene systemically absorbed after Targretin® (bexarotene) gel 1% administration?

Administration of Targretin® (bexarotene) gel 1% results in measurable plasma concentrations of bexarotene. However, the concentrations measured are very low in comparison to concentrations observed following oral dosing of Targretin® (bexarotene) capsules.

The pharmacokinetic database for 1% gel was 841 plasma concentration-time samples which were obtained from 92 patients. Of these 841 samples, 535 were below the lower limit of quantitation (1 ng/mL). Only two samples (both from the same individual whom the Applicant indicates that applied an inordinately large amount of gel) had bexarotene concentrations above 30 ng/mL: one was 55 ng/mL, the other 47 ng/mL. In contrast, mean bexarotene C_{max} following oral administration of Targretin® (bexarotene) capsule at the highest recommended starting dose (300 mg/m^2) is > 1100 ng/mL (see Appendix 5. Clinical Pharmacology/Biopharmaceutics review of Targretin® (bexarotene) capsules).

III.B. What database examining systemic absorption of bexarotene was submitted?

The universally low plasma concentrations following gel administration, together with the knowledge of bexarotene pharmacokinetics following oral administration, eliminate the need for further description of the plasma concentration-time profile following gel administration. However, it is necessary to determine that the database is sufficient for generating a package insert for the product. To accomplish this, the database was examined in three ways. First, the characteristics of all patients receiving the to-be-marketed strength are shown (Table 1.). Next, the data available for CTCL patients receiving 1% gel is grouped according to % body surface area (% BSA) lesioned (Table 2.). Patients with higher BSA lesioned would be expected to have received a higher dose of gel. Finally, patients with high % BSA lesioned and high dose frequency (the single efficacy and safety study was performed using titration of dosing frequency from QOD to QID) are examined (Table 3.). Only 6 CTCL patients with > 20% BSA lesioned and QID dosing were sampled, of these 6 only 2 had > 40% BSA lesioned. The Dosage and Administration portion of the current package insert makes no restrictions regarding BSA lesioned and dosage regimen – treating a patient with >95% BSA lesioned with QID dosing is consistent with the current package insert.

The absence of sampling at the extremes of the package insert recommended dosing regimen impacts the package insert. The language in the package insert will have to be qualified so that it is understood that conclusions can only be drawn for patients at the lower end of the recommended dosing range.

Table 1. sampling following administration of 1% gel to CTCL patients								
			number of samples at each sampling time					
patient type	# patients	# plasma samples	0 - 4 hrs	4.01 - 8 hrs	8.01 - 16 hrs	16.01 - 24 hrs	> 24 hrs	UNK
all	92	841	203	218	194	57	103	66
white males 18-64	25	232	43	38	85	18	38	10
black males 18-64	2	7	1		1	2	2	1
asian males 18-64	1	2	2					
white females 18-64	23	223	68	58	42	17	18	20
black females 18-64	7	59	21	12	9	3	7	7
asian females 18-64	1	10	4	4	0	1	1	0
white males > 64	18	148	36	49	24	9	17	13
black males > 64	1	1	1	0	0	0	0	0
asian males > 64	0							
white females > 64	9	121	21	44	30	4	16	6
black females > 64	4	30	7	10	2	3	3	5
asian females > 64	0							
< 18 = 1 white male	1	8	0	2	1	0	1	4

Table 2.: sampling following 1% gel to CTCL patients as a function of % BSA lesioned								
			number of samples at each sampling time					
patient type/% BSA lesioned	# patients	# plasma samples	0 - 4 hrs	4.01 - 8 hrs	8.01 - 16 hrs	16.01 - 24 hrs	> 24 hrs	UNK
<10	60	494	140	121	101	35	66	31
10-20	24	156	30	44	49	6	14	13
21-40	12	113	18	40	29	13	10	3
> 40	7	26	9	7	2	1	2	5

Table 3.: sampling following 1% gel to CTCL patients with > 20% BSA lesioned dosed QID								
			number of samples at each sampling time					
patient type/% BSA lesioned	# patients	# plasma samples	0 - 4 hrs	4.01 - 8 hrs	8.01 - 16 hrs	16.01 - 24 hrs	> 24 hrs	UNK
21-40	4	11	6	0	1	1	2	1
> 40	2	7	5	0	0	0	1	1
*1 patient contributed 6 samples, the other contributed a single sample which was collected at an unknown time								

III.C. Can Special Population information be included in the Clinical Pharmacology portion of the package insert?

The applicant has attempted to use a number of techniques (regression and NONMEM analyses) to conclude that plasma concentrations following topical gel administration do not differ across genders, patients of varying age and patients of varied ethnic background. As demonstrated in Tables 1. - 3. above, few patients with high BSA and intense dosing regimens were sampled. Thus, under the only circumstances where plasma concentrations are potentially significant, there is insufficient data to determine if there are sub-population differences. Because of this, potentially relevant sub-population differences are not known and the Clinical Pharmacology portion of the package insert should not include language indicating that there are no differences due to the relevant patient characteristics.

III.D. Are there bioequivalence issues for this product?

There are no bioequivalence issues for this product.

The to-be-marketed formulation, and only the to-be-marketed formulation, was studied in the single safety and efficacy study (Study L1069T-25).). Thirty-eight of the patients in this study were sampled for pharmacokinetics (total number entered in study = 50); these 38 patients produced 301 plasma samples.

III.E. Is the release rate specification adequate to assure adequate quality control of the drug product?

There is no release rate specification but, according to our current regulatory standard, a release rate specifcation is not necessary to assure adequate quality control of this drug product.

The drug product is a topical gel solution containing 1.0% (w/w) active ingredient in a base of dehydrated alcohol, USP, polyethylene glycol 400, NF, hydroxypropyl cellulose, NF, and butylated hydroxytoluene, NF).

Appendix 1. Reviewer's package insert modification recommendations.

APPEARS THIS WAY
ON ORIGINAL

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

Appendix 3. Applicant's Human Pharmacokinetic and Bioavailability Technical Summary

APPEARS THIS WAY
ON ORIGINAL

6.1. Tabular Biopharmaceutics Study Summary

APPEARS THIS WAY
ON ORIGINAL

Table 6.1-A. Biopharmaceutics Summary: Concentration Monitoring During Topical Studies With Targretin® Gel

Study Number	Study Design	Route/ Dose Form	Dose Frequency	Strength (% w/w)	Lot (Formulation)	Plant[1]: Manufacture Date	Patient Number[2]	IND # Submission Date	Applicant Conclusions
L1069-94-03T	Phase I-II, Multiple-dose, Safety, Tolerability, Efficacy and PK in patients with KS	Topical/ Gel	QD, BID, TID, QID	0.1 0.5 1.0	9404-001 (TG-2) 9404-002 (TG-3) 9404-003 (TG-4)	D:4/11/94 D:4/12/94 D:4/13/94	14	6/29/94	No or minimal systemic exposure or accumulation of bexarotene occurred. Despite application of gel for up to 80 weeks, 297 (98%) of 303 post-dose samples had bexarotene concentrations below the assay limit of quantitation (LLQ of 1 ng/mL).
L1069T-07	Phase I-II, Multiple-dose, Safety, Tolerability, Efficacy and PK in patients with KS	Topical/ Gel	QD, BID, TID, QID	0.1 0.5 1.0	9408-005 (TG-2) 9408-006 (TG-3) 9412-001 (TG-3) 9408-007 (TG-4) 9412-002 (TG-4)	D:9/7/94 D:9/7/94 D:12/13/94 D:9/12/94 D:12/15/94	11	10/19/94	
L1069T-08	Phase I-II, Multiple-dose, Safety, Tolerability, Efficacy and PK in patients with KS	Topical/ Gel	QD, BID, TID, QID	0.1 0.5 1.0	9408-005 (TG-2) 9408-006 (TG-3) 9408-007 (TG-4)	D:8/23/94 D:9/7/94 D:9/12/94	4	1/27/95	
L1069T-13	Phase I-II, Multiple-dose, Safety, Tolerability, Efficacy and PK in patients with KS	Topical/ Gel	QD, BID, TID, QID	0.1 0.5 1.0	9404-001 (TG-2) 9408-006 (TG-3) 9408-007 (TG-4)	D:4/11/94 D:9/7/94 D:9/12/94	5	8/28/95	
L1069T-15	Phase I-II, Multiple-dose, Safety, Tolerability, Efficacy and PK in patients with KS	Topical/ Gel	QD, BID, TID, QID	0.1 0.5 1.0	9408-005 (TG-2) 9408-006 (TG-3) 9408-007 (TG-4)	D:8/23/94 D:9/7/94 D:9/12/94	11	7/25/95	

(1) Plant: S = A.C. Stiefel;
(2) Patient Number is number of patients providing pharmacokinetic samples.

