Combined Analysis of Studies L1069-93-01 and L1069-93-02: In addition to study-specific assessments, data from these two studies were combined to present an overall synopsis of bexarotene pharmacokinetics in an oncology patient population, results of which are presented below. The combined data set for evaluation was limited to formulations containing micronized bexarotene and to doses up to 650 mg/m^2. Results of the combined assessment are presented below.

The combined data contained 48 patients, of whom 25 were men (52%) and 23 were women (48%). Racial distribution was as follows: 41 White (87%), five Black (11%), one Hispanic (2%), and one categorized as Other (2%). These patients had a mean ± SD (median, range) age of 57 ± 13 (56, 25 to 78) yr and mean ± SD (median, range) weight of 157 ± 33 (149, 108 to 236) lb.

Oral administration of Targretin® capsules resulted in quantifiable systemic exposure to bexarotene at all dose levels (18 to 650 mg/m^2/day) **(Table 6.3-L)**. A mean t_{max} of 2 to 3 hours after either a single dose or multiple oral doses was observed for most dose groups. There was high interpatient variability in C_{max} and AUC_{0-6} values after a single dose or multiple doses. After single doses, increases in C_{max} and AUC_{0-6} were generally proportional to the dose **(Figure 6.3-M** and **Figure 6.3-N)**. Mean C_{max} and AUC_{0-6} values of several dose groups of 230 mg/m^2 or greater were lower after multiple doses compared with those after a single dose. However, mean single-dose and repeat-dose C_{max} and AUC_{0-6} values were similar for the dose groups receiving 300 mg/m^2 or 400 mg/m^2. Thus, although some patients may experience a reduction in concentration with repeat-dose administration at dose levels ≥230 mg/m^2, there is no clear dose-relationship for this reduction. Mean $t_{1/2}$ values were about 1 to 3 hours for all dose levels after a single dose or multiple doses, although these values were calculated based on 6-hour concentration-time profiles. There was little accumulation of bexarotene at any dose level. On average, predose concentrations were 4% of the subsequent C_{max} value, and the extent of accumulation was not correlated with dose level. No evidence of prolonged accumulation was observed.

Table 6.3-L. Mean (SD) Bexarotene Pharmacokinetic Parameters after Single or Multiple Daily Oral Doses of 18 mg/m^2 to 650 mg/m^2 Targretin® Capsules (Micronized Formulation) to Patients with Advanced Cancers (Combined Studies L1069-93-01 and L1069-93-02)

Dose (mg/m^2)	Regimen[1]	N Obs.	Parameter				
			t_{max} (hr)	C_{max} (ng/mL)	C_0 (ng/mL)	AUC_{0-6} (ng·hr/mL)	$t_{1/2}$[2] (hr)
18	S	3	3.3 (1.2)	67 (15)	NA	232 (102)	1.0 -
	M	6	2.3 (1.4)	89 (38)	0 (0)	266 (99)	1.2 (0.4)
21	S	3	1.3 (0.6)	183 (90)	NA	498 (260)	1.5 (0.2)
	M	3	1.3 (0.6)	189 (58)	2 (2)	514 (153)	1.5 (0.4)
50	S	6	1.8 (0.4)	312 (94)	NA	978 (352)	1.7 (0.6)
	M	9	2.3 (1.1)	237 (94)	4 (4)	788 (285)	1.3 (0.5)
83	S	3	1.4 (0.6)	320 (153)	NA	948 (494)	1.4 (0.2)
	M	4	2.0 (0.1)	186 (99)	5 (3)	546 (211)	2.3 (0.5)
140	S	7	2.3 (0.8)	712 (380)	NA	2449 (1120)	2.2 (0.9)
	M	8	2.3 (1.2)	485 (288)	14 (10)	1734 (1074)	2.3 (1.0)
230	S	4	3.0 (1.2)	1640 (1068)	NA	5586 (3544)	2.1 (0.5)
	M	4[3]	3.5 (1.9)	760 (575)	45 (64)	2325 (1623)	1.3 -
300	S	4	2.3 (1.3)	791 (124)	NA	2826 (327)	2.2 (0.9)
	M	6	2.7 (1.0)	1111 (261)	15 (5)	3213 (677)	1.8 (0.6)
380	S	5	3.8 (1.1)	1959 (1215)	NA	7657 (4789)	2.9 (1.8)
	M	4	2.9 (2.3)	850 (550)	117 (173)	2528 (1268)	2.0 (0.8)
400	S	3	3.4 (1.2)	2404 (855)	NA	8127 (2798)	2.5 -
	M	5	3.2 (1.1)	1930 (957)	88 (89)	7322 (4655)	1.8 (0.1)
500	S	4	2.6 (0.9)	3744 (2429)	NA	15496 (9044)	3.4 (2.5)
	M	4	4.1 (1.6)	1648 (794)	66 (44)	6997 (4084)	3.5 -
650	S	6	3.2 (1.1)	2792 (1696)	NA	11310 (6646)	2.3 (0.6)
	M	5	3.3 (1.5)	2065 (1710)	66 (58)	7232 (5808)	1.7 (0.4)

(1) S = Single dose (Day 1); M = Multiple once-daily doses (most samples collected on Day 15 and Day 29).

