Table 6.3-X. Mean (±SD) ^{3}H-Bexarotene Free Fraction and Binding to Human Plasma Proteins as Determined by

Plasma [^{3}H] Bexarotene Concentration (ng/mL)	N	Plasma Protein Binding (%)	Free Fraction (%)
5	6	99.87±0.03	0.13±0.03
10	6	99.88±0.02	0.12±0.02
100	5	99.82±0.06	0.18±0.06
1000	5	99.83±0.03	0.17±0.03
5000	6	99.85±0.03	0.15±0.03

N = Number of replicates.

Therefore, in a test system with nonspecific binding potentially as high as 18%, 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. No studies have been conducted to assess the potential for binding displacement drug interactions.

6.3.5. Population Pharmacokinetics of Targretin® Gel

Population analyses were performed to evaluate the pharmacokinetics of topically applied bexarotene. Data from the Phase I-II program in patients with CTCL (Studies L1069-94-04T, L1069T-11, and L1069T-12), the Phase III study in patients with CTCL (Study L1069T-25), and the Phase I-II program in patients with KS (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15) were pooled and subjected to cross-study statistical and pharmacokinetic analyses. Except for the primary patient disease, the nine studies were similar in terms of objectives, criteria for inclusion/exclusion of patients in the study, and in design, conduct, and collection of plasma samples for determination of plasma bexarotene concentrations. Therefore, in order to enhance the ability to detect significant covariate effects on the pharmacokinetics of Targretin® gel, data from the nine studies were combined into a single database for the pharmacokinetic analyses. A complete description of the methodology and results of these analyses can be found

in Appendix E of the pharmacokinetic study reports **RR-845-99-004, RR-845-99-005,** and **RR-845-99-007.** Details of the analyses and results are summarized below. The studies included in this analysis were open-label, multiple-dose evaluations of Targretin® gel 0.1%, 0.5%, and 1% in patients with CTCL or KS, to determine the safety, tolerability, and antitumor efficacy of Targretin® gel in these patient populations. Based on the escalation schemes within each study, patients were exposed to different application frequencies, including every other day (QOD), once daily (QD), twice daily (BID), three times daily (TID), and/or four times daily (QID), as tolerated. Single-time-point blood samples were collected at regular intervals for measurement of bexarotene plasma concentrations. Descriptions of the study objectives and designs for these studies can be found in **Sections 6.3.3.1.3.1.** to **6.3.3.1.3.3**, and the designs are summarized in **Table 6.3-Y.** Summary statistics on the dosing strength and frequency of application of Targretin® gel for patients who had blood samples collected are displayed in **Table 6.3-Z.**

Table 6.3-Y. Main Pharmacokinetic Characteristics of the Nine Studies Combined for the Population Analysis of the Pharmacokinetics of Targretin® Gel in Patients with CTCL or KS

	Phase I-II KS program	Phase I-II CTCL program	Phase III CTCL study
Study Protocols	L1069-94-03T L1069T-07 L1069T-08 L1069T-13 L1069T-15	L1069-94-04T L1069T-11 L1069T-12	L1069T-25
Patient disease	KS	CTCL	CTCL
Route	Topical	Topical	Topical
Formulation strengths	0.1%, 0.5%, 1%	0.1%, 0.5%, 1%	1%
Dosing frequencies	BID, QID	QOD, QD, BID, TID, QID	QOD, QD, BID, TID, QID
Pharmacokinetic sample collection	Single time-point sample every 2-4 weeks	Single time-point sample every 2-4 weeks	Single time-point sample every 2-4 weeks
Demographics, laboratory variables and disease variables	Available	Available	Available

Table 6.3-Z. Targretin® Gel Dosage Regimens During the Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25)

Dosing regimen	All studies	Phase I-II KS program	Phase I-II CTCL program	Phase III CTCL study
0.1% gel strength formulation	***48***	***0***	***48***	***0***
QD	42	0	42	0
BID	41	0	41	0
0.5% gel strength formulation	***67***	***22***	***45***	***0***
QOD	2	0	2	0
QD	43	1	42	0
BID	56	17	39	0
TID	7	7	0	0
QID	10	10	0	0
1% gel strength formulation	***129***	***37***	***54***	***38***
QOD	19	0	8	11
QD	79	8	48	23
BID	85	27	38	20
TID	52	13	17	22
QID	44	22	1	21

NOTE: Table entries are the number of study patients included in the pharmacokinetic meta-analysis who applied each dosage regimen. Due to escalation of the dosing frequency and gel strength, patients may contribute to more than one dosing regimen.

A total of 187 patients were enrolled into the studies, and a total of 149 patients (99 males and 50 females) from Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, L1069T-15, L1069-94-04T, L1069T-11, L1069T-12, and L1069T-25 had blood samples collected for bexarotene determination. Demographic, selected clinical laboratory, disease, and blood collection data from these nine studies were pooled, and cross-study population pharmacokinetic and statistical analyses were performed. Descriptive summaries of the data used in these analyses are presented below.

Patients in the pooled database ranged in age between 13 and 87 years, and were White (n=127), Black (n=17), or Asian/Oriental (n=5). Baseline variables were compared between study groups using regression analysis, in order to determine if these differed among the groups. The demographics and baseline characteristics of this population and the results of statistical comparisons are summarized in

Table 6.3-AA. In keeping with the demography of the disease, patients in the KS population were younger than the CTCL population.

Table 6.3-AA. Descriptive Statistics of Baseline Demographics for the 149 Patients Participating in the Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25) and Included in the Pharmacokinetic Population Analysis

Baseline demographics[1]		All studies (n=149)	Phase I-II KS program (n=45)	Phase I-II CTCL program (n=66)	Phase III CTCL study (n=38)
Age (yr)	Mean ± SD	53.4 ± 14.5	40.7 ± 6.6 †	57.6 ± 13.0	61.3 ± 14.3
	Median	52	40	60	63
	Range	13 – 87	23 – 53	30 – 87	13 – 85
	n	149	45	66	38
Gender	Males	99	45	36	18
	Females	50	0	30	20
Weight (kg)	Mean ± SD	81.0 ± 18.9	73.4 ± 10.5 †	85.2 ± 21.1	82.1 ± 19.9
	Median	78.5	71.6	83.8	79.0
	Range	41.8 – 162.0	54.5 – 95.7	50.4 ± 162.0	41.8 – 145.9
	n	145	42	66	37
Height (cm)	Mean ± SD	173 ± 9	178 ± 6 †	172 ± 9	171 ± 10
	Median	174	178	173	170
	Range	147 – 196	163 – 191	147 – 196	150 – 193
	n	141	42	66	33
Calculated Total Body Surface Area[2] (m^2)	Mean ± SD	1.98 ± 0.25	1.91 ± 0.16	2.02 ± 0.28	1.97 ± 0.26
	Median	1.96	1.89	2.02	1.96
	Range	1.33 – 2.89	1.62 – 2.24	1.49 – 2.89	1.33 – 2.67
	n	141	42	66	33
Race	White	127	41	56	30
	Black	17	1	8	8
	Asian/Oriental	5	3	2	0

(1) Baseline demographics were obtained at screening.
(2) Calculated using formula by Gehan & George (1) as BSA = 0.0235 x weight $^{0.51456}$ x height $^{0.42246}$
† Statistically significant difference at $p<0.05$.

Baseline laboratory variables, as assessed on the day of the first blood collection for plasma bexarotene determination, are presented for patients in the pooled database in **Table 6.3-BB.** This baseline visit occurred on Day 0 prior to the application of the first Targretin® gel dose (n=94), Day 15 (n=44), Day 29 (n=9), Week 8 (n=1), or Week 12 (n=1). Patients with KS demonstrated significantly higher ALT and AST levels, slightly but significantly higher protein levels, and significantly lower

cholesterol levels than patients with CTCL. Patients with CTCL in the Phase III study had significantly lower bilirubin levels than patients with KS or patients with CTCL in the Phase I-II program, and patients with CTCL in the Phase I-II program had significantly lower alkaline phosphatase levels than patients with KS or the patients with CTCL in the Phase III study.

Table 6.3-BB. Descriptive Statistics of Baseline Laboratory Variables for the 149 Patients Participating in Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL study (Study L1069T-25) and Included in the Pharmacokinetic Population Analysis

Baseline laboratory variables[1]		All studies (n=149)	Phase I-II KS program (n=45)	Phase I-II CTCL program (n=66)	Phase III CTCL study (n=38)
Alkaline Phosphatase (U/L)	Mean ± SD	82.7 ± 35.6	93.5 ± 43.1	71.4 ± 21.9 †	86.5 ± 38.2
	Median	78	83	66	83.5
	Range	34 – 261	43 – 261	34 – 124	46 – 251
	n	133	42	53	38
Bilirubin (mg/dL)	Mean ± SD	0.624 ± 0.250	0.643 ± 0.176	0.681 ± 0.296	0.522 ± 0.221 †
	Median	0.6	0.6	0.7	0.5
	Range	0.2 – 2.28	0.4 – 1.10	0.2 – 2.28	0.2 – 1.20
	n	132	42	53	37
BUN (mg/dL)	Mean ± SD	14.5 ± 4.6	13.3 ± 3.8	14.6 ± 4.1	15.8 ± 5.8
	Median	14.0	14.0	14.0	15.5
	Range	6 – 39	6 – 22	9 – 25	9 – 39
	n	133	42	53	38
Creatinine (mg/dL)	Mean ± SD	0.936 ± 0.253	0.933 ± 0.182	0.974 ± 0.277	0.887 ± 0.280
	Median	0.9	0.95	1.0	0.8
	Range	0.5 – 2.0	0.6 – 1.4	0.6 – 1.9	0.5 – 2.0
	n	133	42	53	38
Creatinine Clearance[2] (mL/min)	Mean ± SD	103 ± 33	109 ± 25	99.3 ± 33	101 ± 40
	Median	100	102	95	100
	Range	28 – 262	72 – 177	45 – 202	28 – 262
	n	130	40	53	37
Cholesterol (mg/dL)	Mean ± SD	185 ± 49	159 ± 39 †	226 ± 33	200 ± 47
	Median	181	156	231	202
	Range	99 – 350	99 – 261	167 – 283	105 – 350
	n	92	42	12	38
Total Protein (g/dL)	Mean ± SD	7.46 ± 0.55	7.72 ± 0.68 †	7.37 ± 0.43	7.30 ± 0.46
	Median	7.40	7.70	7.40	7.25
	Range	6.3 – 9.5	6.5 – 9.5	6.3 – 8.4	6.5 – 8.3
	n	133	42	53	38
AST (SGOT) (U/L)	Mean ± SD	26.7 ± 14.8	38.6 ± 19.3 †	20.4 ± 8.4	22.3 ± 6.1
	Median	22	35	19	22
	Range	10 – 102	14 – 102	10 – 64	10 – 42
	n	133	42	53	38
ALT (SGPT) (U/L)	Mean ± SD	27.4 ± 20.2	39.8 ± 27.1 †	19.8 ± 9.2	24.2 ± 15.8
	Median	21.0	31.0	18.0	20.5
	Range	6 – 115	8 – 115	6 – 59	8 – 105
	n	133	42	53	38

(1) Baseline values were obtained the day of first blood collection for bexarotene determination.

(2) Calculated using the formula by Lott & Hayton (2) as: CrCL = [(140 - age) x weight] / [α x creat], where α is 72 in males, and 85 in females.

† Statistically significant difference at $p<0.05$.

Baseline disease characteristics of patients on Day 1, and results of statistical comparisons between study groups, are presented in **Table 6.3-CC**. Based on the clinical characteristics of the disease, the number of lesions and the surface area of treated lesions were significantly less in patients with KS than in patients with CTCL. Since patients from the Phase I-II CTCL program were not graded according to the TNM staging used in the Phase III study, the following algorithm was used to convert staging of these Phase I-II patients to TNM staging for comparison purposes: Stage was IA, if CTCL stage was 1, and if the surface area of lesions was lower than 10% of total BSA; Stage was IB, if CTCL stage was 1, and if the surface area of lesions was 10% or higher than 10% of total BSA; and Stage was IIA, if CTCL stage was 2. Therefore, by definition, mean (±SD) treated BSA generally increased with increasing disease stage in these pharmacokinetic patients with CTCL in the Phase I-II program, being 3.6% ± 2.3% for Stage IA patients, 23.8% ± 12.8% for Stage IB patients, and 22.8% ± 17.9% for Stage IIA patients. Similarly, in the Phase III study, mean (±SD) treated BSA generally increased with advancing disease stage, being 4.4% ± 3.9% for Stage IA patients, 28.2% ± 25.3% for Stage IB patients, 50.0% for the single Stage IIA patient, and 14.0% for the single Stage IIB patient.