Table 6.1-A. Biopharmaceutics Summary: Concentration Monitoring During Topical Studies With Targretin® Gel (continued)

Study Number	Study Design	Route/ Dose Form	Dose Frequency	Strength (% w/w)	Lot (Formulation)	Plant[1]: Manufacture Date	Patient Number[2]	IND # Submission Date	Applicant Conclusions
L1069-94-04T	Phase I-II, Multiple-dose, Safety, Tolerability, Efficacy and PK in patients with CTCL	Topical/ Gel	QOD, QD, BID, TID, QID	0.1	9408-005 (TG-2) 9401-001 (TG-2) 9604-010 (TG-7)	D:8/23/94 S: 4/30/96 S: 4/30/96	21	[redacted] 10/5/94	Systemic exposure to bexarotene was low and accumulation was minimal. Despite application of gel for up to 135 weeks, most (96%) post-dose samples were <5 ng/mL. Bexarotene concentrations tended to increase with increasing surface area treated or increasing gel strength or frequency of application.
				0.5	9404-002 (TG-3) 9412-001 (TG-3)	D:4/12/94 D:12/13/94			
				1.0	9404-003 (TG-4) 9412-002 (TG-4) 9612-003 (TG-5) 9710-002 (TG-5)	D:4/13/94 D:12/15/94 S:12/10/96 S:1/26/98			
				Placebo	9604-013 (PTG-2)	S: 4/24/96			
L1069T-11	Phase I-II, Multiple-dose, Safety, Tolerability, Efficacy and PK in patients with CTCL	Topical/ Gel	QOD, QD, BID, TID, QID	0.1	9411-001 (TG-2) 9604-010 (TG-7) 9607-005 (TG-7)	D:11/17/94 S:4/30/96 S:8/28/96	33	[redacted] 4/18/95	
				0.5	9411-002 (TG-3) 9605-005 (TG-6)	D:11/21/94 S:5/15/96			
				1.0	9408-007 (TG-4) 9411-003 (TG-4) 9412-002 (TG-4) 9608-002 (TG-5) 9612-003 (TG-5) 9710-002 (TG-5)	D:9/12/94 D:11/23/94 D:12/15/94 S:10/3/96 S:12/10/96 S:1/26/98			
				Placebo	9604-013 (PTG-2)	S: 4/24/96			
L1069T-12	Phase I-II, Multiple-dose, Safety, Tolerability, Efficacy and PK in patients with CTCL	Topical/ Gel	QOD, QD, BID, TID, QID	0.1	9411-001 (TG-2)	D:11/17/94	12	[redacted]	
				0.5	9411-002 (TG-3)	D:11/21/94		8/9/95	
				1.0	9411-003 (TG-4) 9412-002 (TG-4)	D:11/23/94 D:12/15/94			
				Placebo	9604-013 (PTG-2)	S:4/24/96			

(1) Plant: S = A.C. Stiefel;
(2) Patient Number is number of patients providing pharmacokinetic samples.

Table 6.1-A. Biopharmaceutics Summary: Concentration Monitoring During Topical Studies With Targretin® Gel (continued)

Study Number	Study Design	Route/ Dose Form	Dose Frequency	Strength (% w/w)	Lot (Formulation)	Plant[1]; Manufacture Date	Patient Number[2]	IND # Submission Date	Applicant Conclusions
L1069T-25	Phase III controlled, multiple-dose, tolerability, safety, efficacy and pharmacokinetic study in patients with refracatory or persistent early stage CTCL	Topical/ Gel	QOD, QD, BID, TID, QID	1.0	9608-002 (TG-5) 9612-003 (TG-5) 9710-002 (TG-5)	S:10/15/96 S:1/3/97 S:2/5/98	36	[redacted] 3/19/97	Systemic exposure to bexarotene was low and accumulation was minimal. Despite application of gel for up to 100 weeks, most (39%) post-dose samples were <5 ng/mL. Bexarotene concentrations tended to increase with increasing surface area treated or increasing frequency of application

(1) Plant: S = A.C. Stiefel;
(2) Patient Number is number of patients providing pharmacokinetic samples.

Table 6.1-B. Biopharmaceutics Summary: Supportive Oral Studies With Targretin® Capsules

Study Number	Study Design	Route	Dose Form	Strength	Batch	Plant[1]/ Manufact. Date	Doses	Number of Patients[2]	IND # Submission Date	Applicant Conclusions
L1069-93-01	Phase I multiple-dose safety, tolerance, efficacy and pharmaco-kinetics in patients with advanced cancers	Oral	Soft Gelatin Capsule	10 mg NM	9309-001	9/10/93	5 mg/m^2 QD (NM)	4	8/23/95	Micronized bexarotene resulted in higher plasma concentrations than nonmicronized bexarotene. For micronized bexarotene: • C_{max} and AUC values were approximately dose-proportional over evaluated dose range. • No reduction in concentrations with repeated daily dosing. • Harmonic mean half-life over a 6-hr sampling period was 1.4 hr. • Only minimal accumulation was observed.
							20 mg/m^2 QD (NM)	3		
				10 mg M	9408-002	7/27/94	40 mg/m^2 QD (NM)	3		
							18 mg/m^2 QD (M)	3		
				25 mg NM	9309-002	9/10/93	50 mg/m^2 QD (M)	3		
							140 mg/m^2 QD (M)	3		
				25 mg M	9408-003	7/27/94	300 mg/m^2 QD (M)	4		
					9502-003	5/3/95	400 mg/m^2 QD (M)	4		

(1)

(2) Number of Patients providing pharmacokinetic samples.
NM = Nonmicronized; M = Micronized.

Table 6.1-B. Biopharmaceutics Summary: Supportive Oral Studies With Targretin® Capsules (continued)

Study Number	Study Design	Route	Dose Form	Strength	Batch	Plant[1]/ Manufact. Date	Doses	Number of Patients[2]	IND # Submission Date	Applicant Conclusions
L1069-93-02	Phase I-II multiple-dose safety, tolerance, efficacy and pharmaco-kinetics in patients with advanced cancers	Oral	Soft Gelatin Capsule	10 mg NM	9309-001	9/10/93	5 mg/m² QD (NM)	3	[redacted]	Micronized bexarotene resulted in higher plasma concentrations than nonmicronized bexarotene. For micronized bexarotene: • C_{max} and AUC values were approximately dose-proportional up to 800 mg/m² dose level. • Dose levels ≥230 mg/m² had reduced concentrations with repeat dosing; there was no clear dose-relationship to reductions. • Harmonic mean half-life over 6-hr sampling period was 1.9 hr. • Only minimal accumulation was observed.
							10 mg/m² QD (NM)	3		
				10 mg M	9408-002	7/27/94	20 mg/m² QD (NM)	3	8/11/98	
					9502-002	5/3/95	30 mg/m² QD (NM)	3		
							45 mg/m² QD (NM)	3		
				25 mg NM	9309-002	9/10/93	75 mg/m² QD (NM)	3		
							21 mg/m² QD (M)	3		
				25 mg M	9408-003	7/27/94	50 mg/m² QD (M)	3		
					9502-003	5/3/95	83 mg/m² QD (M)	3[3]		
							140 mg/m² QD (M)	4		
				50 mg M	9508-001	7/31/95	230 mg/m² QD (M)	5[3]		
							380 mg/m² QD (M)	5		
				75 mg M	9604-001	4/10/96	500 mg/m² QD (M)	4		
					9609-004	10/16/96	650 mg/m² QD (M)	6		
							800 mg/m² QD (M)	6		
							1000 mg/m² QD (M)	6		

(1)

(2) Number of patients providing pharmacokinetic samples.

(3) One patient provided pharmacokinetic data at both the 83 mg/m² and 230 mg/m² dose levels.

NM = Nonmicronized; M= Micronized.