(2) $t_{1/2}$ values could not be calculated for all patients; N=2 for dose levels 18 mg/m^2 and 400 mg/m^2, single dose and 230 mg/m^2 and 500 mg/m^2, multiple doses; N=3 for dose level 380 mg/m^2, multiple doses; N=4 for dose level 400 mg/m^2, multiple dose and 650 mg/m^2, single and multiple doses; N=5 for dose level 300 mg/m^2, multiple doses, and N=7 for dose level 140 mg/m^2, multiple doses. Standard deviation values are not reported for N=2 or less.

(3) There were five observations for C_0.

N Obs. = Number of observations.

NA = Not applicable.

- = Not determined.

Figure 6.3-M. Mean Bexarotene C_{max} Values after a Single Dose (with Linear Regression) or Multiple Daily Oral Doses of 18 mg/m^2/day to 650 mg/m^2/day Targretin® Capsules (Combined Studies L1069-93-01 and L1069-93-02)

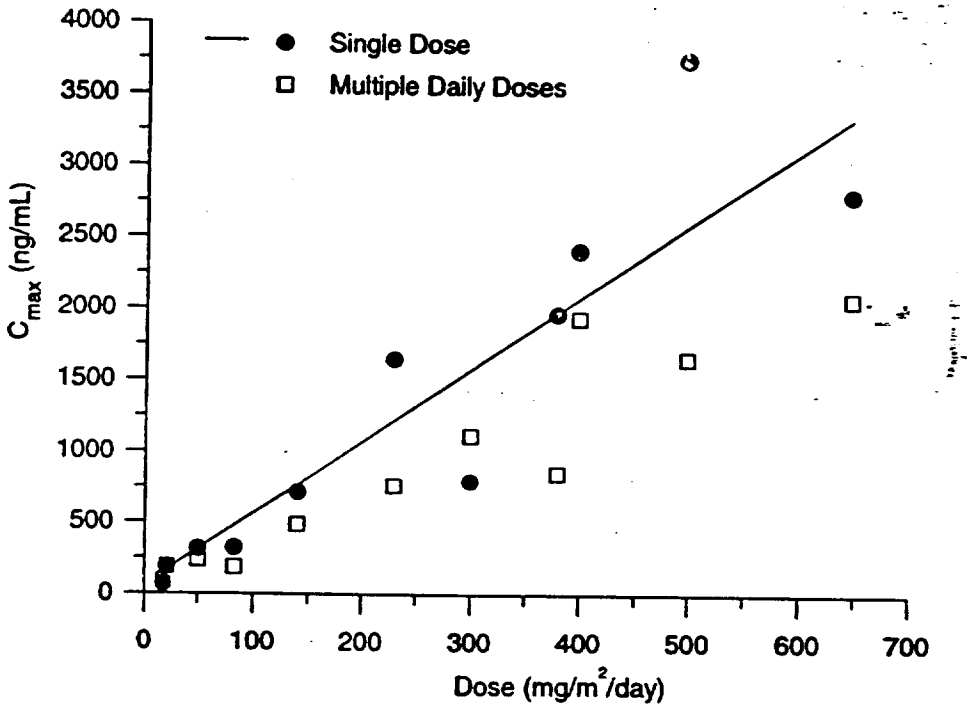
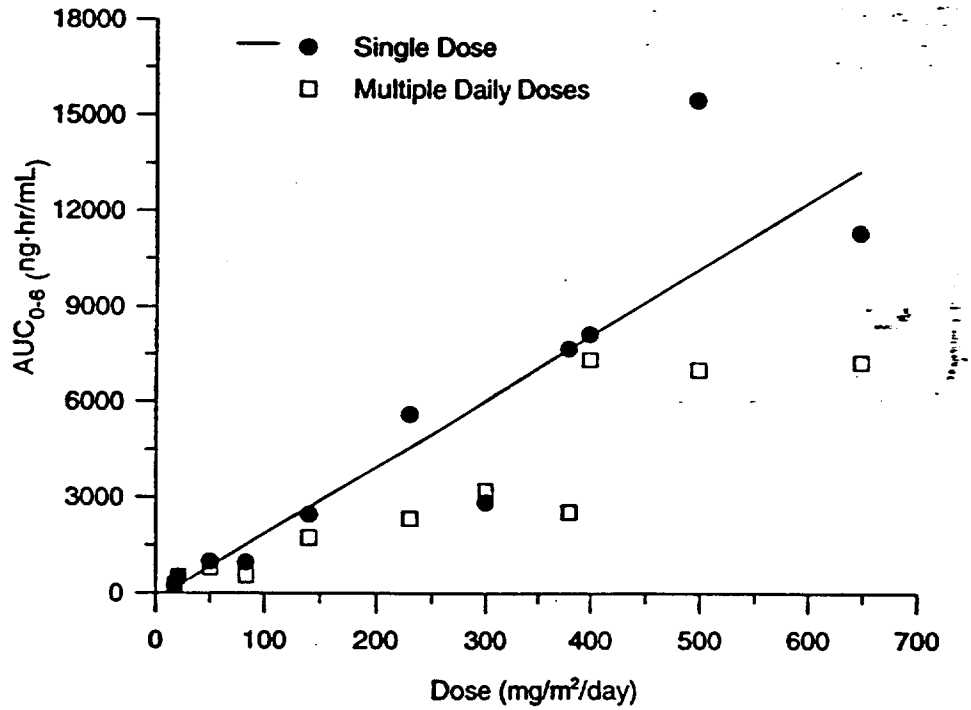