Table 6.3-CC. Descriptive Statistics of Baseline Disease Characteristics for the 149 Patients Participating in Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25) and Included in the Pharmacokinetic Population Analysis

Baseline disease characteristics[1]		All studies (n=149)	Phase I-II KS program (n=45)	Phase I-II CTCL program (n=66)	Phase III CTCL study (n=38)
CTCL stage	Stage IA	63	N/A	42	21
	Stage IB	33		18	15
	Stage IIA	7		6	1
	Stage IIB	1		0	1
Number of treated lesions	Mean ± SD	5.77 ± 3.43	4.69 ± 2.66 †	N/A[3]	7.67 ± 3.84
	Median	5	4		8
	Range	1 – 16	1 – 10		2 – 16
	n	66	42		24
Surface area of treated Lesions[2] (% BSA)	Mean ± SD	9.02 ± 14.7	0.212 ± 0.300 †	10.9 ± 12.8	15.8 ± 20.8
	Median	3	0.1	5	8.5
	Range	0.01 – 90	0.01 – 1.4	0.1 – 50	0.9 – 90
	n	140	40	66	34

(1) Baseline demographics were obtained on Day 1.
(2) Surface area of treated lesions was measured based on the surface area of the patient hand palm for patients with CTCL or was calculated based upon the lesion diameters and expressed as percentage of total BSA for patients with KS.
(3) Only the number of index lesions was recorded for the Phase I-II CTCL studies
† Statistically significant difference at $p<0.05$

Table 6.3-DD describes the bexarotene concentration data available in the pooled database. Plasma bexarotene concentrations were quantifiable in only 362 (24.6%) of the 1471 post-dose blood samples collected and assayed. Of the 362 post-dose plasma samples with quantifiable concentrations across all studies, 297 had bexarotene concentrations lower than 5 ng/mL, 35 were ≥5 ng/mL but <10 ng/mL, 16 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. Thus, despite long term-application of Targretin® gel (0.1, 0.5, or 1% for up to 135 weeks), the large majority of blood samples had non-quantifiable (<0.5 – 1 ng/mL) or generally sporadic low (<5 ng/mL) plasma bexarotene concentrations, indicating minimal systemic exposure and low potential for accumulation.

Table 6.3-DD. Description of Bexarotene Pharmacokinetic Samples Obtained in Patients Participating in Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25)

Data Descriptors	Number			
	All studies	Phase I-II KS program	Phase I-II CTCL program	Phase III CTCL study
Patient information				
Clinical sites collecting pharmacokinetic samples	22[4]	5	3	17
Patients enrolled in the study	187	70	67	50
Patients with pharmacokinetic samples collected	149	45	66	38
Patients having at least one sample with quantifiable bexarotene concentration[1]	78	1	42	35
Patients having no sample with a quantifiable concentration[1]	71	44	24	3
Sample information				
Pharmacokinetic samples collected	1569	303	965	301
Pre-dose samples collected	96	0	62	34
Samples collected postdose with a quantifiable bexarotene concentration[1]	362	6	190	166
Samples collected postdose without a quantifiable bexarotene concentration[1]	1109	297	711	101
Number of samples not assayable	2	0	2	0
Documentation				
Postdose samples[2] with complete dosing and sampling records[3]	1398	284	874	240
Postdose samples[2] with complete dosing and sampling records[3] and quantifiable bexarotene concentration	345	6	183	156
Postdose samples[2] with complete dosing and sampling records[3] and quantifiable bexarotene concentration available for NONMEM analysis	313	6	179	128
Postdose samples[2] with complete dosing and sampling records[3] and non-quantifiable bexarotene concentration	1051	278	689	84
Postdose samples[2] with complete dosing and sampling records[3] but not assayable	2	0	2	0
Predose samples and/or samples with incomplete dosing and sampling records	171	19	91	61

(1) LLQ was 1 ng/mL for Phase I-II KS and CTCL programs, and 0.5 ng/mL for Phase III CTCL study.
(2) Count includes samples collected more than 96 hr post-dose, but not evaluated in the meta-analysis.
(3) Plasma samples with inconsistent, incomplete, or missing date and time of last dose and blood collection are not included.
(4) Three clinical sites were common to Phase I-II CTCL program, Phase I-II KS program and Phase III study.

The highest plasma concentrations tended to be observed within 12 hr of gel application and following application of the 1% gel strength (**Figure 6.3-AA**). The time interval between the last application of Targretin® gel and blood collection was available for 1398 (89.1%) of the 1569 samples collected. Blood collection generally occurred within 24 hr of the last application of Targretin® gel (1206 of 1398 samples; 86.3%). The majority of samples were obtained during the time period 0-8 hr, where concentrations would be expected to be maximal (n=721). A total of 92 samples were collected at late time points (from 96 hrs up to 28 days post dose [follow-up visit]). From these 92 late blood samples, 83 had bexarotene plasma concentrations below the limit of quantification. The remaining nine plasma samples had low bexarotene levels that averaged 4.94 ± 8.63 ng/mL (median = 1.54 ng/mL). Samples collected at ≥96 hrs were not included in the population analyses because of uncertainties about the accurate recording of date and time of the last dosing.

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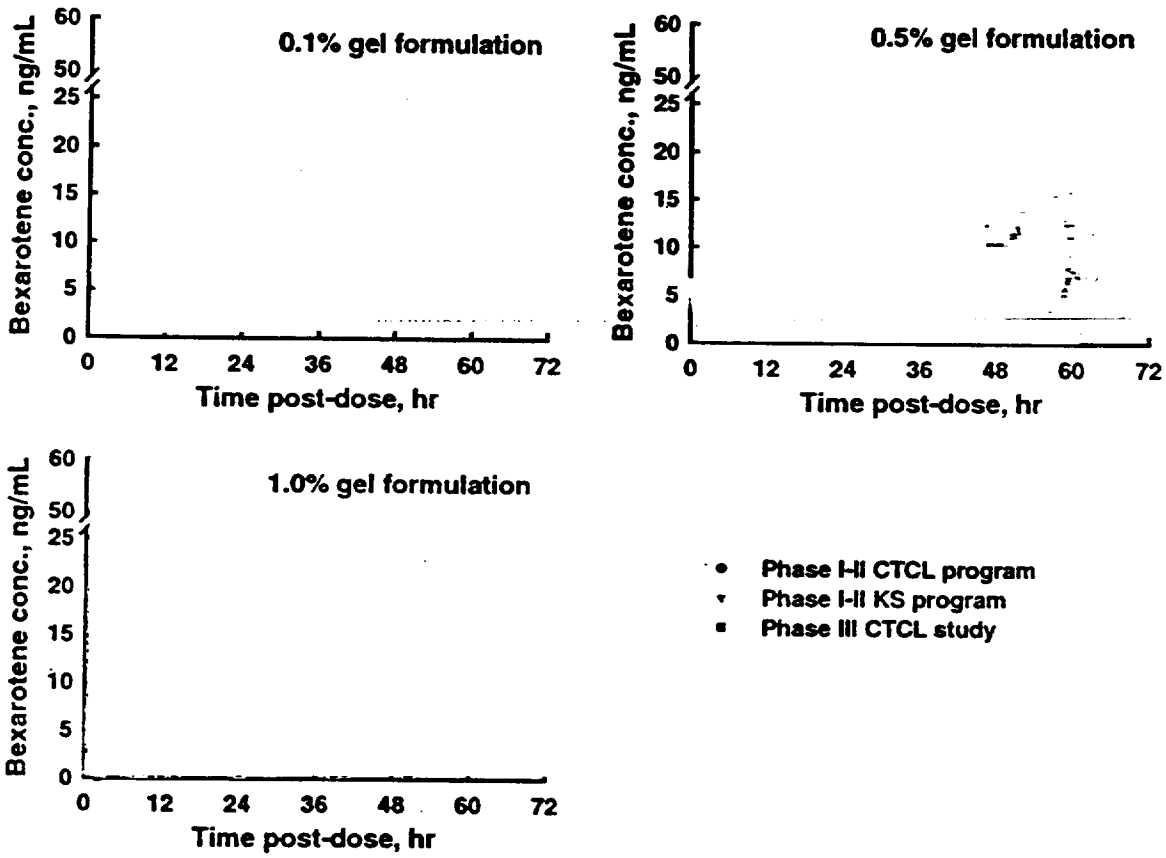
Figure 6.3-AA. Pooled Plasma Bexarotene Concentrations Obtained from Samples Collected in Patients Participating in Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25)



Note: Only plasma bexarotene concentrations measured in samples with known post-dose values are displayed in the figure.
Any bexarotene concentrations obtained in the 92 plasma samples collected more than 96 hr after Targretin® gel application were not evaluated in the meta-analysis and are not plotted in the figure.

The pooled data were subjected to the following population analyses: (1) multivariate stepwise linear regression; (2) linear mixed effects modeling; and (3) non-linear mixed effects modeling (NONMEM). The purpose of each of these analyses was to determine the influence of various patient variables and study variables (assay, study, disease population [CTCL or KS]) of interest on bexarotene concentrations or pharmacokinetic parameters. **Table 6.3-EE** provides a list of patient covariates

studied in each analysis. The methodology and results of each analysis is summarized in the following text.

Table 6.3-EE. Patient Covariates Studied in the Cross-Study Population Analyses for Targretin® Gel (Appendix E of Reports RR-845-99-004, RR-845-99-005, RR-845-99-007)

Demographics	Disease State	Dose	Laboratory Values	Concomitant Medications
Age Gender Weight Height Total BSA Race (white vs. non-white)	Surface area of treated lesions Local dermal irritation[3] CTCL stage	Gel Strength[3] Dosing frequency[3] Daily exposure[4]	Serum creatinine Creatinine clearance Alkaline phosphatase Total bilirubin BUN Protein Total cholesterol[3] AST (SGOT) ALT (SGPT)	CYP3A4 inhibitors[1,3] CYP3A4 inducers[2,3] Gemfibrozil[3]

[1] CYP3A4 inhibitors included: clarithromycin, dronabinol, erythromycin, fluconazole, fluoxetine, indinavir, itraconazole, ketoconazole, metronidazole, nefazodone, nelfinavir, omeprazole, paroxetine, ritonavir, saquinavir, sertraline
[2] CYP3A4 inducers included: carbamazepine, dexamethasone, nevirapine, phenytoin, rifabutin, troglitazone
[3] Variables not included in multivariate stepwise linear regression
[4] Defined as the product of dosing frequency and gel strength. Used in linear mixed-effects analysis only
Note: In addition to the patient-specific covariates listed above, study-related covariates included in the analyses were assay, study, and disease population (KS or CTCL).