Table 6.1-B. Biopharmaceutics Summary: Supportive Oral Studies With Targretin® Capsules (continued)

Study Number	Study Design	Route	Dose Form	Strength	Batch	Plant[1]/ Manufact. Date	Doses	Number of Patients[2]	IND # Submission Date	Applicant Conclusions
L1069-94-02	Phase II multiple-dose safety, tolerance, efficacy and pharmaco-kinetics in patients with advanced head and neck cancer	Oral	Soft Gelatin Capsule	10 mg NM	9309-001	9/10/93	10 mg/m^2 QD (NM)	[redacted]	[redacted]	Micronized bexarotene resulted in higher plasma concentrations than nonmicronized bexarotene. For micronized bexarotene: • C_{max} and AUC values were approximately dose-proportional. • Dose-independent reduction in concentrations observed with repeat BID dosing at all dose levels. • Harmonic mean half-life over 6-hr sampling period was 1.6 hr. • Only minimal accumulation was observed.
				10 mg M	9408-002	7/27/94	25 mg/m^2 BID (M)	[redacted]		
					9502-002	5/3/95	50 mg/m^2 BID (M)	[redacted]	10/29/97	
				25 mg M	9408-003	7/27/94	150 mg/m^2 BID (M)	[redacted]		
					9502-003	5/3/95	200 mg/m^2 BID (M)	[redacted]		
				50 mg M	9508-001	7/31/95	300 mg/m^2 BID (M)	3		
				75 mg M	9604-006	4/24/96				
					9604-007	4/25/96				
					9606-001	6/17/96				
					9608-008	8/21/96				

(1)

(2) Number of patients providing pharmacokinetic samples.
NM = Nonmicronized; M = Micronized.

Table 6.1-B. Biopharmaceutics Summary: Supportive Oral Studies With Targretin® Capsules (continued)

Study Number	Study Design	Route	Dose Form	Strength	Batch	Plant[1]/ Manufact. Date	Doses[2]	Number of Patients[3]	IND # Submission Date	Applicant Conclusions
L1069-23	Phase II-III open-label, controlled, multiple-dose tolerability, safety, efficacy and pharmaco-kinetic study in patients with refractory or persistent early stage CTCL	Oral	Soft Gelatin Capsule	10 mg M 75 mg M	9502-002 9704-004 9604-001 9604-007 9606-001 9608-008 9609-004 9704-005 9706-012 9709-009	5/3/95 4/10/97 4/10/96 4/25/96 6/17/96 8/21/96 10/16/96 4/22/97 6/12/97 9/9/97	6.5 mg/m^2 QD (M) 300 mg/m^2 QD (M) 500 mg/m^2 QD (M) 650 mg/m^2 QD (M)	12 23 11 5	7/21/98	• Large variability in plasma bexarotene concentrations; however, plasma concentrations increased with increasing dose. • Plasma bexarotene concentrations were higher when patients ingested gemfibrozil. • No other concomitant medication or demographic characteristic was associated with altered bexarotene concentrations. • Only minimal accumulation was observed.

(1)

(2) Initial starting dose.

(3) Number of patients providing pharmacokinetic samples.

M = Micronized.

Table 6.1-B. Biopharmaceutics Summary: Supportive Oral Studies With Targretin® Capsules (continued)

Study Number	Study Design	Route	Dose Form	Strength	Batch	Plant[1]/ Manufact. Date	Doses[2]	Number of Patients[3]	IND # Submission Date	Applicant Conclusions
L1069-24	Phase II-III open-label, controlled, multiple-dose tolerability, safety, efficacy and pharmaco-kinetic study in patients with advanced CTCL	Oral	Soft Gelatin Capsule	75 mg M	9604-001 9604-006 9606-001 9608-008 9609-004 9704-005 9706-012 9709-009	4/10/96 4/24/96 6/17/96 8/21/96 10/16/96 4/22/97 6/12/97 9/9/97	300 mg/m^2 QD (M) 400 mg/m^2 QD (M) 500 mg/m^2 QD (M) 650 mg/m^2 QD (M)	38 [illegible] 21 12	7/21/98	• Large variability in plasma bexarotene concentrations; however, plasma concentrations increased with increasing dose. • Plasma bexarotene concentrations were higher when patients ingested gemfibrozil. • No other concomitant medication or demographic characteristic was associated with altered bexarotene concentrations. • Only minimal accumulation was observed. • PK parameters in CTCL patients were similar to respective values in patients with other advanced cancers.

(1)
(2) Initial starting dose.
(3) Number of patients providing pharmacokinetic samples.
M = Micronized.

Table 6.1-B. Biopharmaceutics Summary: Supportive Oral Studies With Targretin® Capsules (continued)

Study Number	Study Design	Route	Dose Form	Strength	Batch	Plant[1]/ Manufact. Date	Doses	Number of Patients[2]	IND # Submission Date	Applicant Conclusions
L1069DM-01	Phase II open-label, multiple-dose, dose-escalation, tolerability, safety, efficacy and pharmaco-kinetic study in patients with Type II diabetes mellitus, with a supplementary relative bioavailability study in normal volunteers.	Oral	Soft Gelatin Capsule	75 mg M	9608-008	8/21/96	75 mg QD (M) 150 mg QD (M) 300 mg QD (M)	6 9 7	Ex-US Study	Preliminary report results: • Mean bexarotene terminal elimination half-life value of 7 hr to 9 hr over a 24-hr sampling interval. • No detectable urinary excretion of bexarotene, bexarotene acyl glucuronide or 6/7-oxo-bexarotene. Only trace amounts of 6/7-hydroxy-bexarotene were observed in urine. • Bexarotene C_{max} and AUC values were 48% and 35% greater, respectively, when a fat-containing meal substitute was administered after dosing relative to values observed when a glucose solution was administered after dosing. • Bexarotene C_{max} and AUC values after Targretin® capsules or a bexarotene suspension were similar.
					9710-004	10/29/97	75 mg QD	12[3]		

(1)

(2) Number of patients providing pharmacokinetic samples.

(3) Normal volunteers in a subgroup comparing the relative bioavailability of Targretin® capsules and a bexarotene suspension.

M = Micronized.

6.2. Tabular Clinical Pharmacology Study Summary

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table 6.2-A. Targretin® Gel Clinical Pharmacology Study Summary

Protocol #, Investigators, Publications[1]	Completion Status (Starting Date)	Location, (Product Code[2])	Full Report[3] Data Listings[4]	CRFs[5]	Designs (Blinding, Assignments, etc.)	Treatment, Doses	Number Entered Each Treatment	Age Range (mean)	% M/F B/W/O[6]	Duration of Drug Treatment
L1069-94-03T Duvic a, b	Complete (9/23/94)	US (TG-2, TG-3, TG-4)	50 : 8 N/A		Open-label, randomized, multiple dose, safety evaluation study in KS Patients	Targretin® gel 1% or 0.5%. Study drug application initiated at BID increasing to QID. 0.1% used if toxicity occurred	0.5% - 7 1% - 8	33 – 52 (39.8)	100/0 0/87/13	4 wk+
L1069T-07 Leoung a, b	Complete (11/30/94)	US (TG-2, TG-3 TG-4)	50 : 8 N/A		Open-label, randomized, multiple dose, safety evaluation study in KS Patients	Targretin® gel 1% or 0.5%. Study drug application initiated at BID increasing to QID. 0.1% used if toxicity occurred	0.5% - 17 1% - 17	23 – 52 (42.2)	100/0 3/82/15	4 wk+
L1069T-08 Aboulafia a, b	Complete (3/10/95)	US (TG-2, TG-3 TG-4)	50 : 8 N/A		Open-label, randomized, multiple dose, safety evaluation study in KS Patients	Targretin® gel 1% or 0.5%. Study drug application initiated at BID increasing to QID. 0.1% used if toxicity occurred	0.5% - 6 1% - 7	30 – 45 (37.4)	100/0 0/85/15	4 wk+

1. Publications:
   a. Millikan LE, Leoung GS, Aboulafia D, Duvic M, MacGregor RR, Gill G, Truglia J, Yocum R. Treatment of Kaposi's Sarcoma Using Targretin® (LGD 1069) (Abstract). The Nineteenth World Congress of Dermatology, Sydney, Australia, June 1997.
   b. Leoung GS, Aboulafia D, Millikan LE, Duvic M, MacGregor RR, Gill G, Truglia J, Yocum R. Treatment of Kaposi's Sarcoma Using Targretin® (LGD 1069), a Topical Retinoid Gel (Abstract). Int Conf AIDS 1996; 11:98.
2. Product Codes: Product codes are defined in Attachment 2: Drug Formulation Summary.
3. Report Location: (Volume:Page).
4. Data Listing: Volume:Page of first CRF tabulation.
5. Case Report Forms are provided electronically. Please see Section 12 of this NDA for instructions on how to access these electronic data.
6. M = Male; F = Female; B = Black; W = White; O = Other.