Figure 6.3-N. Mean Bexarotene AUC_{0-6} Values after a Single Dose (with Linear Regression) or Multiple Daily Oral Doses of 18 mg/m²/day to 650 mg/m²/day Targretin® Capsules (Combined Studies L1069-93-01 and L1069-93-02)



L1069-94-02 was a Phase I-II open-label, uncontrolled, multiple-dose, dose-escalation, safety evaluation of oral Targretin® capsules given twice each day (BID) to patients with proven, advanced, recurrent head and neck squamous cell cancer **(RR-845-98-011, NDA 21-055, Section 6.7.5)**. A treatment duration of 4 weeks was intended, with an allowance to continue treatment in 4-week increments if clinically indicated. Targretin® capsules were administered with food or a liquid dietary supplement. Doses of 10 mg/m² of the nonmicronized formulation and 25, 50, 150, 200, and 300 mg/m² of the micronized formulation were administered BID and serial blood samples were collected on Days 1 and 15, up to 6 hours postdose, for the determination of plasma bexarotene concentrations. On pharmacokinetic sampling days, doses were administered with 250 mL of a liquid dietary supplement.

Of the 29 patients enrolled in this study, 14 had blood samples drawn for pharmacokinetic evaluations. Pharmacokinetic data were obtained from a total of 12 patients. These eight (67%) men and four (33%) women had a mean ± SD (median, range) age of 59 ± 7 (57, 47 to 75) yr and mean ± SD (median, range) weight of 148 ± 32 (150, 89 to 192) lb. Racial distribution was as follows: eight White (67%), one Black (8%), and three categorized as Other (25%). Of these patients, only one received the nonmicronized formulation and the remainder received the micronized formulation. The following summary of pharmacokinetics pertains to subjects who received the micronized formulation only.

Values for t_{max} ranged from 2 to 6 hours on Day 1 and Day 15 (Table 6.3-M). The $t_{1/2}$ of bexarotene, although often poorly defined, was similar for all dose groups on Day 1 and Day 15 with an overall harmonic mean of 1.6 hours. After single doses, C_{max} and AUC_{0-6} increased approximately dose-proportionally over the range of doses administered in this study (25 to 300 mg/m^2 of the micronized formulation). After multiple BID administration, bexarotene C_{max} and AUC_{0-6} values tended to be lower than those observed on Day 1. The reduction in repeat-dose parameter values appeared to occur independent of dose. These reductions suggested an increase in the oral clearance of bexarotene with repeated dosing, though they may also have been due to intra-patient variability. The apparent increase in oral clearance in this study occurred at total daily-dose levels (≥50 mg/m^2/day [25 mg/m^2 BID]) lower than those observed in studies with once daily dosing (≥230 mg/m^2/day). All patients had measurable predose levels on Day 15. Day 15 predose concentrations were 11.7% ± 9.5% of the respective Day 15 C_{max} values, indicating there was only slight accumulation of bexarotene with repeated BID dosing.

Table 6.3-M. Mean (SD) Bexarotene Pharmacokinetic Parameters after Single and Multiple Twice-Daily Oral Doses of Targretin® Capsules (Micronized Formulation) to Patients with Advanced Cancers (Study L1069-94-02)

Dose (mg/m^2 BID)	Day	N[2]	Parameter[1]				
			T_{max} (hr)	C_{max} (ng/mL)	C_0 (ng/mL)	AUC_{0-6} (ng·hr/mL)	$t_{1/2}$[3] (hr)
25	1	3	2.1 (0.1)	130 (2)	NA	438 (33)	1.2 (0.5)
	15	3	2.1 (0.0)	93 (18)	10 (7)	273 (43)	2.7 (2.1)
50	1	2	2.1	336	NA	1091	1.6
	15	3	4.1 (2.0)	166 (123)	12 (7)	607 (406)	1.5
150	1	1	6.0	883	NA	3659	ND
	15	1	6.0	551	176	2446	ND
200	1	1	4.0	1230	NA	4528	0.9
	15	1	2.0	396	38	1086	2.0
300	1	3	5.4 (1.1)	1878 (2105)	NA	6140 (6409)	4.2
	15	2	3.0	723	58	2197	2.1

(1) Standard deviation not shown if N<3.
(2) The number of patients (the number of observations was identical).
(3) $t_{1/2}$ values could not be calculated for all patients; N=2 for dose level 50 mg/m^2, Day 15; N=1 for dose level 300 mg/m^2, Day 1.
NA = Not applicable.
ND = Not determined.