Concomitant medications of interest that were included in the pooled population analyses were drugs that are known to be inhibitors or inducers of CYP3A4, since bexarotene is metabolized by CYP3A4 (**Section 6.3.3.**), and gemfibrozil, since orally administered gemfibrozil has been shown to interact with orally administered bexarotene to produce elevated bexarotene concentrations (Targretin® capsules; Section 6.3.7.2.). Concomitant medications that fell into these three groups were categorized as CYP3A4 inducers, CYP3A4 inhibitors, or gemfibrozil and included in the analyses. A total of 54 out of the 149 pharmacokinetic patients were reported to have taken at least one medication of interest concomitantly with Targretin® gel at some time during the study. Of these 54 patients, 43 patients took at least one CYP3A4 inhibitor, 12 patients took at least one CYP3A4 inducer, and four patients took gemfibrozil. These statistics are summarized in **Table 6.3-FF.**

Table 6.3-FF. Description of Medications Taken Concomitantly with Targretin® Gel by the 149 Patients Participating in the Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25)

	All studies (n=149)	Phase I-II KS program (n=45)	Phase I-II CTCL program (n=66)	Phase III CTCL study (n=38)
Any pertinent medications	54 (36.2%)	34 (75.6%)	16 (24.2%)	4 (10.5%)
CYP3A4 inhibitor	43 (28.9%)	27 (60.0%)	13 (19.7%)	3 (7.9%)
CYP3A4 inducer	12 (8.1%)	11 (24.4%)	0 (0.0%)	1 (2.6%)
Gemfibrozil	4 (2.7%)	1 (2.2%)	3 (4.5%)	0 (0.0%)

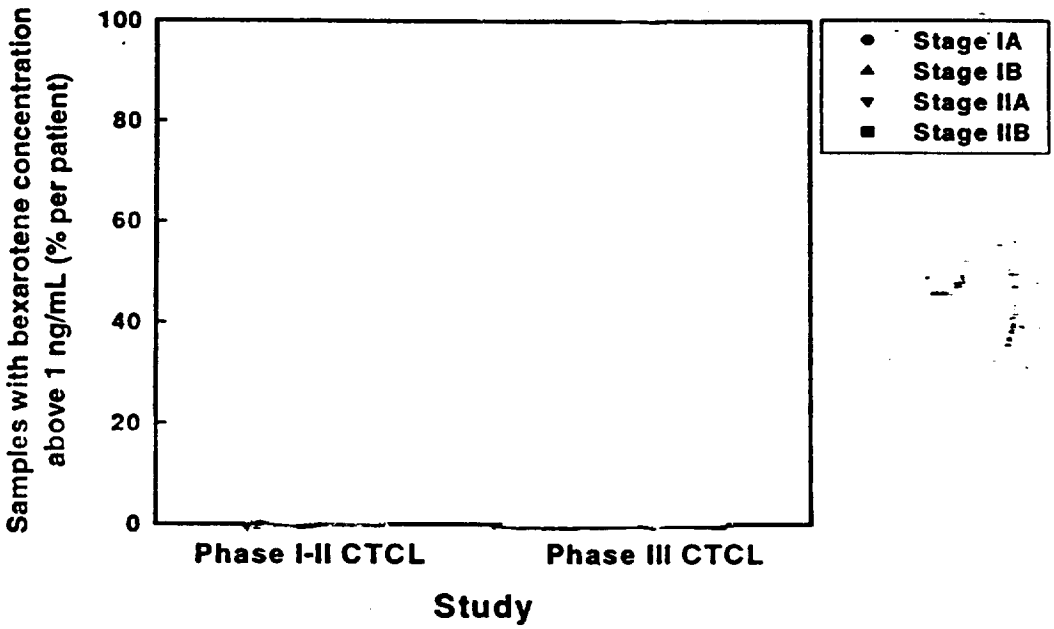
Note: Table entries are the number of patients having taken at least one concomitant medication during the study.
Percentages refer to the total number of patients (n) with pharmacokinetic samples.

Multivariate stepwise linear regression (using SAS, PROC REG) was used to examine the impact of potential baseline covariates (measured at predose or at the time of first blood draw) on the percentage of samples from individual patients with quantifiable bexarotene plasma concentrations. A list of baseline covariates examined in this analysis is listed in **Table 6.3-EE**. Some covariates could not be examined in this analysis because of too many missing data or because the values of these variables varied during the study. Preliminary analysis yielded a disease effect (CTCL or KS), and an assay effect. The assay effect was considered to be artifactual since different assays with different LLQs (0.5 or 1 ng/mL) were used in the studies (**Table 6.3Y**). The disease effect was likely related to the generally non-quantifiable bexarotene levels in blood samples collected during the Phase I-II KS program (297 of 303 samples were BLQ). Since the treated KS lesion areas were generally smaller than the treated CTCL lesion areas (**Table 6.3-CC**), this accounted for a lower topical exposure of the patients with KS to Targretin® gel. Consequently, the analysis was rerun after setting bexarotene concentrations <1 ng/mL to zero to adjust for the artifactual assay effect, and excluding patients with KS to adjust for the disease effect. Additionally, since the patients in this subsequent analysis only comprised of patients with CTCL, CTCL stage was evaluated as an additional potential covariate.

Results of the analysis of the impact of CTCL patient characteristics (surface area of treated lesions and CTCL stage) and baseline demographics on the percentage of samples with bexarotene concentrations higher than 1 ng/mL indicated that patients with a more advanced CTCL stage, which by definition was related to surface area of lesions, were more likely to have bexarotene concentrations higher than 1 ng/mL (actual or adjusted LLQ; $p<0.01$). A study effect was also noted in the analysis of these patients with CTCL alone. This was likely due to the higher percentage of plasma samples with quantifiable bexarotene concentrations in the Phase III study compared to the Phase I-II CTCL program, since patients in the Phase III study were treated with the highest strength of Targretin® gel (1%) and applied the gel to a larger number of lesions and larger surface area than the Phase I-II patients (**Table 6.3-CC**).

The results of the linear regression analysis are also in agreement with results of the evaluation of bexarotene concentration data from CTCL patients in the pooled database, which showed an increase in the percent of quantifiable bexarotene concentrations >1 ng/mL with increasing surface area of treated lesions or advancing stage of CTCL (**Figure 6.3-BB**).

Figure 6.3-BB. Distribution of Samples with Bexarotene Plasma Concentration above 1 ng/mL (expressed as % per patient) as a Function of Study and CTCL Stage in Patients Participating in Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25)



Note: The thick horizontal lines are the mean percentages of samples with measurable concentrations within each study; thin horizontal lines are the mean percentage of samples with measurable concentrations within each study and for each CTCL stage.

In conclusion, the stepwise multivariate regression analysis suggested that the percentage of samples with quantifiable bexarotene concentrations was likely related to patient exposure to Targretin® gel, with surface area of treated lesions and CTCL stage being statistically correlated with the proportion of bexarotene concentrations higher than 1 ng/mL. There was no other statistically significant effect of baseline demographics.

Linear mixed-effects modeling was performed on the data to examine the correlation between bexarotene plasma concentrations and covariates of interest (Table 6.3-EE). In contrast to the multivariate stepwise linear regression which used baseline covariate values, this analysis accounted for intra-individual variability of covariates, because plasma concentrations were regressed against covariates

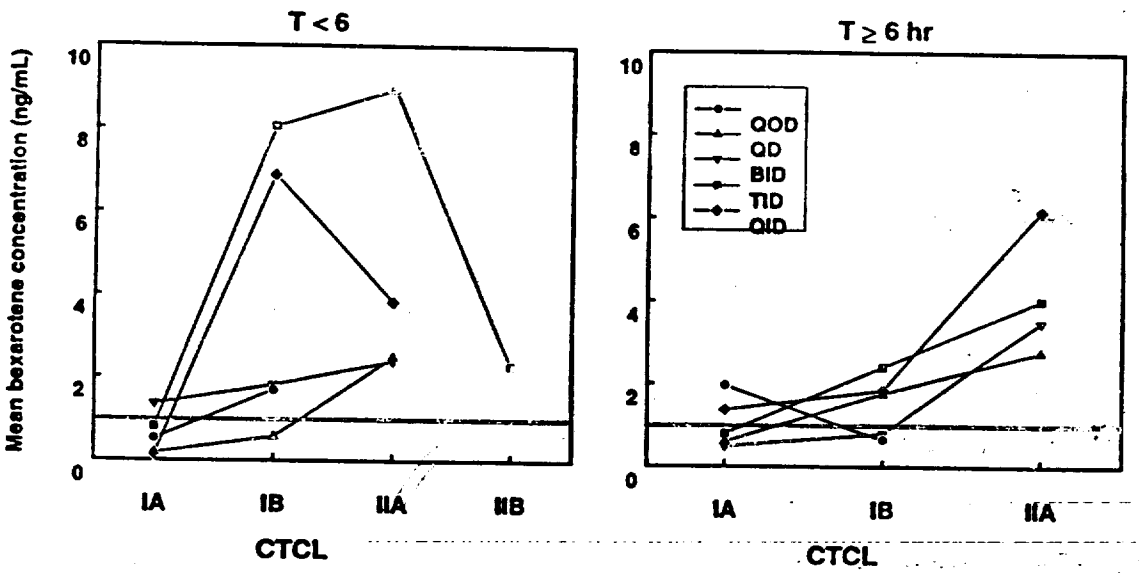
measured on the same visit day as the day of blood collection. An additional computed covariate, "daily exposure" to Targretin® gel, defined as dosing frequency multiplied by gel strength, was also evaluated in this analysis. Plasma bexarotene concentrations were linearly related to a subset of fixed parameters (sampling time post-dose and covariates of interest) and random parameters with a model-independent pharmacokinetic analysis (SAS, PROC MIXED). Due to sample size limitations and in order to increase the likelihood of detecting a potential relationship, covariates were initially evaluated individually in sequential order. Only the covariates that showed some influence on bexarotene plasma concentrations ($p<0.15$) were jointly evaluated in a subsequent model. Post-dose intervals were segregated into two groups in order to account for potential time-dependent variation in plasma concentrations. Thus separate linear mixed-effects models were examined for samples collected at T <6 hr and T ≥6 hr post-dose, based on the observation that peak plasma bexarotene concentrations occur at approximately 6 hr post-application.

For early blood collections (samples collected at T <6 hr), only daily exposure and surface area of treated lesions showed a statistically significant correlation with plasma bexarotene concentrations ($p<0.01$). This finding suggested that plasma bexarotene concentrations were significantly related to overall patient exposure to Targretin® gel (i.e., gel strength, frequency of application, and surface area of application). Similarly, when considering patients with CTCL alone, patient exposure was again a significant predictor of plasma bexarotene concentration, with daily exposure and stage of CTCL being selected as covariates of influence. For samples taken within 6 hr of Targretin® gel application, an increase in bexarotene plasma concentrations was predicted with increasing time post-dose, increasing patient daily exposure (frequency of application and gel strength), and with more advanced CTCL stage (which was likely related to surface area of treated lesions). The relationship between observed bexarotene concentrations and CTCL stage is demonstrated in **Figure 6.3-CC** for the subset of patients treated with the 1% commercially intended formulation of Targretin® gel.

For later blood collections (samples collected at T ≥6 hr), a correlation between plasma bexarotene concentrations and the surface area of treated lesions was observed. No correlation was observed between an increase in daily topical exposure (dosing frequency and gel strength) and an increase in plasma concentrations in this subset of samples. However, stage of CTCL was again shown to be a statistically significant predictor of plasma concentrations in the CTCL patient population.

Thus, similar to the results of multivariate stepwise linear regression, the overall results of this analysis indicated that plasma bexarotene concentrations were related to patient exposure (frequency of gel application, strength of the gel applied, surface area of lesions treated, and/or CTCL stage) to Targretin® gel.

Figure 6.3-CC. Distribution of the Mean Bexarotene Plasma Concentrations Measured in Blood Samples Collected in Patients Participating in the Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25), and Applying Targretin® Gel 1%



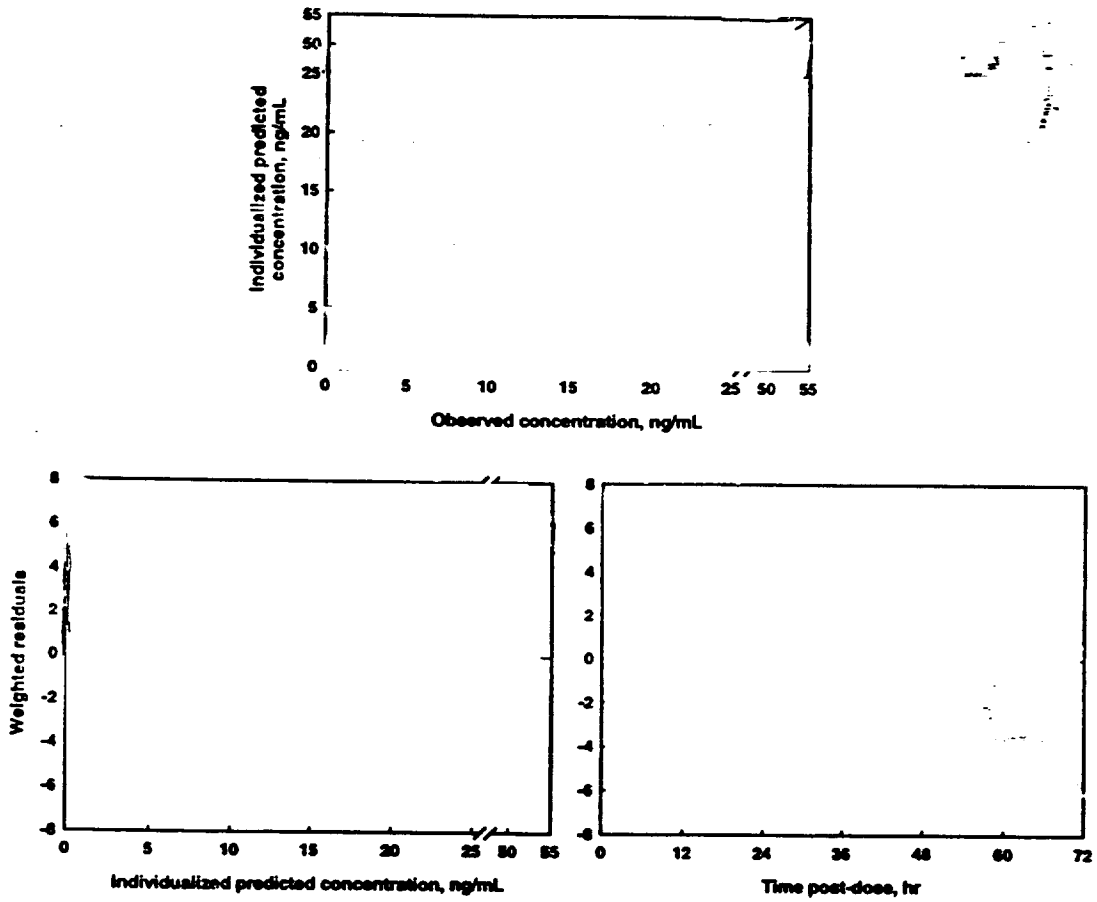
Note: The solid gray line represents the actual or adjusted assay LLQ of 1 ng/mL.