Table 6.2-A. Targretin® gel Clinical Pharmacology Study Summary (continued)

Protocol #, Investigators, Publications[1]	Completion Status (Starting Date)	Location, (Product Code[2])	Full Report[3] Data Listings[4]	CRFs[5]	Designs (Blinding, Assignments, etc.)	Treatment, Doses	Number Entered Each Treatment	Age Range (mean)	% M/F B/W/O[6]	Duration of Drug Treatment
L1069T-13 MacGregor a, b	Complete (10/13/95)	US (TG-2, TG-3, TG-4)	50 : 8 N/A		Open-label, randomized, multiple dose, safety evaluation study in KS Patients	Targretin® gel 1% or 0.5%. Study drug application initiated at BID increasing to QID. 0.1% used if toxicity occurred	0.5% - 3 1% - 2	36 –53 (42.6)	100/0 0/100/0	4 wk+
L1069T-15 Millikan a, b	Complete (8/10/95)	US (TG-2, TG-3 TG-4)	50 : 8 N/A		Open-label, randomized, multiple dose, safety evaluation study in KS Patients	Targretin® gel 1% or 0.5%. Study drug application initiated at BID increasing to QID. 0.1% used if toxicity occurred	0.5% - 5 1% - 6	32 – 52 (40.3)	100/0 9/91/0	4 wk+

1. Publications: a. Millikan LE, Leoung GS, Aboulafia D, Duvic M, MacGregor RR, Gill G, Truglia J, Yocum R. Treatment of Kaposi's Sarcoma Using Targretin® (LGD 1069) (Abstract). The Nineteenth World Congress of Dermatology, Sydney, Australia, June 1997.
   b. Leoung GS, Aboulafia D, Millikan LE, Duvic M, MacGregor RR, Gill G, Truglia J, Yocum R. Treatment of Kaposi's Sarcoma Using Targretin® (LGD 1069), a Topical Retinoid Gel (Abstract). Int Conf AIDS 1996; 11:98.
2. Product Codes: Product codes are defined in Attachment 2: Drug Formulation Summary.
3. Report Location: (Volume:Page).
4. Data Listing: Volume:Page of first CRF tabulation.
5. Case Report Forms are provided electronically. Please see Section 12 of this NDA for instructions on how to access these electronic data.
6. M = Male; F = Female; B = Black; W = White; O = Other.

Table 6.2-A. Targretin® gel Clinical Pharmacology Study Summary (continued)

Protocol #, Investigators, Publications [1]	Completion Status (Starting Date)	Location, Product Code[2]	Full Report[3] Data Listings[4]	CRFs[5]	Designs (Blinding, Assignments, etc.)	Treatment, Doses	Number Entered Each Treatment	Age Range (mean)	% M/F B/W/O (6)	Duration of Drug Treatment
L1069-94-04T Duvic a, b, c	Ongoing (1/11/95)	US (TG-2, TG-3 TG-4, TG-5, TG-7)	35 : 1 105 : 1		Open-label, multiple dose, safety study in Cutaneous T-cell Lymphoma Patients	Targretin® gel 1%, 0.5%, 0.1%. Study drug application was initiated at 0.1% QD or 1% QOD and then escalated every 1 or 2 weeks to 1% QID as tolerated.	21	33-77 (56.8)	48/52 10/80/10	12 wk+
L1069T-11 Breneman a, b, c	Ongoing (8/24/95)	US (TG-2, TG-3, TG-4, TG-5, TG-6, TG-7)	35 : 1 105 : 1		Open-label, multiple dose, safety study in Cutaneous T-cell Lymphoma Patients	Targretin® gel 1%, 0.5%, 0.1%. Study drug application was initiated at 0.1% QD or 1% QOD and then escalated every 1 or 2 weeks to 1% QID.	33	30-87 (58.5)	49/51 12/88/0	12 wk+
L1069T-12 Kuzel a, b, c	Ongoing (9/5/95)	US (TG-2 TG-3, TG-4)	35 : 1 105 : 1		Open-label, multiple dose, safety study in Cutaneous T-cell Lymphoma Patients	Targretin® gel 1%, 0.5%, 0.1%. Study drug application was initiated at 0.1% QD or 1% QOD and then escalated every 1 or 2 weeks to 1% QID.	13	34-79 (57.7)	31/69 15/85/0	12 wk+
L1069T-25 Multicenter Trial	Ongoing (3/18/97)	US (TG-5)	25 : 7 99 : 12		Open-label, controlled freuency-of-application escalation, Phase III study in Cutaneous T-cell Lymphoma Patients	Targretin® gel 1%. Study drug application was initiated at 1% QOD and then escalated every 1 week to 1% QID.	38	13-85 (61.3)	47/53 21/79/0	16 wk+

1. Publications:
   a. Duvic M. New therapeutic agents in clinical trials for CTCL. The European Society of Dermatological Research Cutaneous Lymphomas, Berlin, Germany, September 1997 (Abstract).
   b. Duvic M, Breneman D, Kuzel T, Straus D, Stevens V, Yocum R. LGD1069, A novel RXR-selective retinoid analogue, in the treatment of cutaneous T-cell lymphoma (Abstract No. 26). The International Society for Cutaneous Lymphomas, First Consensus Conference on Classification, Terminology, Prognostic Factors, Staging, Therapy, Epidemiology, and Registry, June 14, 1997, Sydney Australia.
   c. Duvic M, Thiers B. New therapies for cutaneous T-cell lymphoma. The American Dematological Association, Inc. Santa Fe, NM, August 1998 (Abstract).
2. Product Codes: Product codes are defined in Attachment 2: Drug Formulation Summary.
3. Report Location: (Volume:Page).
4. Data Listing: Volume:Page of first CRF tabulation.
5. Case Report Forms are provided electronically. Please see Section 12 of this NDA for instructions on how to access these electronic data.
6. M = Male; F = Female; B = Black; W = White; O = Other.

Table 6.2-B. Supportive Targretin® Capsule Clinical Pharmacology Study Summary

Protocol # Investigators, Publications[1]	Completion Status (Starting Date)	Location, Product Code[2]	Full Report[3] (Volume : Page)	Designs (Blinding, Assignment, etc.)	Treatment, Initial Doses	Number Entered Each Treatment	Age Range (mean)	% M/F B/W/O[4]	Duration of Drug Treatment
L1069-93-01 Warrell a, b, c, d, e, f, g	Complete (30 March 1994)	US (SG-1, SG-2, SG-3)	123 : 015	Phase I open-label, safety, tolerance, efficacy, and pharmacokinetic dose-escalation	Nonmicronized: 5 mg/m² QD 10 mg/m² QD 20 mg/m² QD 40 mg/m² QD 65 mg/m² QD Micronized: 18 mg/m² QD 30 mg/m² QD 50 mg/m² QD 83 mg/m² QD 140 mg/m² QD 230 mg/m² QD 300 mg/m² QD 400 mg/m² QD 500 mg/m² QD Total	 4 3 3 3 4 3 4 3 3 3 3 10 5 1 52	25-82 (56)	58/42 6/83/12	4 wk+

1. Publications:
   a. Miller VA, Benedetti FM, Rigas JR, et al. Initial clinical trial of a selective retinoid X receptor ligand, LGD1069. J Clin Oncol 1997;15(2):790-795.
   b. Miller V, Benedetti F, Rigas J, et al. Initial clinical trial of a selective retinoid X receptor (RXR) ligand, 3-methyl TTNEB (LGD1069). Ann Oncol 1996;7(62 Suppl 1):62. (abstract #209).
   c. Miller VA, Benedetti FM, Rigas JR, et al. Initial clinical trial of a selective retinoid X receptor (RXR) ligand, 3-methyl TTNEB (LGD1069). Proc Amer Soc Oncol 1995;14:12. (abstract 371).
   d. Loewen GR, Hawkins MJ, Warrell RP, Jr, et al. Pharmacokinetics of LGD1069 following oral administration of micronized and non-micronized formulations to patients with cancer. Pharm Res 1995;12(9 Suppl.):S103. (abstract #CS3008).
   e. Miller VA, Benedetti FM, Rigas JR, et al. Initial clinical study of a selective retinoid "X" receptor (RXR) agonist. Proc Amer Assoc Cancer Res 1995;36:242. (abstract #1445)
   f. Nervi AM, Rigas JR, Miller VA, et al. Plasma lipoproteins associated with three novel retinoids: All-trans-retinoic acid, 9-cis-retinoic acid and oral Targretin. J Invest Med 1997;45 (3): 260A
   g. Rigas JR, Miller VA, Levine, DM, et al. Lipoprotein alterations in patients treated with novel retinoids, Proc Amer Assoc Cancer Res, 1995 (36):508. (abstract #3012).
2. Product Codes: Product codes are defined in Table 2 in Section 6.2 of NDA 21-055.
3. Report location (Volume:Page) in NDA 21-055.
4. M = Male; F = Female; B = Black; W = White; O = Other.