6.3.3.2.2. Oral Pharmacokinetics in Patients with Type II Diabetes Mellitus

The oral pharmacokinetics of bexarotene were determined in Study L1069DM-01, a Phase II open-label, uncontrolled, multiple-dose, dose-escalation, safety and tolerability study in patients with Type II diabetes mellitus **(RR-845-99-001, NDA 21-055, Section 6.7.6)**. Patients received a Targretin® capsule dose of 75 mg, 150 mg, or 300 mg once daily for 12 weeks.

A preliminary assessment of the Day 1 (single dose) pharmacokinetic observations for those patients who received ≥75 mg Targretin® capsules has been performed. Fasted patients received a Targretin® capsule dose followed 1 hour later by either a fat-containing liquid dietary supplement (meal tolerance test [MTT], N=16) or a glucose solution (oral glucose tolerance test [OGTT], N=6). Serial blood samples

were collected up to 7 hours postdose for OGTT patients and up to 24 hours postdose for most MTT patients. Total urinary outputs for the 12-hour period prior to dosing and for the 24-hour period following Day 1 dosing were collected from most MTT patients.

Preliminary Day 1 pharmacokinetic data have been estimated from 22 of the patients enrolled. These patients received a single Targretin® capsule dose of 75 mg (N=6), 150 mg (N=9), or 300 mg (N=7) on Day 1. The 7 male (32%) and 15 female (68%) patients had a mean (range) age of 56 (35 to 69) yr and a mean (range) weight of 207 (163 to 248) lbs. All patients were White and all patients received a Targretin® capsule formulation containing micronized bexarotene.

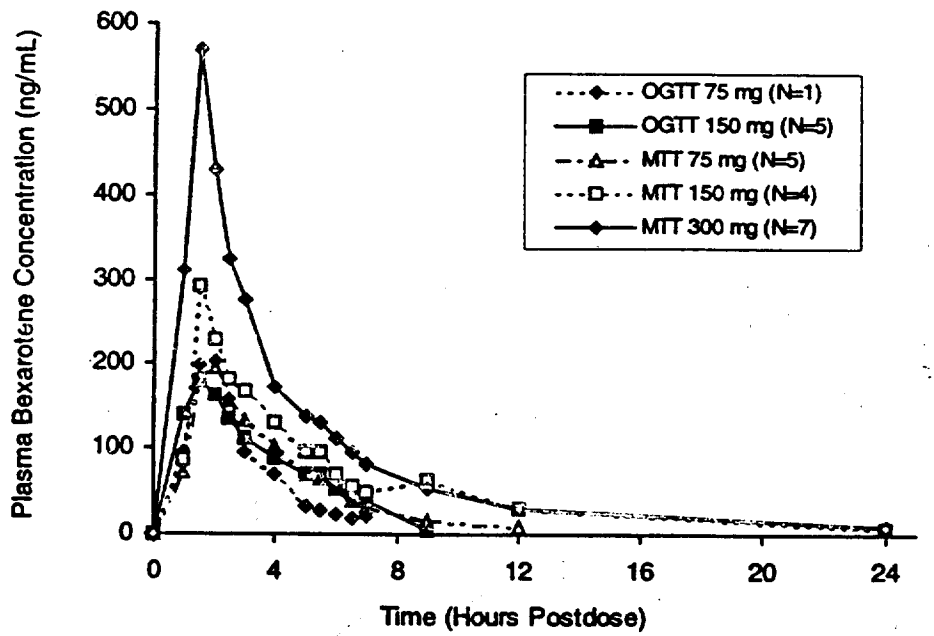
Although there was considerable variability, plasma bexarotene concentrations increased with increasing dose (**Table 6.3-N** and **Figure 6.3-O**). Peak plasma bexarotene concentrations were observed within 1 to 2 hours of dosing. Apparent elimination $t_{1/2}$ values were generally 1 to 2 hours for those patients with measured or quantifiable plasma bexarotene concentrations only out to 7 to 12 hours postdose. This $t_{1/2}$ range is consistent with observations in patients with advanced cancers (**Section 6.3.3.2.1**). Elimination $t_{1/2}$ values were 7 to 9 hours for those patients with measured and quantifiable plasma bexarotene concentrations until at least 24 hours postdose. Thus, through sampling over an entire 24-hour dosing interval, an elimination phase was identified that was not discernible during earlier studies with sampling out to 6 hours postdose. The 7 to 9 hours $t_{1/2}$ is consistent with only slight accumulation of bexarotene during once-daily oral dosing, as observed in patients with advanced cancers (**Section 6.3.3.2.1**).