Nonlinear mixed-effects modeling (NONMEM) was the third method used to evaluate the population pharmacokinetics of bexarotene and ascertain if and how potential covariates such as patient demographics, clinical laboratory values, disease characteristics, concomitant medications and bioanalytical assay (**Table 6.3-EE**) might affect the disposition of topical bexarotene. Of the total 1569 blood samples collected, 313 plasma concentration records obtained from 77 patients were utilized in the NONMEM analysis, representing only a fifth (20%) of the total number of plasma samples collected (**Table 6.3-DD**). The remaining data were excluded for several reasons: 171 samples (10.9%) were pre-dose samples or they had incomplete dosing and/or sampling record information, 1051 samples (67.0%) were below the quantifiable limit of the assay (and were therefore not analyzable by NONMEM), 32 samples (2.0%) were not utilized for lack of information on the frequency of application and/or strength of gel applied, and two samples (0.1%) had insufficient plasma volume for assay of bexarotene concentrations. The modeling process included the identification of a preliminary or base pharmacokinetic model, evaluation of potential covariates using multivariate stepwise linear regression and their subsequent inclusion into the base population pharmacokinetic model, followed by final analysis and estimation of individual patient pharmacokinetic parameters using the posterior conditional estimation (post-hoc) technique of NONMEM. Since the actual amount of Targretin® gel applied to lesions was not known, strength of gel, defined as % (w/w), was used instead of dose in the pharmacokinetic model. Consequently, units for clearance and volume were expressed as L/hr/dose-unit and L/dose-unit, respectively.

The population pharmacokinetics of Targretin® gel was best described by a linear one-compartment model without an absorption phase, and with an additive residual error. The lack of absorption phase was likely caused by the large inter- and intra-individual variability in observed plasma concentrations. The goodness of fit of the final model to the data was examined from the plots of predicted versus observed concentrations, unweighted/weighted residuals versus predicted concentrations and time post-dose (**Figure 6.3-DD**). The model described the data

well, though a slight underestimation of bexarotene concentrations at high concentrations at early time points was seen.

Figure 6.3-DD. Illustration of the Goodness of Fit of the Final Population Model from NONMEM Analysis of Bexarotene Plasma Concentration Obtained in Patients Participating in Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25)



Note: The solid line represents the line of identity. The dotted line was fit to data by linear regression.

No clinically significant effects of demographics and concomitant medications on plasma bexarotene concentrations were observed. However, since only quantifiable bexarotene concentrations could be included in the NONMEM analysis, data included for concomitant medications were limited in this analysis. No significant effects of most laboratory values were observed. Adjustment of apparent clearance

of bexarotene for creatinine clearance resulted in a small but statistically significant improvement in the goodness of fit of the population model to the data, and this effect was subsequently kept in the model (as a multiplicative effect). While the model predicted a modest increase in apparent topical clearance of bexarotene with increasing creatinine clearance (**Figure 6.3-EE**), the validity of this result was questionable since it was based on data from only a subset of patients with measurable bexarotene concentrations (only 20% of the total database could be used in the NONMEM analysis), and consequently could not be confirmed in the entire population of patients, the majority of whom had bexarotene concentrations below limits of quantitation (BLQ). Additionally, it is unlikely that renal impairment would exert a clinical significant influence on bexarotene pharmacokinetics since renal excretion of bexarotene (<0.04%) and its metabolites is negligible (**Section 6.3.3.4.**). In support of this, individual patient data demonstrated that even in patients with measurable concentrations, no clear trends were evident in bexarotene concentrations as a function of individual creatinine clearance values. For example, Patient 801 from Study L1069T-25, who had the lowest creatinine clearance measured during the study (20.7 mL/min at Week 24), had a low plasma bexarotene concentration of 2.1 ng/mL. Therefore, in conclusion, renal function (as measured by serum creatinine and creatinine clearance) is unlikely to have a clinically significant effect on bexarotene pharmacokinetics following topical administration.

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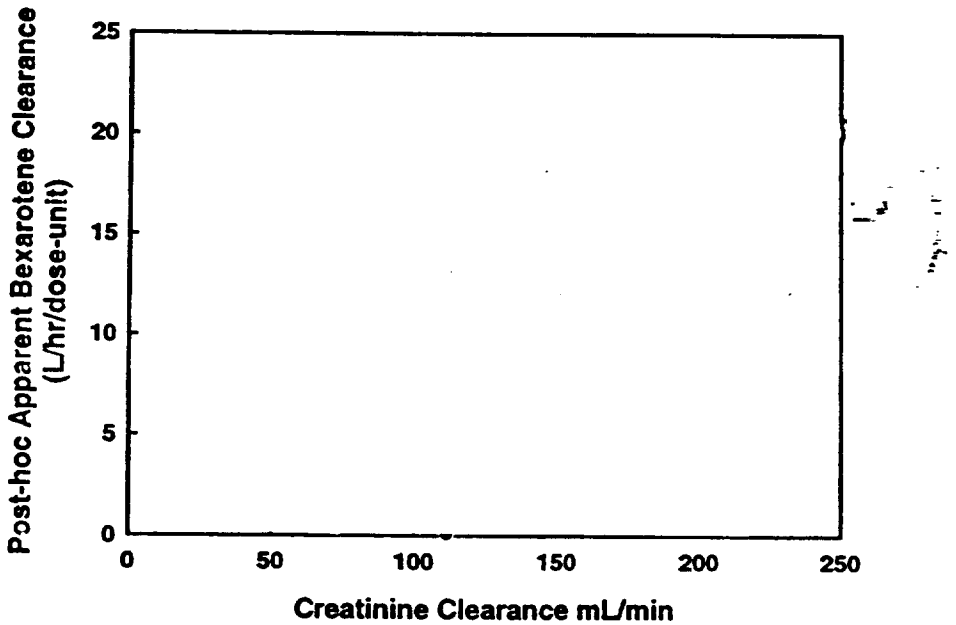
Figure 6.3-EE. Distribution of Post-Hoc Bexarotene Topical Clearance Estimates (L/hr/dose-unit) from the Final NONMEM Model Versus Creatinine Clearance Values for Patients Participating in Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25)



Note: Nine patients had missing creatinine clearance value. They were set to the median 104 mL/min for NONMEM analysis

In summary, the results of these population analyses showed that bexarotene pharmacokinetics correlated well with topical exposure of patients to Targretin® gel. Higher and more frequently quantifiable bexarotene plasma concentrations were observed in patients who treated a larger surface area of lesions, in patients who used the 1% commercially intended Targretin® gel formulation, and in patients who applied Targretin® gel more frequently. Patient demographics and concomitant medications had no clinically meaningful effect on the pharmacokinetics of Targretin® gel in the study population.

6.3.6. Bexarotene Pharmacokinetics in Special Populations

No formal studies to assess bexarotene pharmacokinetics in special patient populations (age, gender, ethnic origin, renal impairment and hepatic impairment) have been conducted. However, the relationship between bexarotene pharmacokinetics and age, gender, and ethnic origin have been assessed in a cross-study population analysis of data from the clinical studies using Targretin® gel. The pharmacokinetic databases from the Phase I-II CTCL studies (Studies L1069-94-04T, L1069T-11, and L1069T-12), the Phase III CTCL Study (Study L1069T-25), and the Phase I-II KS studies (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15) were combined and analyzed using several techniques (multivariate stepwise linear regression, linear mixed effects modeling, and non-linear mixed effects modeling [NONMEM]). The methodology and results of these analyses are discussed in detail in **Section 6.3.5.** The effects of demographic parameters on the pharmacokinetics of topically applied bexarotene are summarized in the following subsections. No relationship between age, gender and ethnic origin and bexarotene concentrations or pharmacokinetic parameters was found following topical application.

The effect of demographics on bexarotene pharmacokinetics following oral administration of Targretin® capsules has also been examined in patients with advanced cancers. The results of these evaluations have been submitted in the NDA for Targretin® capsules (NDA 21-055) and are summarized in the following sections **(Sections 6.3.6.1 - 6.3.6.3.).** Previous data have shown that patients with CTCL have comparable oral bexarotene pharmacokinetics to patients with advanced cancers other than CTCL **(Section 6.3.3.2.3.).** For the evaluation of demographic effects, the pharmacokinetic databases from the Targretin® capsule studies, Studies L1069-93-01 and L1069-93-02, were combined to provide an overall characterization of bexarotene pharmacokinetics **(Section 6.3.3.2.1.).** The combined database included pharmacokinetic data over an 18 mg/m^2 to 650 mg/m^2 dose range. The single-dose data from this combined database were examined to

determine if bexarotene pharmacokinetics were associated with the demographic characteristics of patients. Because of the wide range of Targretin® capsule doses used, dose-normalized C_{max} and AUC_{0-6} parameters were compared among demographic groups. No relationship between age, gender, or ethnic origin and bexarotene pharmacokinetic parameters was apparent.

In addition to demographic assessments, the potential for an alteration in bexarotene pharmacokinetics in patients with renal or hepatic dysfunction is discussed in **Sections 6.3.6.4. and 6.3.6.5.** No formal studies have been conducted to examine the effect of renal or hepatic dysfunction on bexarotene pharmacokinetics. However, based on the oxidative metabolism of bexarotene and the no or minimal detectable renal excretion of either unchanged bexarotene or its oxidative metabolites, patients with renal dysfunction are unlikely to have altered bexarotene pharmacokinetics whereas patients with hepatic dysfunction could potentially have an altered disposition of bexarotene. The relationship between laboratory measures of renal and hepatic function and bexarotene pharmacokinetics was assessed in the cross-study population analysis of data from the clinical studies using Targretin® gel. No clinically significant relationship was found between these parameters and bexarotene concentrations or pharmacokinetic parameters.

6.3.6.1. Effect of Age on Bexarotene Pharmacokinetics

The effect of patient age on the population pharmacokinetics of topically applied bexarotene was evaluated in cross-study population analyses of pooled data from the Phase I-II CTCL program (Studies L1069-94-04T, L1069T-11, and L1069T-12), the Phase III CTCL Study (Study L1069T-25), and the Phase I-II KS program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15). The methodology and results of these analyses are discussed in detail in **Section 6.3.5.** Patients in this pooled population ranged in age from 13 to 87 years **(Table 6.3-GG)**, of which only one patient (Patient 731, Study L1069T-25, age 13 years) was below 18 years. Patients with KS were generally younger than patients with CTCL.