Table 6.2-B. Supportive Targretin® Capsule Clinical Pharmacology Study Summary (continued)

Protocol # Investigators, Publications[1]	Completion Status (Starting Date)	Location, Product Code[2]	Full Report[3] (Volume : Page)	Designs (Blinding, Assignment, etc.)	Treatment, Initial Doses	Number Entered Each Treatment	Age Range (mean)	% M/F B/W/O[4]	Duration of Drug Treatment
L1069-93-02 Hawkins h, l	Ongoing (18 March 1994)	US (SG-1, SG-2, SG-3, SG-4, SG-5, SG-6)	131 : 001	Phase I-II open-label, safety, tolerance, efficacy, and pharmacokinetic dose-escalation	Nonmicronized: 5 mg/m^2 QD 10 mg/m^2 QD 20 mg/m^2 QD 30 mg/m^2 QD 45 mg/m^2 QD 75 mg/m^2 QD Micronized: 21 mg/m^2 QD 50 mg/m^2 QD 83 mg/m^2 QD 140 mg/m^2 QD 230 mg/m^2 QD 380 mg/m^2 QD 500 mg/m^2 QD 650 mg/m^2 QD 800 mg/m^2 QD 1000 mg/m^2 QD Total	 3 3 3 3 3 3 3 3 3 4 3 5 3 6 6 6 60	27-80 (60)	52/48 18/75/7	4 wk+

1. Publications: h. Loewen GR, Hawkins MJ, Warrell RP, Jr, et al. Pharmacokinetics of LGD1069 following oral administration of micronized and non-micronized formulations to patients with cancer. Pharm Res 1995;12(9 Suppl.):S103. (abstract #CS3009)
   l. Rizvi NA, Marshall JL, Loewen GR, et al. A Phase I study of Targretin, an RXR-selective retinoid agonist. Proc Amer Assoc for Cancer Res 1996;37:165.
2. Product Codes: Product codes are defined in Table 2 in Section 6.2 of NDA 21-055.
3. Report location (Volume: Page) in NDA 21-055.
4. M = Male; F = Female; B = Black; W = White; O = Other.

Table 6.2-B. Supportive Targretin® Capsule Clinical Pharmacology Study Summary (continued)

Protocol # Investigators, Publications[1]	Completion Status (Starting Date)	Location, Product Code[2]	Full Report[3] (Volume : Page)	Designs (Blinding, Assignment, etc.)	Treatment, Initial Doses	Number Entered Each Treatment	Age Range (mean)	% M/F B/W/O[4]	Duration of Drug Treatment
L1069-94-02 Multicenter j, k	Complete (25 July 1994)	US (SG-1, SG-2, SG-3, SG-4, SG-5, SG-6)	143 : 001	Phase II open-label, safety, tolerance, efficacy and pharmacokinetic dose-escalation	Nonmicronized: 10 mg/m^2 QD Micronized: 25 mg/m^2 BID 50 mg/m^2 BID 75 mg/m^2 BID 150 mg/m^2 BID 200 mg/m^2 BID 300 mg/m^2 BID Total	 4 3 3 4 3 2 9 28[a]	31-76 (57)	64/36 14/64/21	4 wk+

[a] One additional patient was enrolled in the study but did not receive treatment.

1. Publications: j. Papadimitrakopoulou V, Khuri FR, Lippman SM, et al. Phase I/II evaluation of Targretin (LGD1069), a novel, RXR-specific retinoid, in patients with recurrent squamous cell carcinoma of the head and neck. Proceedings of ASCO. 1998;17:392a.
   k. Papadimitrakopoulou V, Khuri FR, Lippman SM, et al. Phase I/II evaluation of Targretin, a novel RXR-specific retinoid, in patients with recurrent squamous cell carcinoma of the head and neck. Oncol Forum 1998:22-23.
2. Product Codes: Product codes are defined in Table 2 in Section 6.2 of NDA 21-055.
3. Report location (Volume: Page) in NDA 21-055.
4. M = Male; F = Female; B = Black; W = White; O = Other.

Table 6.2-B. Supportive Targretin® Capsule Clinical Pharmacology Study Summary (continued)

Protocol # Investigators, Publications[1]	Completion Status (Starting Date)	Location, Product Code[2]	Full Report[3] (Volume : Page)	Designs (Blinding, Assignment, etc.)	Treatment, Initial Doses	Number Entered Each Treatment	Age Range (mean)	% M/F B/W/O[4]	Duration of Drug Treatment
L1069DM-01 Multicenter	Ongoing (06 May 1997)	Ex-US (SG-6, SG-7)	69 : 280	Phase II open-label, safety, tolerance, efficacy, and pharmacokinetic dose-escalation	20 mg BID 75 mg QD 150 mg QD 300 mg QD Total	3[a] 6[a] 10[a] 7[a] 26[a]	35-73[a] (63)[a]	42/58[a] 0/100/0[a]	12 wk[a]
L1069DM-01 Pharmacokinetic Supplement DeVries	(20 May 1999)	Ex-US (SG-6)	69 : 001	Phase I open-label, cross-over, single-dose relative bioavailability study	75 mg QD	12[b]	19-45[b] (26)[b]	100/0[b] 0/83/17[b]	1 day[b]

a Patients with Type II diabetes mellitus.
b Twelve normal volunteers enrolled under this protocol to assess the relative bioavailability of a single 75 mg Targretin® capsule or 75 mg bexarotene suspension.
1. No publications.
2. Product Codes: Product codes are defined in Table 2 in Section 6.2 of NDA 21-055.
3. Report location (Volume: Page) in NDA 21-055.
4. M = Male; F = Female; B = Black; W = White; O = Other

Table 6.2-B Supportive Targretin® Capsule Clinical Pharmacology Study Summary (continued)

Protocol # Investigators, Publications [1]	Completion Status (Starting Date)	Location, Product Code [2]	Full Report [3] (Volume : Page)	Designs (Blinding, Assignment, etc.)	Treatment, Initial Doses	Number Entered Each Treatment	Age Range (mean)	% M/F B/W/O [4]	Duration of Drug Treatment
L1069-23 Multicenter l, m, n, o, p	Ongoing (10 Feb 1997)	U.S., Canada, Europe, and Australia (SG-2, SG-5, SG-6, SG-7)	73 : 235	Phase II-III Controlled, randomized, open-label, safety, tolerability and efficacy study	6.5 mg/m^2 QD 300 mg/m^2 QD 500 mg/m^2 QD 650 mg/m^2 QD Total	15 28 11 4 58	24-88 (61)	69/31 10/84/5	16 wk+
L1069-24 Multicenter l, m, n, o, p	Ongoing (8 Nov 1996)	U.S., Canada, Europe, and Australia (SG-5, SG-6)	95 : 001	Phase II-III Controlled, open-label safety, tolerability and efficacy study	300 mg/m^2 QD 400 mg/m^2 QD 500 mg/m^2 QD 650 mg/m^2 QD Total	56 1 21 16 94	27-89 (63)	57/43 14/82/4	16 wk+

1. Publications:
   - l. Duvic M, Thiers B. New therapies for cutaneous T-cell lymphoma. The American Dermatological Association, Inc. Santa Fe, NM, August 1998.
   - m. Duvic M. New therapeutic agents in clinical trials for CTCL. The European Society of Dermatological Research, Berlin, Germany, Sep 1997.
   - n. Duvic M, Broneman D, Kuzel T, et al. LGD1069, a novel RXR-selective retinoid analogue, in the treatment of cutaneous T-cell lymphoma. The International Society for Cutaneous Lymphomas, First Consensus Conference on Classification, Terminology, Prognostic factors, Staging, Therapy, Epidemiology, and Registry, Sydney, Australia, Jun 1997.
   - o. Sherman S, Chiu A, Gopal J, et al. Thyroid axis alterations in CTCL patients receiving an RXR-selective ligand (Abstract OR35-6). 80th Annual Meeting of the Endocrine Society, New Orleans, LA. Sep 1997.
   - p. Sherman S, Gopal J, Haugen BR, et al. Central hypothyroidism associated with retinoid X receptor-selective ligands. N Engl J Med, 1999; 340 (14); pp:1075-1079.
2. Product Codes: Product codes are defined in Table 2 in Section 6.2 of NDA 21-055.
3. Report Location (Volume:Page) in NDA 21-055.
4. M = Male; F = Female; B = Black; W = White; O = Other.