Table 6.3-N. Mean (SD) Bexarotene Pharmacokinetic Parameters Following Single Oral Dose Administration of 75 mg to 300 mg Targretin® Capsules to Patients with Type II Diabetes Mellitus (Study L1069DM-01)

Dose (mg)	Meal[1]	Patients (N)	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-7} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
75	OGTT	1	2.0	204	560	603	1.4
150	OGTT	5	1.5 (0.4)	199 (169)	651 (524)	757 (596)	2.2 (0.8)
75	MTT	5	2.0 (1.2)	222 (86)	671 (270)	768 (312)	2.1 (0.6)
150	MTT	4	1.6 (0.2)	333 (97)	880 (245)	1498 (358)	9.1 (10.1)
300	MTT	7	1.5 (0.0)	570 (259)	1590 (806)	2190 (873)	7.2 (3.5)

[1] OGTT = Oral Glucose Tolerance Test (75 gm glucose in water) 1 hour after dosing. MTT = Meal Tolerance Test (250 mL Ensure Plus®) 1 hour after dosing.
SD not determined if N<3.

Figure 6.3-O. Mean Plasma Bexarotene Concentration-Time Profiles Following Single Oral Dose Administration of Targretin® Capsules to Patients with Type II Diabetes Mellitus. Patients Received Either a Fat-Containing Liquid Dietary Supplement (MTT) or a Glucose Solution (OGTT) at 1 Hour Postdose (Study L1069DM-01)



Mean plasma bexarotene concentrations were higher in MTT patients than respective values in OGTT patients. The higher concentrations in MTT patients are believed to be due to an enhancement in the extent of bexarotene absorption when a fat-containing meal was administered at 1 hour postdose. Mean dose-normalized C_{max} and AUC_{0-7} values were 48% and 35% higher in patients who received the fat-containing dietary supplement than respective values in patients who received a glucose solution.

A detailed description of the results of urine collection in the 24-hour interval following dosing are presented in **Section 6.3.3.5.2**. Bexarotene was not detectable in any of the urine samples (LLQ: 10 ng/mL) indicating that the maximum possible urine bexarotene concentration in any of the samples was 10 ng/mL. Based on the maximum possible urine concentration and individual patient dose and urine volumes, less than 0.04% of the administered dose was excreted unchanged in urine. Additionally, based on bexarotene plasma AUC_{0-24} values and the maximum potential amount of drug excreted in urine, CL_r of bexarotene was less than 1 mL/min for all patients. Thus, renal excretion of bexarotene is negligible following oral administration of Targretin® capsules.

The bexarotene [redacted] in urine samples collected 0 to 24 hours postdose from three patients administered a single dose of 300 mg Targretin® capsules were also determined. Details of the results of the evaluation are presented in **Section 6.3.3.5.1**. In brief, no bexarotene, 6- or 7-oxo-bexarotene or bexarotene acyl glucuronide were detectable in the urine samples. Only trace quantities of 6- or 7-hydroxy-bexarotene were observed in urine. Several small peaks thought to represent minor bexarotene metabolites were observed in the urine [redacted] Although quantification was not possible, the small peaks probably do not reflect significant renal elimination of bexarotene metabolites.

6.3.3.2.3. Oral Pharmacokinetics in Patients With CTCL

Bexarotene oral pharmacokinetic data in patients with CTCL are available from one of the Phase I studies in patients with advanced cancers (Study L1069-93-01), from a Phase II-III clinical study in patients with refractory or persistent early stage CTCL (Study L1069-23), and from a Phase II-III clinical study in patients with refractory advanced stage CTCL (Study L1069-24). Serial-sample pharmacokinetic profiles were obtained from six patients with CTCL during Study L1069-93-01 and three patients with CTCL during Study L1069-24. Single-time-point pharmacokinetic samples were obtained during the two Phase II-III studies, L1069-23 and L1069-24, and the relationship between observed plasma concentrations and variables that may affect plasma concentrations (dose, study period, demographics and other patient characteristics, and concomitant medications) was examined. The results of these analyses are presented below.

Study L1069-93-01 was a Phase I open-label, uncontrolled, multiple-dose, dose-escalation, safety and efficacy evaluation study of oral Targretin® capsules administered once daily to patients with proven, advanced cancers. Details of this study are discussed in **Section 6.3.3.2.1.** Single-dose and repeat-dose pharmacokinetic plasma bexarotene concentration-time profiles were obtained from six patients with CTCL following administration of 5 mg/m^2 (N=1) or 20 mg/m^2 (N=3) of the nonmicronized formulation, or 300 mg/m^2 (N=1) or 400 mg/m^2 (N=1) of the micronized formulation of Targretin® capsules. These five (83%) men and one (17%) woman had a mean ± SD (median, range) age of 52 ± 18 (52, 25 to 73) yr and mean ± SD (median, range) weight of 177 ± 28 (175, 139 to 224) lb. All patients were White.

Single-dose and repeat-dose peak plasma concentrations and AUC_{0-6} values for the patients with CTCL were compared with respective values observed in patients with advanced cancers other than CTCL (**Table 6.3-O**). In general, bexarotene pharmacokinetic parameters were similar between the two groups, indicating that

general pharmacokinetic characteristics of bexarotene are comparable in the two patient populations.