Table 6.3-GG. Descriptive Statistics of Age for the 149 Patients Participating in Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25) and Included in the Pharmacokinetic Population Analysis

Baseline demographic		All studies (n=149)	Phase I-II KS program (n=45)	Phase I-II CTCL program (n=66)	Phase III CTCL study (n=38)
Age (yr)	Mean ± SD	53.4 ± 14.5	40.7 ± 6.6 †	57.6 ± 13.0	61.3 ± 14.3
	Median	52	40	60	63
	Range	13 – 87	23 – 53	30 – 87	13 – 85
	n	149	45	66	38

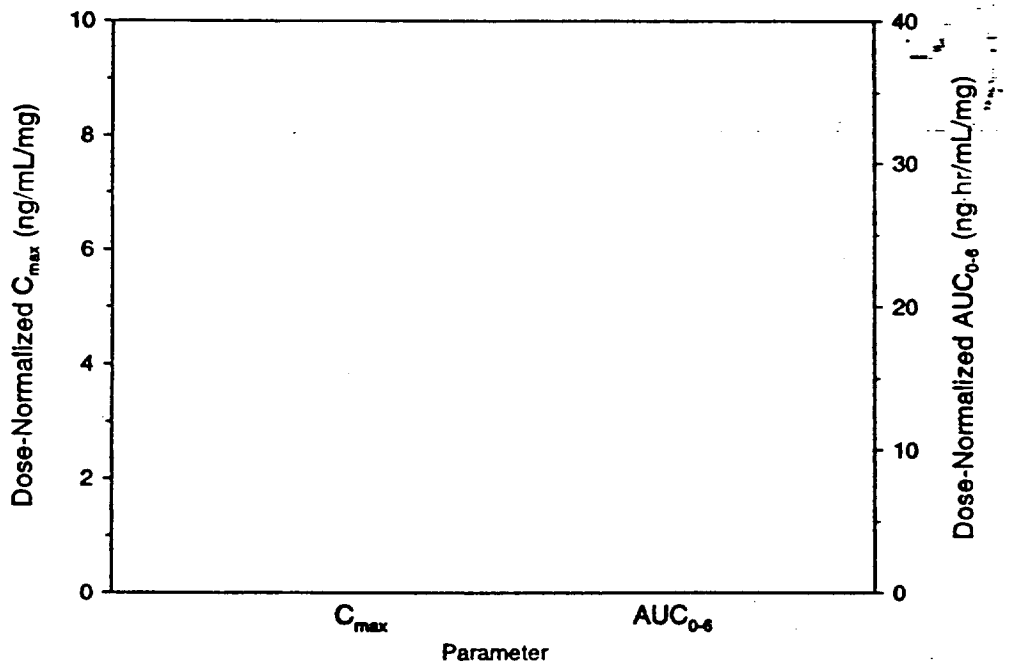
Note: Data were recorded at screening.
† Statistically significant difference at $p<0.05$.

No relationship was found between age and bexarotene pharmacokinetics over the age range studied. Although the pharmacokinetics of bexarotene in a pediatric population could not be studied because only one patient (Patient 731, Study L1069T-25) was younger than 18 years, plasma concentration data in this 13-year old boy were consistent with concentration data observed in adult patients.

In addition to the evaluation of age effects on topically applied bexarotene, the effect of age has also been examined after oral administration of Targretin® capsules. The pharmacokinetic databases from the Targretin® capsule studies, Studies L1069-93-01 and L1069-93-02, were combined as detailed in **Section 6.3.6.**, and evaluated to determine if bexarotene pharmacokinetics were affected by patient age. Day 1 pharmacokinetic data (48 observations) from 47 patients who had a mean ± SD (median, range) age of 56 ± 13 (56, 25 to 78) years were included in the analysis. The database was subdivided into two groups based on patient age. Adult patients (N=28; 29 total observations) were defined as those patients with baseline ages of 18 to 59 years. Elderly patients (N=19) were defined as those individuals who were ≥60 years of age at baseline. Individual patient and mean dose-normalized Day 1 C_{max} and AUC_{0-6} parameter values for each of the two groups are provided in **Figure 6.3-FF.** The dose-normalized bexarotene pharmacokinetic parameter values for the two age groups were similar. In addition,

dose-normalized C_{max} and AUC_{0-6} values in the limited subgroup (N=8) of patients ≥70 years were similar to respective values in adult patients. Therefore, in this patient population ranging in age from 25 to 78 years, there was no relationship between age and oral bexarotene pharmacokinetics.

Figure 6.3-FF. Individual Patient and Mean (Bars) Dose-Normalized Bexarotene C_{max} and AUC_{0-6} Values in Adult and Elderly Patients After Single Oral Doses of 18 mg/m^2 to 650 mg/m^2 Targretin® Capsules (Combined Studies L1069-93-01 and L1069-93-02)



Adult (<60 years, N=28) and elderly (≥60 years, N=19) patients are represented by closed and open circles, respectively. Open triangles represent the subset of patients ≥70 years (N=8).

6.3.6.2. Effect of Gender on Bexarotene Pharmacokinetics

The effect of patient gender on the population pharmacokinetics of topically applied bexarotene was evaluated in cross-study population analyses of pooled data from the Phase I-II CTCL program (Studies L1069-94-04T, L1069T-11, and L1069T-12), the Phase III CTCL Study (Study L1069T-25), and the Phase I-II KS program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15). The methodology and results of these analyses are discussed in detail in **Section 6.3.5.**

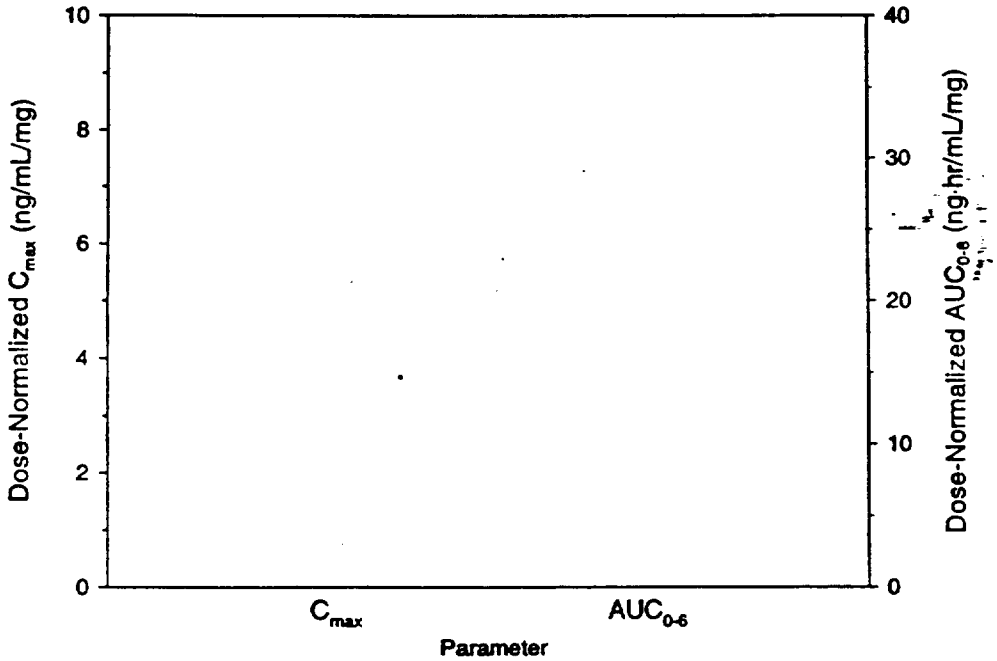
There were 99 males and 50 females in this pooled population and all patients with KS were males (**Table 6.3-HH**). No relationship was found between gender and bexarotene pharmacokinetics following topical administration.

Table 6.3-HH. Descriptive Statistics of Gender for the 149 Patients Participating in Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25) and Included in the Pharmacokinetic Population Analysis

Baseline demographic		All studies (n=149)	Phase I-II KS program (n=45)	Phase I-II CTCL program (n=66)	Phase III CTCL study (n=38)
Gender	Males	99	45	36	18
	Females	50	0	30	20

In addition to the evaluation of gender effects on topically applied bexarotene, the effect of gender has also been examined after oral administration of Targretin® capsules. The pharmacokinetic databases from the Targretin® capsule studies, Studies L1069-93-01 and L1069-93-02, were combined as detailed in **Section 6.3.6**, and evaluated to determine if bexarotene pharmacokinetics were affected by patient gender. Individual patient and mean dose-normalized Day 1 C_{max} and AUC_{0-6} parameter values for male (N=25) and female (N=22; 23 total observations) patients are shown in **Figure 6.3-GG**. While mean dose-normalized parameter values were higher in females than males, there was considerable variability in the individual patient data and there was no consistent gender effect on the dose-normalized parameter values. These data suggest that the oral pharmacokinetics of bexarotene in male and female patients are similar.

Figure 6.3-GG. Individual Patient and Mean (Bar) Dose-Normalized Bexarotene C_{max} and AUC_{0-6} Values in Male and Female Patients After Single Oral Doses of 18 mg/m^2 to 650 mg/m^2 Targretin® Capsules to Patients With Advanced Cancers (Combined Studies L1069-93-01 and L1069-93-02)



Closed and open circles correspond to men (n=25) and women (n=22), respectively.

6.3.6.3. Effect of Ethnic Origin on Bexarotene Pharmacokinetics

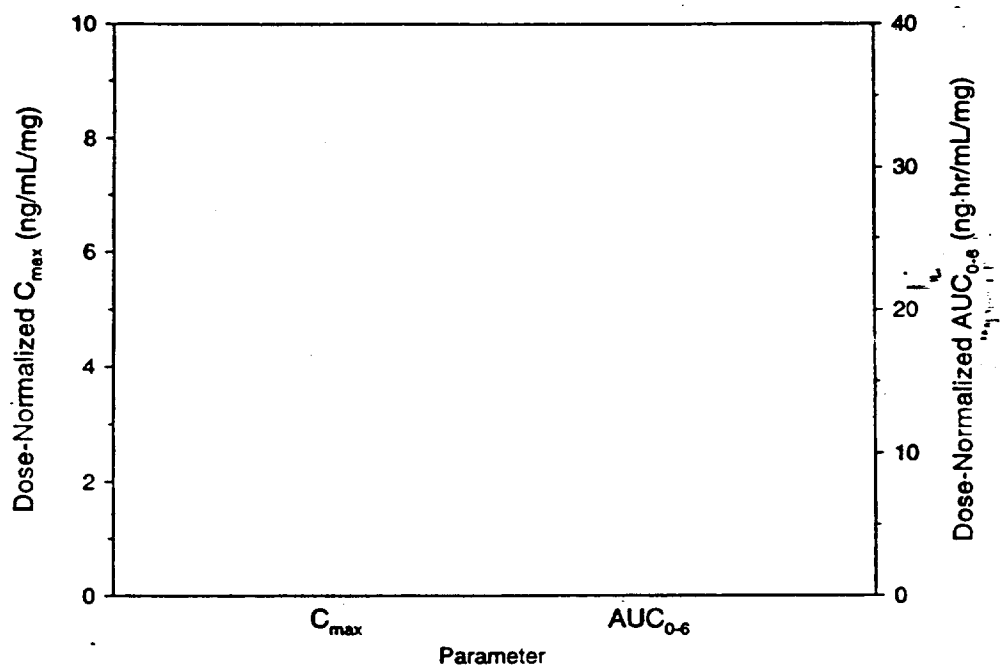
The effect of ethnic origin of patients on the population pharmacokinetics of topically applied bexarotene was evaluated in cross-study population analyses of pooled data from the Phase I-II CTCL program (Studies L1069-94-04T, L1069T-11, and L1069T-12), the Phase III CTCL Study (Study L1069T-25), and the Phase I-II KS program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15). The methodology and results of these analyses are discussed in detail in **Section 6.3.5**. There were 127 White, 17 Black, and five Asian/Oriental patients included in these analyses (**Table 6.3-II**). Patients were grouped as "White" or "Non-White" for population analysis. No relationship was found between ethnic origin (White or non-White) and bexarotene pharmacokinetics following topical administration.

Table 6.3-II. **Descriptive Statistics of Ethnic Origin for the 149 Patients Participating in Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25) and Included in the Pharmacokinetic Population Analysis**

Baseline demographic		All studies (n=149)	Phase I-II KS program (n=45)	Phase I-II CTCL program (n=66)	Phase III CTCL study (n=38)
Race	White	127	41	56	30
	Black	17	1	8	8
	Asian/Oriental	5	3	2	0

In addition to the evaluation of the effects of ethnic origin on topically applied bexarotene, the effect of ethnic origin has also been examined after oral administration of Targretin® capsules. The pharmacokinetic databases from the Targretin® capsule studies, Studies L1069-93-01 and L1069-93-02, were combined, as detailed in **Section 6.3.6.**, and evaluated to determine if bexarotene pharmacokinetics were affected by ethnic origin. Patients were categorized as White (N=40), Black (N=5; six total observations), Hispanic/Spanish American (N=1), or Other (N=1). Because the study population consisted primarily of White patients (85%), mean parameters were determined for this group only. Individual patient observations for patients of ethnic origin other than White were compared to the mean parameter value and range of values observed in White patients. Dose-normalized pharmacokinetic parameter values for non-White patients were within the range of mean values observed in White patients (**Figure 6.3-HH**). These data indicate that the oral pharmacokinetics of bexarotene are similar in patients of differing ethnic origin.