6.2.4. Abbreviations

AE	Amount excreted unchanged in urine
AUC	Area under the plasma concentration-time curve
BID	Twice-daily dosing
C_0	Concentration at Time zero (predose)
CL_r	Renal Clearance
C_{max}	Peak observed plasma concentration
CTCL	Cutaneous T-cell lymphoma
CV	Coefficient of variation
CYP	Cytochrome P450
F(%)	Absolute percent bioavailability
FL	Fluorescence
F_{rel}	Relative bioavailability
GC	Gas chromatography
HPLC	High performance liquid chromatography
LFT	Liver function test
LLQ	Lower limit of quantification
LOD	Limit of detection
LU	Luminescence units
M	Micronized
MS	Mass spectrometry
MTT	Meal tolerance test
mV	Millivolt
N	Number
NM	Nonmicronized
OGTT	Oral glucose tolerance test
P450	Cytochrome P450
PEG	Polyethylene glycol
PK	Pharmacokinetic
PXR	Pregnane X receptor

Q	Dissolution acceptance criterion
QD	Once-daily dosing
QID	Four-times-daily dosing
QOD	Every-other-day dosing
RAR	Retinoic acid receptor
RH	Relative humidity
RXR	Retinoid X receptor
SD	Standard deviation
SE	Standard error of the mean
$t_{1/2}$	Elimination half-life
TID	Three-times-daily dosing
t_{max}	Time of observed peak plasma concentration
UV	Ultraviolet
ULN	Upper limit of normal
USP	United States Pharmacopeia
λ_z	Elimination rate constant

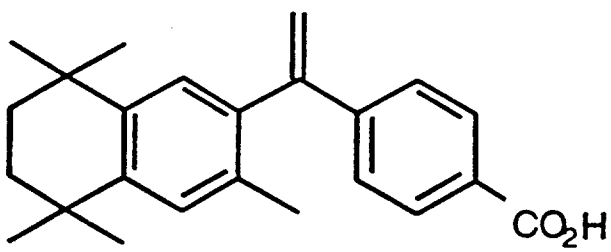
6.3. Human Pharmacokinetics and Bioavailability Technical Summary

6.3.1. Summary of Bexarotene Pharmacokinetics

6.3.1.1. Introduction

The intended marketing formulation is Targretin® gel 1%, which is a 1% (w/w) gelled solution of bexarotene in a polyethylene glycol (PEG) 400 and dehydrated alcohol base. Targretin® gel 1% is indicated for the topical treatment of cutaneous lesions in patients with CTCL (Stage IA, IB, or IIA) who have not tolerated other therapies or who have refractory or persistent disease. The chemical structure of bexarotene is provided in **Figure 6.3-A**.

Figure 6.3-A. Chemical Structure of Bexarotene



IUPAC Name:	4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)vinyl]benzenecarboxylic acid
Trade Name:	Targretin® gel
Generic Name:	bexarotene
Other Names:	LG100069, LGD1069, Targretin® drug substance
CAS Number:	153559-49-0
MW:	348.48 Daltons

The pharmacokinetics of bexarotene have been characterized in a non-clinical study in human cadaver skin, in several clinical studies utilizing topical Targretin® gel, and in clinical studies utilizing oral Targretin® capsules. Additionally, the metabolism, excretion, and plasma protein binding of bexarotene have been evaluated following in vitro studies and/or ex vivo studies after oral administration of Targretin® capsules. Targretin® capsules are an oral soft gelatin capsule dosage form of bexarotene, that are currently being reviewed by the Food and Drug Administration (FDA) for the treatment of patients with refractory advanced stage cutaneous T-cell lymphoma (CTCL), patients with refractory or persistent early stage CTCL, and patients with early stage CTCL who have not tolerated other therapies (**NDA 21-055; Submission Date: June 1999**). Pharmacokinetic data from the Targretin® gel clinical studies are submitted in this NDA in their entirety. Data from the Targretin® capsule studies have only been summarized and are cross-referenced in this review, since they mainly provide supportive pharmacokinetic information for this topical submission, and since the reports for these studies have previously been submitted in NDA 21-055.

A list of the topical and oral clinical studies summarized in this submission and their corresponding pharmacokinetic reports are provided in **Table 6.3-A**.

Table 6.3-A. List of Clinical Studies Summarized in this Review, their Corresponding Pharmacokinetic Study Reports, and their Locations

Study Number	Pharmacokinetic Report Number	Route	Contribution to Submission	Study Description	NDA Number	Document Location	
						Volume	Page
L1069-94-04T L1069T-11 L1069T-12	RR-845-99-004	Topical	Primary	Phase I-II program in patients with CTCL	21-056	7	2
L1069-94-03T L1069T-07 L1069T-08 L1069T-13 L1069T-15	RR-845-99-007	Topical	Primary	Phase I-II program in patients with cutaneous KS[1]	21-056	13	2
L1069T-25	RR-845-99-005	Topical	Primary	Phase III study in patients with CTCL	21-056	19	1
L1069-93-01	RR-845-98-010.a	Oral	Supportive	Phase I, dose escalation study in patients with advanced cancers	21-055[2]	58	001
L1069-93-02	RR-845-98-015.a	Oral	Supportive	Phase I-II, dose escalation study in patients with advanced cancers	21-055[2]	61	001
L1069-94-02	RR-845-98-011	Oral	Supportive	Phase I-II, dose escalation study in patients with advanced head and neck cancers	21-055[2]	68	001
L1069-23	RR-845-98-016	Oral	Supportive	Phase II-III study in patients with CTCL	21-055[2]	66	001
L1069-24	RR-845-98-017	Oral	Supportive	Phase II-III study in patients with CTCL	21-055[2]	67	001
L1069DM-01	RR-845-99-001	Oral	Supportive	Phase II, dose escalation study in patients with NIDDM	21-055[2]	69	001
	RR-854-99-003	Oral	Supportive	Bioavailability sub-study in healthy volunteers	21-055[2]	69	280

[1] Although Kaposi's sarcoma (KS) is not the indication for which this NDA is being submitted, this program is considered primary since it is included in a population analysis of Targretin® gel.

[2] Study reports for the oral studies have been previously submitted in NDA 21-055 (Targretin® capsules) and are only cross-referenced in this submission.

The pharmacokinetics of bexarotene following topical administration have been characterized using single-time-point (sparse) concentration data that were collected in a Phase I-II program in patients with cutaneous T-cell lymphoma (CTCL), in a Phase I-II program in patients with AIDS-related Kaposi's sarcoma (KS), and in a Phase III study of Targretin® gel in patients with CTCL. Pharmacokinetic data from

each of these programs as well as the results of cross-study population pharmacokinetic analyses are presented in this review.

Additionally, since readily assayable systemic concentrations are achieved after oral dosing, allowing detailed pharmacokinetic characterization of bexarotene, studies using Targretin® capsules, are supportive to this submission, and are also summarized in this review. The pharmacokinetics generated from these studies would be expected to apply to the systemic disposition of any bexarotene that reached the systemic circulation after topical administration. For characterization of pharmacokinetics following oral dosing, pharmacokinetic profiles were obtained in patients with advanced cancers, patients with advanced head and neck cancer, patients with Type II diabetes mellitus, patients with CTCL, and normal volunteers who had been administered Targretin® capsules. The urinary excretion of bexarotene and its metabolites were determined in patients with Type II diabetes mellitus. A single-time-point sample pharmacokinetic database was generated during the two Phase II-III studies evaluating the safety and efficacy of Targretin® capsules in patients with CTCL to assess the effect of patient demographic and baseline characteristics and concomitant medications on the pharmacokinetics of bexarotene following oral dosing.

A detailed description of the organization of this Human Pharmacokinetics and Bioavailability review is provided in the Reviewer's Guide for this section.

6.3.1.2. Overall Summary and Conclusions

Targretin® gel 1% is a 1% (w/w) gelled solution of bexarotene in a polyethylene glycol (PEG) 400 and dehydrated alcohol base, and is indicated for the topical treatment of cutaneous lesions in patients with CTCL (Stage IA, IB, or IIA) who have refractory or persistent disease or who have not tolerated other therapies. Since Targretin® gel 1% is intended for dermal application, measured systemic

concentrations of bexarotene may not be indicative of its local therapeutic efficacy. However, the pharmacokinetics of topically applied bexarotene are expected to be relevant from a perspective of safety and tolerability of this product.