Table 6.3-O. Comparison of Bexarotene Pharmacokinetic Parameters in Patients with CTCL to Respective Parameters Observed in Patients with Other Advanced Cancers During Study L1069-93-01

Dose (mg/m^2) and Formulation	Study Day	Patients With CTCL				Patients With Advanced Cancers			
		N Pts.	N Obs.	C_{max} (ng/mL)	AUC_{0-6} (ng·hr/mL)	N Pts.	N Obs.	C_{max} (ng/mL)	AUC_{0-6} (ng·hr/mL)
5 NM	1	1	1	6	10	3	3	5	10
	15-29	1	2	3	11	2	4	6	8.5
20 NM	1	3	3	12	51	0	0	--	--
	15-29	3	6	14	52	0	0	--	--
300 M	1	1	1	688	2754	3	3	826	2850
	15-29	0	0	--	--	3	6	1110	3213
400 M	1	1	1	1686	5817	2	2	2763	9282
	15-29	1	1	2022	7057	3	4	1907	7389

N Pts. = Number of patients.
N Obs. = Number of observations.
C_{max} = Maximum observed concentration.
AUC_{0-6} = Area under the plasma concentration-time curve from Time zero to 6 hours.
NM = Nonmicronized; M = Micronized.
-- = No data available.

Study L1069-23 was a Phase II-III multicenter, open-label, controlled, multiple-dose, tolerability, safety and efficacy study of Targretin® capsules in patients with refractory or persistent early stage persistent CTCL (**RR-845-98-016, NDA 21-055, Section 6.7.3**). The study was conducted with 10 mg and 75 mg Targretin® capsule formulations containing micronized bexarotene, which were to be dosed once daily, with or immediately following a moderate or full evening meal. Patients were assigned to either a high dose or a low dose treatment. Patients assigned a low dose received 6.5 mg/m^2. The initial starting dose for patients assigned the high dose was 650 mg/m^2, but following a series of protocol revisions, the starting high dose was reduced to 300 mg/m^2. Additionally, provisions were included in the protocol for dose adjustments as necessitated by toxicity (dose reductions) or lack of response with no unacceptable toxicity (dose escalation up to 400 mg/m^2). Patients receiving the low dose could also have their dose increased to that administered for

the high dose group, if disease progression was observed after 8 or more weeks of therapy or if no response was observed after 16 weeks of therapy.

Single-time-point blood samples were to have been collected before the first dose, after 2 and 4 weeks of therapy, and every 4 weeks thereafter while patients remained enrolled in the study, for bexarotene plasma concentration monitoring.

Samples for pharmacokinetic evaluation were obtained from 51 patients enrolled in this study. These 36 (71%) men and 15 (29%) women had a mean ± SD (median, range) age of 61 ± 14 (64, 24 to 88) yr and mean ± SD (median, range) weight of 84 ± 14 (84, 47 to 114) kg. There were 43 White (84%), five Black (10%), two Hispanic (4%), and one patient with race categorized as Other (2%).

Most samples were obtained 12 to 24 hours postdose. All dose levels, except the 6.5 mg/m^2 low-dose level, resulted in measurable concentrations. Although there was high variability in plasma bexarotene concentrations, higher doses generally led to higher concentrations. No significant accumulation of bexarotene was observed at any dose level after daily doses for at least 64 weeks, the longest duration of administration of Targretin® capsules with pharmacokinetic sample collection in this study.

The potential relationship between patient demographics and patient-specific variables and plasma bexarotene concentrations was assessed for those patients who were identified as having higher absolute or dose-normalized plasma bexarotene concentrations. No apparent relationship between evaluated variables (e.g., concomitant medications or liver function test [LFT] elevations) and the eight highest dose-normalized or the seven highest absolute bexarotene concentrations could be established. Therefore, the high concentrations observed relative to those of other patients appear to be a reflection of the high variability in the disposition of bexarotene for this patient population rather than to be related to concomitantly administered drugs or other evaluated patient characteristics.

A population analysis approach was also used to evaluate the effect of concomitant administration of frequently coadministered medications (levothyroxine, atorvastatin and gemfibrozil) on plasma bexarotene concentrations. The results of this evaluation are discussed in detail in **Section 6.3.7.2**. Based on this analysis, concomitant administration of gemfibrozil with bexarotene led to higher absolute and dose-normalized plasma bexarotene concentrations compared with administration of bexarotene without gemfibrozil. In contrast, concomitant administration of levothyroxine or atorvastatin did not appear to affect plasma bexarotene concentrations. Individual patient plasma concentration data supported these observations from the population analysis. The mechanism of the apparent drug-drug interaction between bexarotene and gemfibrozil is unknown but, as detailed in **Section 6.3.7.**, may be an inhibition of the oxidative metabolism of bexarotene.