Figure 6.3-HH. Individual Patient Dose-Normalized C_{max} and AUC_{0-6} Values After a Single Oral Dose of 18 mg/m^2/day to 650 mg/m^2/day Targretin® Capsules Compared Across Race (Combined Studies L1069-93-01 and L1069-93-02)



Closed circles correspond to whites (N=40, bars represent means). Values for all other races are represented in the Figure by the first letter of their race: black, hispanic, or other

6.3.6.4. Effect of Renal Dysfunction on Bexarotene Pharmacokinetics

The renal excretion of bexarotene and its metabolites has been studied in an ongoing oral study in patients with Type II diabetes mellitus. Details of the urinary excretion of bexarotene and its metabolites are described in **Section 6.3.3.5.** In brief, no bexarotene, 6- or 7-oxo-bexarotene or bexarotene glucuronide were detected in urine and only trace quantities of 6- or 7-hydroxy-bexarotene were observed. Renal clearance of bexarotene was estimated to be less than 1 mL/minute in all patients. Thus, based on its negligible excretion, the pharmacokinetics of bexarotene are unlikely to be affected by renal dysfunction.

The effects of varying levels of renal dysfunction, as measured by serum creatinine levels and creatinine clearance values, on the population pharmacokinetics of topically applied bexarotene was evaluated in cross-study population analyses of pooled data from the Phase I-II CTCL program (Studies L1069-94-04T, L1069T-11, and L1069T-12), the Phase III CTCL Study (Study L1069T-25), and the Phase I-II KS program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15). The methodology and results of these analyses are discussed in detail in **Section 6.3.5.** Baseline (as assessed on the day of the first blood collection for plasma bexarotene determination) serum creatinine, creatinine clearance, and blood urea nitrogen (BUN) values for patients in this pooled population are summarized in **Table 6.3-JJ**. Serum creatinine levels for patients ranged from 0.5 to 2.0 mg/dL. Corresponding baseline creatinine clearance values (calculated from serum creatinine values using the method of Lott and Hayton (2)) ranged from 28 to 262 mL/min.

Table 6.3-JJ. Descriptive Statistics for Baseline Laboratory Variables of Renal Function for the 149 Patients Participating in Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL study (Study L1069T-25) and Included in the Pharmacokinetic Population Analysis

Baseline laboratory variables[1]		All studies (n=149)	Phase I-II KS program (n=45)	Phase I-II CTCL program (n=66)	Phase III CTCL study (n=38)
BUN (mg/dL)	Mean ± SD Median Range n	14.5 ± 4.6 14.0 6 – 39 133	13.3 ± 3.8 14.0 6 – 22 42	14.6 ± 4.1 14.0 9 – 25 53	15.8 ± 5.8 15.5 9 – 39 38
Creatinine (mg/dL)	Mean ± SD Median Range n	0.936 ± 0.253 0.9 0.5 – 2.0 133	0.933 ± 0.182 0.95 0.6 – 1.4 42	0.974 ± 0.277 1.0 0.6 – 1.9 53	0.887 ± 0.280 0.8 0.5 – 2.0 38
Creatinine Clearance[2] (mL/min)	Mean ± SD Median Range n	103 ± 33 100 28 – 262 130	109 ± 25 102 72 – 177 40	99.3 ± 33 95 45 – 202 53	101 ± 40 100 28 – 262 37

(1) Baseline data were obtained on the day of first blood collection for bexarotene determination.
(2) Calculated using the formula by Lott & Hayton (2) as: CrCL = [(140 - Age) x Weight] / [α x Creat], where α is 72 in males, and 85 in females.

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. For example, Patient 801 from study L1069T-25, who had the lowest creatinine clearance measured during the study (20.7 mL/min at Week 24), had a relatively low plasma bexarotene concentration of 2.1 ng/mL.

Following oral administration of Targretin® Capsules, no evidence for altered bexarotene pharmacokinetics was observed in patients with CTCL with elevated serum creatinine concentrations (≥1.5 upper limit of normal [ULN]) who were administered Targretin® Capsules. It is therefore not anticipated that patients with renal dysfunction will require adjustment of bexarotene dose.

6.3.6.5. Effect of Hepatic Dysfunction on Bexarotene Pharmacokinetics

The hepatic metabolism of bexarotene has been assessed using in vitro and ex vivo techniques. Details of the metabolism of bexarotene are described in **Section 6.3.3.3**. In brief, in vitro studies have indicated that human liver microsomes are capable of metabolizing bexarotene primarily to oxidative metabolites (6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene) and to an acyl glucuronide conjugate. Although the oxidative metabolites were present in plasma samples from clinical studies following oral administration of Targretin® Capsules, no bexarotene and only trace quantities of some of the oxidative metabolites were detected in the evaluated urine samples (**Section 6.3.3.4**.). Acyl glucuronide was not detected in plasma or urine. Based on these observations, urinary elimination of bexarotene is considered to be insignificant, but hepatobiliary mechanisms may be important to the elimination of bexarotene and its oxidative metabolites. Therefore, patients with hepatic dysfunction might have the potential for altered bexarotene pharmacokinetics.

While no formal studies to assess bexarotene pharmacokinetics in patients with hepatic impairment were conducted, the effects of varying clinical laboratory measures of hepatic function (AST, ALT, serum bilirubin, BUN, alkaline phosphatase, total protein, and cholesterol) on the population pharmacokinetics of topically applied bexarotene were evaluated in cross-study population analyses of pooled single-time-point data from the Phase I-II CTCL program (Studies L1069-94-04T, L1069T-11, and L1069T-12), the Phase III CTCL Study (Study L1069T-25), and the Phase I-II KS program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15). The methodology and results of these analyses are discussed in detail in **Section 6.3.5**. Baseline laboratory parameters (as assessed on the day of the first blood collection for plasma bexarotene determination) for patients included in this pooled analysis are presented in **Table 6.3-KK**. Patients with CTCL in the Phase I-II program had significantly lower alkaline phosphatase levels than patients with KS and patients with CTCL in the

Phase III study, and patients with CTCL in the Phase III study had significantly lower bilirubin levels than patients with KS and patients with CTCL in the Phase I-II program. Patients with KS (who often manifest asymptomatic liver disease secondary to AIDS-related opportunistic infections, neoplasms or drug treatments) had significantly higher ALT and AST levels. They also had slightly increased but significant levels of total protein compared to patients with CTCL in this pooled population.

Table 6.3-KK. Descriptive Statistics for Baseline Laboratory Variables of Hepatic Function for the 149 Patients Participating in Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL study (Study L1069T-25) and Included in the Pharmacokinetic Population Analysis

Baseline laboratory variables*		All studies (n=149)	Phase I-II KS program (n=45)	Phase I-II CTCL program (n=66)	Phase III CTCL study (n=38)
Alkaline Phosphatase (U/L)	Mean ± SD	82.7 ± 35.6	93.5 ± 43.1	71.4 ± 21.9 †	86.5 ± 38.2
	Median	78	83	66	83.5
	Range	34 – 261	43 – 261	34 – 124	46 – 251
	n	133	42	53	38
Bilirubin (mg/dL)	Mean ± SD	0.624 ± 0.250	0.643 ± 0.176	0.681 ± 0.296	0.522 ± 0.221 †
	Median	0.6	0.6	0.7	0.5
	Range	0.2 – 2.28	0.4 – 1.10	0.2 – 2.28	0.2 – 1.20
	n	132	42	53	37
Total Protein (g/dL)	Mean ± SD	7.46 ± 0.55	7.72 ± 0.68 †	7.37 ± 0.43	7.30 ± 0.46
	Median	7.40	7.70	7.40	7.25
	Range	6.3 – 9.5	6.5 – 9.5	6.3 – 8.4	6.5 – 8.3
	n	133	42	53	38
AST (SGOT) (U/L)	Mean ± SD	26.7 ± 14.8	38.6 ± 19.3 †	20.4 ± 8.4	22.3 ± 6.1
	Median	22	35	19	22
	Range	10 – 102	14 – 102	10 – 64	10 – 42
	n	133	42	53	38
ALT (SGPT) (U/L)	Mean ± SD	27.4 ± 20.2	39.8 ± 27.1 †	19.8 ± 9.2	24.2 ± 15.8
	Median	21.0	31.0	18.0	20.5
	Range	6 – 115	8 – 115	6 – 59	8 – 105
	n	133	42	53	38

* Baseline data were obtained on the day of first blood collection for bexarotene determination.
† Statistically significant difference at $p<0.05$.

While the degree of hepatic dysfunction that could be evaluated following topical administration was limited to the mild range of laboratory abnormalities encountered in these populations, results of population analysis showed no relationship between these laboratory measures of liver function and bexarotene pharmacokinetics following topical administration.

Similarly, evaluation of patients with CTCL treated orally with Targretin® Capsules showed no evidence for altered bexarotene pharmacokinetics in those patients with elevated serum bilirubin (>ULN) or elevated serum ALT, AST, or alkaline phosphatase (≥2.5 ULN).

6.3.6.6. Overall Summary of Bexarotene Pharmacokinetics in Special Populations

No formal studies have been conducted to assess the pharmacokinetics of bexarotene in special patient populations. However, the potential relationship between patient characteristics and bexarotene pharmacokinetics was assessed following both topical application of Targretin® gel and oral administration of Targretin® capsules.

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 result 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.

Bexarotene is primarily metabolized by human liver microsomes to oxidative metabolites (6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene) and to an acyl glucuronide conjugate. The oxidative metabolites have been shown to appear in plasma following oral administration. No unchanged bexarotene and only trace amounts of some of the oxidative metabolites have been detected in urine. No acyl glucuronide has been detected in plasma or urine. The renal clearance of bexarotene has been estimated to be less than 1 mL/min. Thus, while renal dysfunction should have no clinically significant effect on bexarotene pharmacokinetics, hepatic dysfunction could theoretically alter bexarotene pharmacokinetics.

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.

No formal study was conducted to determine bexarotene pharmacokinetics in patients with renal insufficiency. However, population analysis of pharmacokinetic data following application of Targretin® gel showed that plasma bexarotene concentrations were not significantly elevated in patients with lower derived creatinine clearance values.

6.3.7. Drug Interactions

Formal drug interaction studies of Targretin® gel with concomitant medications of interest have not been conducted. However, interactions of systemically administered concomitant medications with bexarotene have been evaluated using data collected from clinical studies utilizing topically applied Targretin® gel and from studies utilizing orally administered Targretin® capsules. Medications examined have included those considered to have the potential to affect the pharmacokinetics of bexarotene and/or those that have been observed to be frequently coadministered with bexarotene. The details and results of these evaluations are discussed in the following sections. Data from the Targretin® gel studies are being submitted in this NDA. Data from the Targretin® capsule studies have been previously submitted in NDA 21-055, and are only summarized in the following sections.

Bexarotene is metabolized in humans to oxidative metabolites (6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene), and bexarotene acyl glucuronide (**Section 6.3.3.4.**). The oxidative metabolites are the major plasma metabolites of bexarotene, and their formation has been shown to be mediated by CYP3A4. Consequently, drugs that induce (e.g., rifampin, phenytoin, or phenobarbital) or inhibit (e.g., ketoconazole, itraconazole, or erythromycin) CYP3A4 may have the potential to affect bexarotene pharmacokinetics. The effect of CYP3A4 modulators on bexarotene has been evaluated using data from the Targretin® gel studies and Targretin® capsule studies. Results from evaluation of individual bexarotene concentration data in the Targretin® gel studies as well as population analyses of pooled data from these studies have shown no effects of CYP3A4

inducers or inhibitors on bexarotene pharmacokinetics. Similarly, based on limited data, no evidence for a drug interaction with CYP3A4 inhibitors (azole antifungals and macrolide antibiotics) has been observed during clinical studies of Targretin® capsules (**Studies L1069-23 and L1069-24; Section 6.3.3.2.3.**). However, the potential for an interaction between bexarotene and CYP3A4 inducers or inhibitors cannot be ruled out.

On oral administration of Targretin® capsules, concomitant administration of gemfibrozil was shown to be associated with increased plasma bexarotene concentrations (**Section 6.3.7.2.**). Consequently, gemfibrozil was considered a systemic concomitant medication of interest for evaluation in the Targretin® gel studies. Only four patients in the Targretin® gel studies were on concomitant gemfibrozil during the period of pharmacokinetic evaluations. Based on these limited data, bexarotene plasma concentrations appeared to be elevated in one patient on concomitant gemfibrozil, though concentrations were still relatively low in comparison to concentrations achieved following oral dosing.