The pharmacokinetics of topically applied Targretin® gel have been studied in a Phase I-II program in a total of 66 of 67 patients with CTCL (Studies L1069-94-04T, L1069T-11, and L1069T-12), in a Phase III study in 38 of 50 patients with CTCL (Study L1069T-25), and in a Phase I-II program in a total of 45 of 78 patients with AIDS-related KS (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15). In the Phase III study, Targretin® gel 1% was applied at varying application frequencies (QOD, QD, BID, TID, or QID) to lesions for a period of up to 100 weeks for pharmacokinetic sampling. In the Phase I-II CTCL and Phase I-II KS programs, Targretin® gel of varying gel strengths (0.1%, 0.5%, or 1%) and frequencies (QOD, QD, BID, TID, and/or QID) was applied to lesions for a duration of up to 135 and 80 weeks for pharmacokinetic sampling, respectively. In all studies, sparse blood samples were collected every two to four weeks for monitoring of bexarotene concentrations. These concentration data were evaluated separately by clinical program and then pooled across studies and subjected to population analyses for determination of bexarotene pharmacokinetics. The results of the evaluations of the pharmacokinetic data for each program and the results of the population analyses are summarized below.

The pharmacokinetics of bexarotene following oral administration of Targretin® capsules have also been studied in patients with advanced cancers, patients with advanced head and neck cancer, patients with Type II diabetes mellitus, patients with CTCL and normal volunteers. The pertinent pharmacokinetic results of these studies have also been summarized below. The pharmacokinetics elucidated in these Targretin® capsule studies would be expected to apply to the systemic disposition of any bexarotene that reached the systemic circulation after topical administration.

Finally, information on the metabolism, excretion, and protein binding of bexarotene obtained from in vitro studies, and from ex vivo studies following oral administration of Targretin® capsules has been summarized.

Pharmacokinetics of Targretin® gel

Targretin® gel is capable of penetrating into the skin. In a non-clinical study utilizing human cadaver skin, a total of 25.3% of topically applied drug was recovered in the epidermis, dermis, and stratum corneum.

Systemic exposure to bexarotene following application of Targretin® gel is low. Plasma bexarotene concentrations, measured primarily within 24 hours of dosing, were generally very low (<5 ng/mL) and only sporadically quantifiable. Following topical application, the highest plasma levels were observed within 12 hr of Targretin® gel application. For patients treated with Targretin gel 1% in the Phase I-II CTCL program and the Phase III CTCL study, plasma bexarotene concentrations were quantifiable in only 300 (37.2%) of the 807 post-dose blood samples collected and assayed. Of the 300 samples with quantifiable concentrations, 245 had bexarotene concentrations lower than 5 ng/mL, 28 were ≥5 ng/mL but <10 ng/mL, 13 were ≥10 ng/mL but <15 ng/mL, five were ≥15 ng/mL but <20 ng/mL, and only nine were higher than 20 ng/mL. The highest concentrations (47.1 and 54.9 ng/mL) measured across all studies were obtained in one patient in the Phase III study, who is believed to have applied an inordinately large amount of Targretin® gel 1% during the course of the study. In this patient, systemic exposure was relatively low, being about 5% of mean C_{max} values obtained following oral dosing (300 mg/m^2 QD) with Targretin® capsules.

Consistent with a short half-life of generally 1-3 hours observed following oral administration, accumulation of bexarotene following topical application is minimal. Despite long-term application of Targretin® gel (0.1%, 0.5%, or 1% gel strengths for up to 135 weeks) over up to 90% of body surface area in CTCL patients, the large majority of blood samples had non-quantifiable (<1 ng/mL) or generally sporadically low (<5 ng/mL) plasma bexarotene concentrations.

Systemic concentrations of bexarotene achieved following topical application are related to the extent of topical exposure to Targretin® gel. Results of population analyses of pooled data from the Targretin® gel studies demonstrated that higher bexarotene plasma concentrations were obtained in patients who treated a larger surface area of lesions (which correlated with CTCL stage), in patients who utilized a higher gel strength, and in patients who applied Targretin® gel more frequently. These results were in agreement with results of a descriptive evaluation of bexarotene concentration data in the individual clinical programs, which showed an increase in the percent of quantifiable bexarotene concentrations (>1 ng/mL) in patients, with increasing surface area of treated lesions or advancing stage of CTCL. The correlation between plasma concentrations and gel strength applied was also evident in the observation that the largest percentage of quantifiable bexarotene concentrations were observed in the Phase III L1069T-25 study (46.1% of samlpes had post-dose concentrations >1 ng/mL in Study L1069T-25 compared to 21.1% of samples in the Phase I-II CTCL in which Targretin® gel 1% was used exclusively.

Pharmacokinetics of Targretin® Capsules Relevant to Topical Administration

The oral pharmacokinetics of bexarotene were evaluated during studies in patients with CTCL, advanced cancer, or Type II diabetes mellitus, and in normal volunteers.

Bexarotene was eliminated relatively rapidly from the body following oral administration. Following both single-dose and repeat-dose administration, the elimination half-life of bexarotene was approximately 1 to 3 hours when determined over a 6-hour sampling interval. In some patients with 24-hour postdose sampling schedules, the estimated elimination half-life was 7 to 9 hours.

Consistent with its relatively rapid elimination, minimal accumulation of bexarotene occurred with repeat once-daily dosing, even after up to 520 days on study. At dose levels <230 mg/m^2 QD, single-dose $AUC_{0\text{-}6}$ values were generally comparable to multiple-dose values. Predose concentrations of bexarotene following multiple dosing were low (approximately 4-6% of C_{max}).

The pharmacokinetics of bexarotene in patients with CTCL were similar to the pharmacokinetics observed in patients with advanced cancers other than CTCL.

At the recommended oral daily-dose level (300 mg/m^2 QD) for treatment of patients with early or advanced stage CTCL, single-dose and repeated daily-dose pharmacokinetic parameters were similar. Mean (±SD) C_{max} values were 922 ng/mL ± 339 ng/mL and 1130 ng/mL ± 269 ng/mL following single-dose and repeated daily-dose administration of Targretin® capsules, respectively. Mean (±SD) $AUC_{0\text{-}6}$ values were 3877 ng·hr/mL ± 2640 ng·hr/mL and 3797 ng·hr/mL ± 1526 ng·hr/mL following single-dose and repeated daily-dose administration of Targretin® capsules, respectively. Bexarotene concentrations in predose plasma samples obtained during repeat-dose administration ranged from 6.14 ng/mL to 22.01 ng/mL, indicating patients were exposed to bexarotene during the entire once-daily dosing interval.

Metabolism and Excretion of Bexarotene

The human metabolism and elimination of bexarotene was assessed using in vitro and ex vivo methods (utilizing samples from studies with Targretin® capsules). Bexarotene was metabolized in humans to 6- and 7-oxo-bexarotene, 6- and 7-hydroxy-bexarotene and bexarotene acyl glucuronide. All of these metabolites were also observed in the toxicology species (rat and dog). For both the hydroxy and oxo metabolites, the C-6 isomer was predominant over the C-7 isomer. The oxidative metabolites were the major plasma metabolites of bexarotene. Cytochrome P450 3A4 was identified as the primary enzyme responsible for the oxidative metabolism of bexarotene. No bexarotene acyl glucuronide was observed in plasma. Because of their low affinity for retinoid receptors and their low activity profile in retinoid receptor assays assessing transcriptional activity, the oxidative metabolites are not expected to contribute significantly to the in vivo retinoid receptor activation profile of bexarotene. No or minimal bexarotene, oxidative metabolites or bexarotene acyl glucuronide were detectable in urine. The renal clearance of bexarotene was estimated to be less than 1 mL/min. Other bexarotene metabolites were excreted renally, but they did not represent a significant fraction of the administered dose of bexarotene. Although fecal excretion of bexarotene and metabolites was not evaluated, bexarotene elimination is thought to occur primarily through hepatobiliary mechanisms since very little bexarotene was excreted renally.

Protein Binding of Bexarotene

In a test system with up to 18% nonspecific binding, the in vitro binding of bexarotene to human plasma proteins over a 5 ng/mL to 5000 ng/mL concentration range was greater than 99% and was independent of total plasma bexarotene concentration.