Individual patient plasma concentration data were also examined for the potential effect of any identified concomitantly administered CYP3A4 modulators (i.e., inducers: phenytoin and phenobarbital; inhibitors: azole antifungals and macrolide antibiotics) on plasma bexarotene concentrations. None of the potential CYP3A4 inducers were administered concurrently with Targretin® capsules during this study. Of the CYP3A4 inhibitors, only itraconazole or clarithromycin were administered concomitantly with Targretin® capsules for a limited number of patients in this study. Based on the data for these few patients, neither itraconazole nor clarithromycin concomitant administration appeared to be correlated with higher bexarotene concentrations compared with concentrations when Targretin® capsules were administered without these CYP3A4 inhibitors.

Study L1069-24 was a Phase II-III multicenter, open-label, controlled, multiple-dose tolerability, safety and efficacy study of Targretin® capsules in patients with refractory advanced stage CTCL **(RR-845-98-017, NDA 21-055, Section 6.7.3)**. The study was conducted with 75 mg Targretin® capsule formulations containing

micronized bexarotene, which were to have been ingested once daily, with or immediately following a moderate or full evening meal. The initial starting dose was 650 mg/m^2/day, but through a series of protocol revisions, the starting dose was reduced to 300 mg/m^2/day. Provisions were included in the protocol for dose adjustments as necessitated by toxicity (dose reductions) or lack of response with no unacceptable toxicity (dose escalation up to 400 mg/m^2/day).

Single-time-point blood samples for the determination of bexarotene plasma concentrations were to have been collected before the first dose, after 2 and 4 weeks of therapy, and every 4 weeks thereafter while patients remained enrolled in the study. Plasma bexarotene concentrations and the times postdose, and the relationships between concentration and other parameters, such as dose, patient demographics and other patient characteristics, and selected concomitant medications, were evaluated. In addition, serial plasma samples were obtained on two separate occasions from three patients before dosing and at 1, 2, 4, 8, and 24 hours postdose.

A total of 505 samples for pharmacokinetic evaluation were obtained from 72 patients. These 41 men (57%) and 31 women (43%) had a mean ± SD (median, range) age of 63 ± 13 (64, 27-89) yr and mean ± SD (median, range) weight of 77 ± 15 (77, 48-120) kg. Racial distribution was as follows: 58 White (81%), 11 Black (15%), one Hispanic (1%), one Mixed (1%), and one was categorized as Other (1%). The starting doses ranged from 300 mg/m^2 to 650 mg/m^2 with the majority of patients from whom pharmacokinetic samples were collected starting at 300 mg/m^2 (N=38) or 500 mg/m^2 (N=21).

Most samples were obtained 12 to 24 hours postdose, and the primary analyses are based on this subset of concentrations. The CV for this subset of samples was 182%. Despite the high variability, increasing doses generally resulted in higher plasma bexarotene concentrations. Excluding samples collected from patients being administered gemfibrozil concomitantly with Targretin® capsules, there was no

evidence of significant accumulation of bexarotene with repeated doses for at least up to 72 weeks, the longest duration of administration of Targretin® capsules with pharmacokinetic sample collection in this study.

Some patients had higher bexarotene concentrations relative to those of other patients enrolled in this study. The demographic characteristics, LFTs, and concomitant medications of these patients were assessed for their association with higher bexarotene plasma concentrations. No evaluable variables appeared to be associated with these high plasma bexarotene concentrations. The high bexarotene concentrations in this subset of patients relative to concentrations in other patients therefore appear to be a result of the high variability in the disposition of bexarotene for this patient population rather than to be related to concomitantly administered drugs or other evaluable patient characteristics.

A population analysis approach was also used to evaluate the effect of concomitant administration of frequently coadministered medications (levothyroxine, atorvastatin and gemfibrozil) on plasma bexarotene concentrations. The results of this evaluation are discussed in detail in **Section 6.3.7.2**. Based on this analysis, concomitant administration of gemfibrozil with bexarotene led to higher absolute and dose-normalized plasma bexarotene concentrations compared with administration of bexarotene without gemfibrozil. In contrast, concomitant administration of levothyroxine or atorvastatin did not appear to affect plasma bexarotene concentrations. Individual patient plasma concentration data supported these observations from the population analysis. The mechanism of the apparent drug-drug interaction between bexarotene and gemfibrozil is unknown but, as detailed in **Section 6.3.7.**, may be an inhibition of the oxidative metabolism of bexarotene. Additionally, based on limited data, clarithromycin did not have a substantial effect on plasma bexarotene concentrations.

16 Black (13%), three Hispanic (2%), one Mixed (1%), and two categorized as Other (2%).

Using a population analysis approach, the effect of concomitant administration of frequently coadministered medications (levothyroxine, atorvastatin and gemfibrozil) on plasma bexarotene concentrations was assessed. Based on these analyses, concomitant administration of gemfibrozil with bexarotene led to higher plasma bexarotene concentrations compared to bexarotene without gemfibrozil. In contrast, concomitant administration of levothyroxine or atorvastatin did not appear to affect plasma bexarotene concentrations. Individual patient plasma concentration data support these observations from the population analysis. Although the mechanism of the gemfibrozil drug interaction is unknown, suggest that the interaction between gemfibrozil and bexarotene might be the result of an inhibition of the oxidative metabolism of bexarotene (**Section 6.3.7.2.**).