The actual mechanism for a drug interaction between bexarotene and gemfibrozil is unknown. However, data from the clinical studies of Targretin® capsules have suggested that the observed interaction with gemfibrozil may be due to inhibition of the oxidative metabolism of bexarotene. While no studies have been published that clearly characterize a metabolic drug interaction with gemfibrozil, a possible metabolic interaction with warfarin has been reported in an anecdotal report, in which a single patient who was well-controlled on warfarin therapy experienced a lengthened prothrombin time and prolonged menstrual cycle following initiation of gemfibrozil therapy. (3) These symptoms resolved with a reduction in warfarin dosage, and it was hypothesized by the author that gemfibrozil might inhibit the oxidative metabolism of warfarin, though no supportive data was provided. In contrast, no interaction between gemfibrozil and fluvastatin was observed when these drugs were concomitantly administered to patients (N=17) requiring antilipemic therapy, indicating that gemfibrozil does not affect the oxidative metabolism of

fluvastatin. (4) Other than these two reports, there are no other literature references that provide further insight into the possible interactions of gemfibrozil.

The effect of other commonly administered concomitant medications, atorvastatin and levothyroxine, was examined following administration of Targretin® capsules. No significant effects of either of these agents was observed on bexarotene pharmacokinetics.

6.3.7.1. Assessment of Potential Drug Interactions with Bexarotene Following Application of Targretin® gel

The potential for systemically administered concomitant medications to affect the pharmacokinetics of bexarotene following topical administration was evaluated using population analyses (linear mixed effects modeling, and non-linear mixed effects modeling [NONMEM]) of pooled single-time-point data from the Phase I-II CTCL program (Studies L1069-94-04T, L1069T-11, and L1069T-12), the Phase III CTCL Study (Study L1069T-25), and the Phase I-II KS program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15). Details of the methodology and results of these analyses can be found in **Section 6.3.5**, and results of the evaluation of drug interactions are summarized below.

As expiained in **Section 6.3.7.**, the analysis of concomitant medications focused primarily on pertinent medications that might affect the pharmacokinetics of bexarotene, on the basis of metabolic considerations and results from previous Targretin® capsule studies. Consequently, inhibitors and inducers of CYP3A4, as well as the concurrent administration of gemfibrozil, were primarily studied for potential drug-drug interactions with bexarotene. Concomitant medications were grouped into three categories (CYP3A4 inducers, CYP3A4 inhibitors, or gemfibrozil) and these categories were used in the analysis.

Patients included in population analysis ranged in age from 13 to 87 years. The population included 99 male and 50 female patients; 127 patients were White, 17 were Black, and 5 were Asian/Oriental. A total of 54 out of the 149 patients were reported to have taken at least one medication of interest concomitantly with Targretin® gel at some time during the study. Of these 54 patients, 43 patients took at least one CYP3A4 inhibitor, 12 patients took at least one CYP3A4 inducer, and four patients took gemfibrozil. These statistics are summarized in **Table 6.3-LL**, and a listing of pertinent concomitant medications taken by patients that were included in the pharmacokinetic analysis is provided in **Table 6.3-MM**. Only concomitant medications that were being taken at the time of collection of at least one blood sample were included in the analysis.

Table 6.3-LL. Number of Patients taking Oral Medications of Interest Concomitantly with Targretin® Gel in the Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25) who were Included in the Population Analysis

	All studies (n=149)	Phase I-II KS program (n=45)	Phase I-II CTCL program (n=66)	Phase III CTCL study (n=38)
Any pertinent medications[1]	54 (36.2%)	34 (75.6%)	16 (24.2%)	4 (10.5%)
CYP3A4 inhibitor	43 (28.9%)	27 (60.0%)	13 (19.7%)	3 (7.9%)
CYP3A4 inducer	12 (8.1%)	11 (24.4%)	0 (0.0%)	1 (2.6%)
Gemfibrozil	4 (2.7%)	1 (2.2%)	3 (4.5%)	0 (0.0%)

[1] Only inhibitors or inducers of CYP3A4, and gemfibrozil were considered for potential drug-drug interaction with Targretin® gel.

Note: Table entries are the number of patients having taken at least one concomitant medication during the study.

Percentages refer to the total number of patients (n) with pharmacokinetic samples.

Table 6.3-MM. Oral Medications of Interest Taken Concomitantly with Targretin® Gel by the 149 Patients Participating in Phase I-II KS Program (Studies L1069-94-03T, L1069T-07, L1069T-08, L1069T-13, and L1069T-15), Phase I-II CTCL Program (Studies L1069-94-04T, L1069T-11, and L1069T-12), and Phase III CTCL Study (Study L1069T-25) and Included in the Population Analysis

Pertinent Concomitant Medications[1]	All studies	Phase I-II KS program	Phase I-II CTCL program	Phase III CTCL study
CYP3A4 inhibitors	***43***	***27***	***13***	***3***
Clarithromycin	14	12	1	1
Dronabinol	1	1	0	0
Erythromycin	6	3	3	0
Fluconazole	19	15	3	1
Fluoxetine	2	1	0	1
Indinavir	5	5	0	0
Itraconazole	7	5	2	0
Ketoconazole	8	4	4	0
Metronidazole	4	3	0	1
Nefazodone	2	2	0	0
Nelfinavir	1	1	0	0
Sertraline	1	0	1	0
Omeprazole	7	3	4	0
Paroxetine	3	1	2	0
Ritonavir	1	1	0	0
Saquinavir	2	2	0	0
CYP3A4 inducers	***12***	***11***	***0***	***1***
Carbamazepine	2	1	0	1
Nevirapine	1	1	0	0
Phenytoin	2	1	0	1
Rifabutin	8	8	0	0
Troglitazone	1	0	1	0
Gemfibrozil	*4*	*1*	*3*	*0*

[1] Only inhibitors or inducers of CYP3A4 and gemfibrozil were considered for potential drug-drug interaction with Targretin® gel.

Note: Table entries indicate the number of patients that took the medications at least once during the study. Patients who took more than one concomitant medication are reported more than once in the table.

The results of population analysis using linear mixed effects modeling showed no effect of systemic concomitant medications on bexarotene concentrations. This conclusion was supported by the large number of plasma concentrations in these studies that were below quantitation limits, in spite of the use of concomitant CYP3A4 inhibitors or gemfibrozil. In particular, in the Phase I-II KS program where a large number of patients were using concomitant CYP3A4 inhibitors, 98% (297/303) of the bexarotene plasma concentrations measured in the study were not

quantifiable (**Section 6.3.2.1.3.3.**). Similar to the results obtained from linear mixed effects modeling, NONMEM analysis showed no effect of concomitant medications on bexarotene pharmacokinetics, though the data included in this analysis were limited since only quantifiable bexarotene concentrations could be included in the analysis.

Only four patients in the clinical studies of Targretin® gel took concomitant gemfibrozil: three patients in the Phase I-II CTCL program (Patients 609 and 625 in Study L1069T-11, and Patient 612 in Study L1069T-12) and one patient in the Phase I-II KS program (Patient 630 in Study L1069T-07). Patient 630 in the KS program (Study L1069T-07) had bexarotene concentrations that were below LLQ. Patient 609 in the Phase I-II CTCL program (Study L1069T-11), who took gemfibrozil (600 mg BID PO) during a large part of the study (Week 6 to 64 and Week 88 to 132), had more than half of the samples with bexarotene concentrations below LLQ, and when quantifiable, bexarotene concentrations did not exceed 3.5 ng/mL. In patient 612 (Phase I-II CTCL program, Study L1069T-12), who started taking gemfibrozil (300 mg BID PO) at enrollment and continued on this medication throughout the study, both post-dose blood samples drawn within 24 hrs of dosing showed quantifiable bexarotene concentrations (2.15 and 2.51 ng/mL). One patient (Patient 625; Phase I-II CTCL program, Study L1069T-11), who took gemfibrozil (600 mg BID PO) throughout the study (74 weeks), showed elevated bexarotene levels compared to other patients (average of 11 ng/mL, range of BLQ-24.17 ng/mL, of which 89% [17/19] of samples were above LLQ).

In conclusion, systemically administered CYP3A4 inducers or inhibitors did not have a significant effect on bexarotene pharmacokinetics following topical application of Targretin® gel. While no significant effect of gemfibrozil on topically applied bexarotene was found with population analysis, patient numbers included in this analysis were small. Bexarotene concentrations were elevated in one patient on concomitant gemfibrozil, though concentrations were still relatively low in comparison to concentrations following oral dosing (range of BLQ-24.17 ng/mL,

which is ≤2% of mean C_{max} values following oral dosing with Targretin® capsules at the intended dose of 300 mg/m^2 QD). Thus, concomitant gemfibrozil may have the potential to increase bexarotene concentrations following application of Targretin® gel.

6.3.7.2. Assessment of Potential Drug Interactions with Bexarotene Following Administration of Targretin® Capsules

The potential for drug interactions with bexarotene was also evaluated in studies with Targretin® Capsules. Data from the two oral Phase II-III clinical studies in patients with CTCL (Studies L1069-23 and L1069-24) were combined and assessed for effects of commonly administered concomitant medications and CYP3A4 inducers and inhibitors on plasma bexarotene concentrations. The design, results, and conclusions from these studies are described in **Section 6.3.3.2.3**. The combined data set included pharmacokinetic information from a total of 123 patients. These 77 men (63%) and 46 women (37%) had a mean ± SD (median, range) age of 63 ± 13 (64, 24 to 89) years and mean ± SD (median, range) weight of 80 ± 15 (80, 47 to 120) kg. Racial distribution was as follows: 101 White (82%), 16 Black (13%), three Hispanic (2%), one Mixed (1%), and two categorized as Other (2%).

Drugs that were frequently coadministered with bexarotene and drugs that could potentially modulate CYP3A4 were selected for assessment of a possible drug interaction with bexarotene (**Table 6.3-NN**).

Table 6.3-NN. **Pertinent Orally Administered Medications Evaluated for a Potential Drug-Drug Interaction With Bexarotene When Administered Concomitantly With Targretin® Capsules (Combined Analysis of Studies L1069-23 and L1069-24)**

CYP3A Inhibitors	CYP3A Inducers	Frequently Coadministered With Targretin® Capsules	
		Antilipemics	Others
Azole Antifungals Macrolide Antibiotics Protease Inhibitors	Phenobarbital Phenytoin Rifampin	Atorvastatin Gemfibrozil Pravastatin Simvastatin Lovastatin Fenofibrate Clofibrate Niacin	Levothyroxine

Though the single-time-point plasma concentrations were highly variable, plasma bexarotene concentrations tended to increase with increasing dose. Consequently, plasma concentration data were dose-normalized to minimize the confounding effect of dose in the drug interaction analysis. Additionally, to minimize the confounding effects of time since dosing in the drug interaction assessment, only those samples collected between 12 and 24 hours since the most recent dose were included in the population analysis.

Based on this subset of samples, observations for a population assessment of a potential drug interaction were available only for atorvastatin, levothyroxine, gemfibrozil, and a combined grouping of CYP3A4 inhibitors. Individual patient plasma concentration values were also assessed for possible drug interactions with any other concomitantly administered medication.

The following paradigm was used for the population assessments of potential drug interactions between bexarotene and atorvastatin, levothyroxine, CYP3A4 inhibitors (combined azole antifungals and macrolide antibiotics) and gemfibrozil: For each of the concomitant medications evaluated other than gemfibrozil (i.e. atorvastatin, levothyroxine, and CYP3A4 inhibitors [combined azole antifungals and macrolide antibiotics]), patients who received the concomitant medication of interest at the time

of at least one pharmacokinetic sample were identified, and a dataset was constructed for population analysis that included all plasma samples from this subset of patients that were obtained between 12 and 24 hours postdose, excluding those samples obtained during concomitant gemfibrozil administration. For the gemfibrozil population assessment, the sample dataset included all plasma samples that were obtained between 12 and 24 hours postdose from the subset of patients that had at least one pharmacokinetic sample obtained during concomitant administration of gemfibrozil. All plasma samples were used for the individual patient assessments of the effects of concomitant medications on plasma bexarotene concentrations.