Bexarotene Pharmacokinetics in Special Populations

Population analyses of plasma concentration data in patients applying Targretin® gel did not identify an effect of age on bexarotene pharmacokinetics. Patients included in the analyses ranged in age from 13 to 87 years (mean ± SD of 53.4 ± 14.5; median of 52). While no formal study was conducted to determine bexarotene pharmacokinetics in elderly patients, pharmacokinetic evaluations from the Phase III study (which were included in the population analyses) were obtained in a patient population that included elderly patients (median age of pharmacokinetic patients = 63 yr; range 13-85 yr). Similar to the results obtained in Targretin® gel studies, no relationship was found between dose-normalized bexarotene pharmacokinetic parameters and patient age (adult versus elderly) in studies of Targretin® capsules. No formal study has been conducted to determine bexarotene pharmacokinetics in pediatric patients. However, plasma bexarotene concentrations in a single 13-yr old patient applying Targretin® gel were similar to respective values in adult patients. No relationship was found between gender and race/ethnic origin and bexarotene pharmacokinetics following topical application. The patients included in the population analysis included 127 White, 17 Black, and five Asian/Oriental patients; 99 patients were male and 50 were female. Similar results were obtained in studies utilizing Targretin® capsules, where no relationship between dose-normalized bexarotene pharmacokinetic parameters and patient gender or ethnic origin was identified.

Clinical pharmacokinetic data from Targretin® capsule studies have suggested that bexarotene is likely eliminated through hepatobiliary mechanisms. No formal study was conducted to determine bexarotene pharmacokinetics in patients with hepatic insufficiency. However, population analysis of pharmacokinetic data following application of Targretin® gel indicated that there was no correlation between plasma bexarotene concentrations and liver function test values in the pharmacokinetic patients included in the Targretin® gel studies. Similar results were obtained in studies using Targretin® capsules.

Clinical pharmacokinetic data from Targretin® capsule studies have indicated that urinary elimination of bexarotene and its metabolites is a minor excretory pathway for bexarotene. In all evaluated patients in the Targretin® capsule studies, the renal clearance of bexarotene was less than 1 mL/min. Based on the population analysis and on individual patient observations, no clinically meaningful relationship between creatinine clearance or serum creatinine values and bexarotene concentrations was found.

Drug Interactions

The effects of concomitant administration of medications on plasma bexarotene concentrations were assessed from evaluation of individual patient data and in population analyses of the clinical studies utilizing Targretin® gel, and separately in population evaluations of data obtained from studies of Targretin® capsules. Concomitant medications of particular focus in the oral evaluations included those that were frequently administered systemically during these studies (atorvastatin, gemfibrozil and levothyroxine) and those that could potentially affect bexarotene concentrations due to their ability to modulate CYP3A4, the enzyme responsible for the oxidative metabolism of bexarotene (e.g., CYP3A4 inhibitors). Concomitant medications of particular focus in the topical analyses included those that had previously been shown in the Targretin® capsule studies to affect the pharmacokinetics of bexarotene (gemfibrozil), and those that could potentially affect bexarotene concentrations due to their ability to modulate CYP3A4 (CYP3A4 inducers and CYP3A4 inhibitors). Population analysis of data from the Targretin® gel studies did not identify drug interactions with CYP3A4 inducers or inhibitors, or gemfibrozil. Bexarotene plasma concentrations were elevated (concentrations up to 24.17 ng/mL) in one patient applying Targretin® gel who was on concomitant gemfibrozil. A similar effect has been observed on oral administration of bexarotene, where concomitant administration of gemfibrozil resulted in higher plasma bexarotene concentrations, possibly due to inhibition of the oxidative metabolism of bexarotene. In studies of Targretin® capsules, while an elevation of bexarotene concentrations was seen with concomitant gemfibrozil, frequently

administered medications like atorvastatin and levothyroxine did not alter plasma bexarotene concentrations. Similarly, based on few data, CYP3A4 inhibitors (azole antifungals and macrolide antibiotics) did not alter plasma bexarotene concentrations. Although no evidence for a drug interaction with CYP3A4 inhibitors was observed during either the topical or oral clinical studies, CYP3A4 inhibitors could theoretically lead to an increase in plasma bexarotene concentrations.

Conclusions

In summary, based on evaluation and analysis of the clinical studies on Targretin® gel, and on supportive data obtained from the clinical studies of Targretin® capsules, the primary conclusions are:

- Targretin® gel penetrates well into skin (total recovery of 25% in the epidermis, dermis, and stratum corneum).
- Systemic exposure to bexarotene following topical administration of Targretin® gel 1% is generally very low. Ninety-three percent of the bexarotene concentrations in samples measured following application of the 1% gel at frequencies ranging from once every other day to four times daily were below 5 ng/mL. The maximum concentration measured in any patient was 54.9 ng/mL; this was only about 5% of mean C_{max} values obtained following oral dosing at the recommended dose of Targretin® capsules (300 mg/m^2 QD).
- Following topical application, the highest bexarotene plasma concentrations tended to be observed within 12 hr of Targretin® gel application.
- No appreciable accumulation of bexarotene was observed following topical application at a frequency ranging from QOD to QID for up to 135 weeks.
- Increases in bexarotene plasma concentrations correlated with increasing surface area of treated lesions, increase in gel strength, and increased application frequency of Targretin® gel.
- The major metabolites of bexarotene appearing in plasma after oral administration are 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene. Because of their low affinity for retinoid receptors and their low activity profile in retinoid receptor assays, these metabolites are not expected to contribute significantly to the in vivo retinoid receptor activation profile of bexarotene. A glucuronide metabolite also was observed in an in vitro test system.

- The only identified human P450 isozyme involved in the oxidative metabolism of bexarotene is CYP3A4.
- Bexarotene is highly protein bound (>99%).
- No or only trace quantities of bexarotene and its known oxidative metabolites were detected in urine after oral administration.
- There is no apparent relationship between bexarotene pharmacokinetics and patient demographic characteristics including age, gender and ethnic origin following topical application. While the pharmacokinetics have not been studied in pediatric patients, plasma bexarotene concentrations measured in a single 13-yr old patient applying Targretin® gel were similar to respective values in adult patients.
- Following application of Targretin® gel, plasma bexarotene concentrations were not elevated in patients with lower creatinine clearance values.
- There was no correlation between plasma bexarotene concentrations and values of liver function tests following topical application. While hepatic dysfunction may theoretically alter bexarotene pharmacokinetics, any effect would be unlikely to be clinically significant at the low levels of systemic exposure obtained with Targretin® gel.
- Concomitant systemic administration of cytochrome P450 3A4 inducers or inhibitors did not affect the pharmacokinetics of Targretin® gel. Plasma bexarotene concentrations following topical application were greater in some, but not all patients administered concomitant gemfibrozil. Similar elevations were observed following oral administration of Targretin® capsules concomitantly with gemfibrozil.

6.3.2. Background Information

This section contains a brief summary of chemistry, expected clinical use of Targretin® gel, and its nonclinical pharmacology and ADME. The information on nonclinical pharmacology is based entirely on the nonclinical data package previously submitted in NDA 21-055 for Targretin® capsules **(Section 5.1.0., vol. 10, pg. 120)**.

The information on nonclinical ADME is based entirely on the nonclinical data package submitted in Section 5A of this NDA and the nonclinical data package in NDA 21-055 for Targretin® capsules. Data are provided on the pharmacokinetics of bexarotene in the toxicology species (rat and dog), the pharmacokinetics of bexarotene following topical application (rat), and a contrast of bexarotene pharmacokinetics in rats following topical versus oral administration, in comparison to the relationship observed in humans.

6.3.2.1. Summary of Chemistry, Nonclinical Pharmacology and Expected Clinical Use

6.3.2.1.1. Summary of Chemistry and Expected Clinical Use

Bexarotene or LGD1069 is a retinoid analog intended for both oral and topical administration. Bexarotene is insoluble in water and has limited solubility in vegetable oils and ethanol. The intended marketing formulation is Targretin® gel 1%, which is a 1% (w/w) gelled solution of bexarotene in a polyethylene glycol (PEG) 400 and dehydrated alcohol base.

Targretin® gel 1% is indicated for the topical treatment of cutaneous lesions in patients with CTCL (Stage IA, IB, or IIA) or who have refractory or persistent disease who have not tolerated other therapies.

6.3.2.1.2. Summary of Nonclinical Pharmacology

Bexarotene is a member of a large class of molecules, the retinoids, which include natural derivatives of vitamin A and a large number of synthetic compounds that interact with the retinoid receptors. There are two sub-families of retinoid receptors, each with three members, the retinoic acid receptors (RARα, β and γ) and the retinoid X receptors (RXRα, β and γ). The retinoid receptors are members of the nuclear receptor (NR) superfamily that are ligand dependent transcription factors,