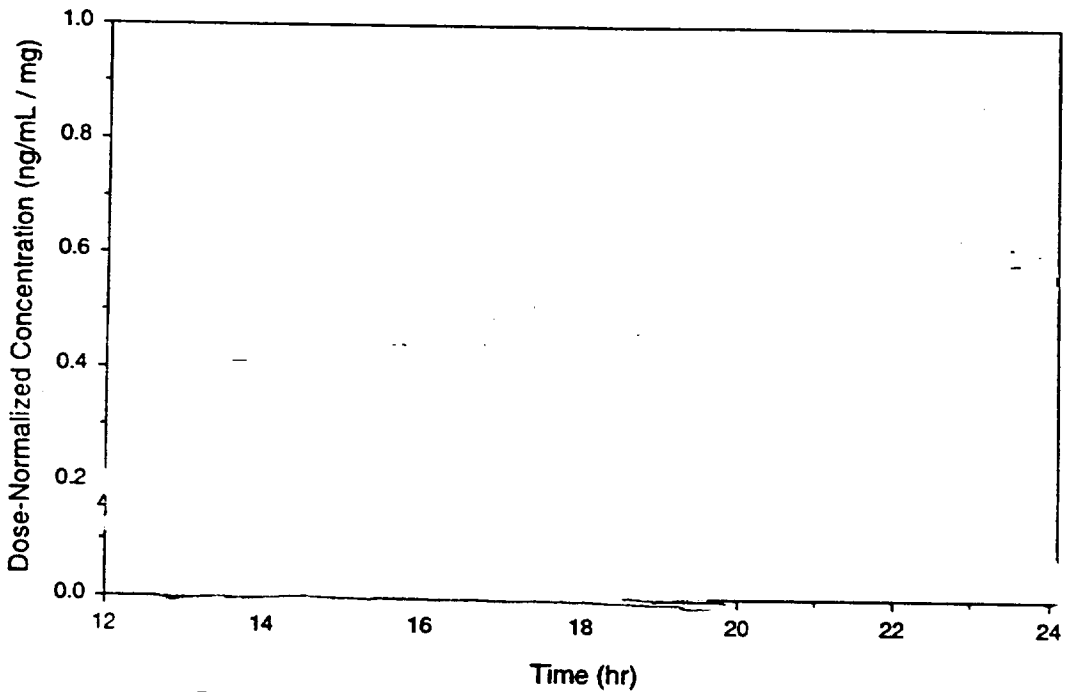
As indicated in **Table 6.3-OO** and **Figure 6.3-II**, dose-normalized plasma bexarotene concentrations were similar with and without concomitant administration of atorvastatin with Targretin® capsules. The similarity in the mean and median dose-normalized concentrations between the two groups suggests that atorvastatin is not associated with alterations in plasma bexarotene concentrations when these two drugs are administered concurrently. The result of this population analysis was supported by individual patient observations.

Table 6.3-OO. Dose-Normalized Plasma Bexarotene Concentrations for Patients with CTCL (N=50) After Administration of Targretin® Capsules With or Without Concomitant Atorvastatin for Samples Collected 12 to 24 Hours Postdose (Combined Data from Studies L1069-23 and L1069-24)

	Dose-Normalized Plasma Bexarotene Concentrations (ng/mL/mg)	
	Targretin® Capsules Without Atorvastatin	Targretin® Capsules With Atorvastatin
N	75	158
Mean	0.119	0.120
SD	0.111	0.138
Median	0.086	0.076

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

Figure 6.3-II. Dose-Normalized Plasma Bexarotene Concentrations in Samples Collected 12 to 24 Hours After an Oral Dose of Targretin® Capsules Administered Daily to Patients (N=50) With (Circles) or Without (Triangles) Concomitant Atorvastatin (Combined Data from Studies L1069-23 and L1069-24)



Excludes samples obtained during concomitant administration of gemfibrozil.

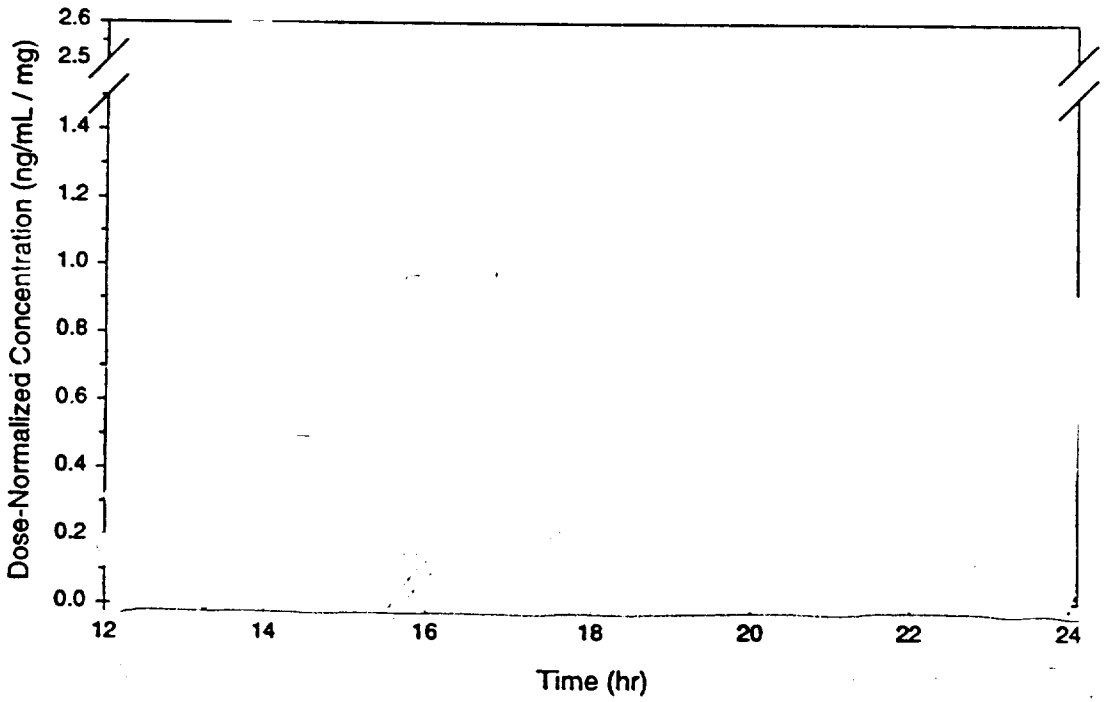
Dose-normalized plasma bexarotene concentrations were similar with and without concomitant administration of levothyroxine with Targretin® capsules (**Table 6.3-PP** and **Figure 6.3-JJ**). The similarity in mean and median dose-normalized concentrations between the two groups suggests that levothyroxine is not associated with alterations in plasma bexarotene concentrations when coadministered with Targretin® capsules. The result of this population analysis was supported by individual patient observations.

Table 6.3-PP. Dose-Normalized Plasma Bexarotene Concentrations for Patients with CTCL (N=45) After Administration of Targretin® Capsules With or Without Concomitant Levothyroxine 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 Levothyroxine	Targretin® Capsules With Levothyroxine
N	82	139
Mean	0.134	0.185
SD	0.130	0.310
Median	0.088	0.090

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

Figure 6.3-JJ. Dose-Normalized Plasma Bexarotene Concentrations in Samples Collected 12 to 24 Hours After an Oral Dose of Targretin® Capsules Administered Daily to Patients (N=45) With (Circles) or Without (Triangles) Concomitant Levothyroxine (Combined Data from Studies L1069-23 and L1069-24)



Excludes samples obtained during concomitant administration of gemfibrozil.

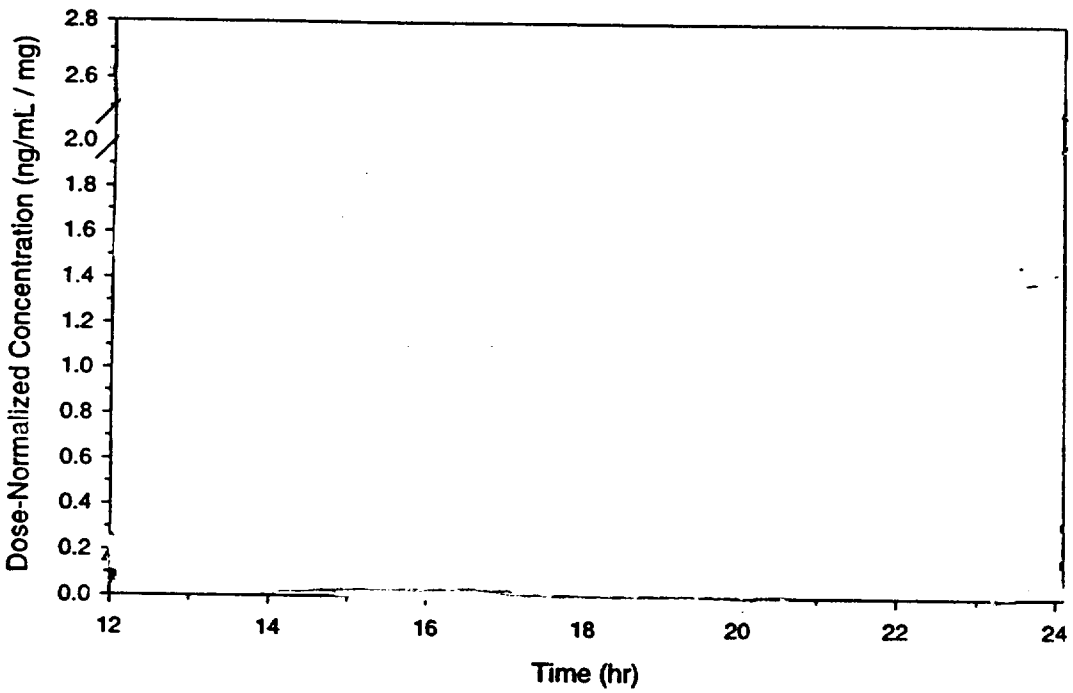
In contrast to the observations with concomitant atorvastatin or levothyroxine, gemfibrozil was associated with higher plasma bexarotene concentrations when administered concurrently with Targretin® capsules (**Table 6.3-QQ** and **Figure 6.3-KK**). The mean dose-normalized plasma bexarotene concentration during concomitant gemfibrozil administration was substantially higher than the dose-normalized bexarotene concentration without concomitant gemfibrozil administration. The increase in plasma bexarotene concentrations was consistent among the patients receiving gemfibrozil.

Table 6.3-QQ. Dose-Normalized Plasma Bexarotene Concentrations for Patients with CTCL (N=27) After Administration of Targretin® Capsules With or Without Concomitant Gemfibrozil for Samples Collected 12 to 24 Hours Postdose (Data from Studies L1069-23 and L1069-24)

	Dose-Normalized Bexarotene Plasma Concentrations (ng/mL/mg)	
	Targretin® Capsules Without Gemfibrozil	Targretin® Capsules With Gemfibrozil
N	97	53
Mean	0.107	0.567
SD	0.136	0.556
Median	0.070	0.355

N = Number of plasma samples.
SD = Standard deviation.

Figure 6.3-KK. Dose-Normalized Plasma Bexarotene Concentrations of Samples Collected 12 to 24 Hours After an Oral Dose of Targretin® Capsules Administered Daily to Patients (N=27) With (Circles) or Without (Triangles) Concomitant Gemfibrozil (Combined Data from Studies L1069-23 and L1069-24)



The mechanism of the observed drug interaction between bexarotene and gemfibrozil has not been elucidated. Bexarotene is metabolized by CYP3A4 and glucuronosyltransferase (**Section 6.3.3.3.**). Gemfibrozil may cause elevations of bexarotene concentrations by inhibiting bexarotene metabolism. If this mechanism were in operation, it would be anticipated that the relative amounts of bexarotene and bexarotene metabolites in plasma would be altered in the presence of gemfibrozil. Although the used to quantitate plasma bexarotene concentrations in this study was not developed to quantitate bexarotene metabolites, the relative amounts of bexarotene and its oxidative metabolites was assessed to provide insight into the possible mechanism of the drug interaction. from a number of patients were examined for evidence of a shift in the relative amounts of bexarotene and its primary oxidative metabolites. Representative from Patient 561, Study L1069-24 are shown in **Figure 6.3-LL.**

With the exception of the pretreatment sample (Panel A), all the [ ] in **Figure 6.3-LL** are from blood samples collected the day after the most recent dose of Targretin® capsules. The height of the bexarotene peak (8 minutes) is small relative to the putative metabolite peaks (2.5 and 3 minutes) in the absence of antilipemic medications (Panel B), during concurrent administration with atorvastatin (Panel C), and during concurrent administration with fenofibrate (Panel F). In contrast, when this patient was administered Targretin® capsules concomitantly with gemfibrozil (Panels D and E), bexarotene was the predominant peak on the chromatogram. These observations are consistent with inhibition of the oxidative metabolism of bexarotene by gemfibrozil, but not by atorvastatin or fenofibrate.. A similar trend was noted in [ ] from other patients who were administered gemfibrozil with Targretin® capsules. The lack of an effect of atorvastatin on the bexarotene metabolite profile is consistent with the results of the population analysis described above. Although the [ ] data suggest that fenofibrate did not have the same effect on the relative amounts of bexarotene and its oxidative metabolites, there were insufficient plasma concentration data to determine if plasma bexarotene concentrations are affected by concomitant fenofibrate administration.