6.3.3.2.4. Oral Pharmacokinetics in Healthy Volunteers

Bexarotene oral pharmacokinetic data in healthy fasted volunteers are available from a pharmacokinetic supplement to Study L1069DM-01 (**RR-845-99-003, NDA 21-055, Section 6.7.7**). This study was a randomized, open-label, two-period, crossover evaluation of the bioavailability of a single dose of a 75-mg Targretin® capsule compared to a 75 mg bexarotene suspension in 12 healthy subjects. All subjects were men, 10 were White, one was Asian, and one had an origin categorized as Other. The mean ± SD (range) age was 26 ± 8 (19 to 45) yr and the mean ± SD (range) weight was 75.9 ± 11.5 (60.0 to 102.4) kg. Serial blood sampling was conducted up to 10 hours post-dose for each treatment, for measurement of bexarotene plasma concentrations.

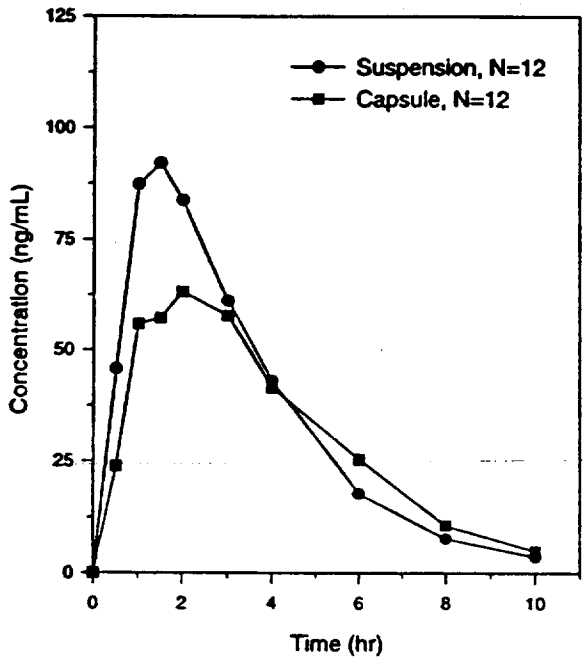
Bexarotene pharmacokinetic parameters were similar between the two formulations (**Figure 6.3-P** and **Table 6.3-Q**. As expected, bexarotene C_{max} was reached earlier for the suspension compared with that of the capsules (averages of 1.5 hour versus 2.8 hour, respectively), suggesting a lag time due to capsule shell disintegration.

Table 6.3-Q. Mean (±SD) Bexarotene Pharmacokinetic Parameters Following Single Oral Dose Administration of a 75 mg Targretin® Capsule or 75 mg Bexarotene Suspension to Normal Fasted Volunteers (Study L1069DM-01)

	Pharmacokinetic Parameter						
Formulation	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-}10}$ (ng·hr/mL)	$AUC_{0\text{-}\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)	C_{max}/Dose (ng/mL/mg)	$AUC_{0\text{-}\infty}$/Dose (ng·hr/mL/mg)
Suspension	1.5 (0.6)	98.5 (53.5)	355 (211)	368 (217)	1.9 (0.6)	ND	ND
Capsule	2.8 (2.1)	77.3 (50.0)	313 (147)	332 (149)	2.2 (1.9)	1.03 (0.67)	3.77 (1.93)

After administration of a capsule, mean bexarotene C_{max} was approximately 78% of the C_{max} after administration of a suspension. Bexarotene AUCs were only slightly lower after administration of a capsule compared with AUCs after administration of a suspension, suggesting that the total exposure to bexarotene was similar after administration of either formulation. The test to reference ratio estimates (90% confidence intervals) for $\ln(C_{max})$ and $\ln(AUC_{0\text{-}\infty})$ for the two one-sided tests procedure were 0.795 (0.599-1.055) and 0.976 (0.751-1.270), respectively. For both formulations, harmonic mean elimination $t_{1/2}$ values were 1.7 hour, and individual $t_{1/2}$ values generally ranged from 1 to 3 hour, which were comparable to the estimates of $t_{1/2}$ obtained in patients with advanced cancer (**Section 6.3.3.2.1.**).

Figure 6.3-P. Mean Plasma Bexarotene Concentrations Following Single Dose Administration of 75 mg Targretin® Capsules or 75 mg Bexarotene Suspension to Normal Fasted Volunteers (Study L1069DM-01)



6.3.3.2.5. Overall Summary of Bexarotene Oral Absorption and Pharmacokinetics

The oral pharmacokinetics of bexarotene were evaluated during studies in patients with CTCL, advanced cancers, or Type II diabetes mellitus, and in normal volunteers. Most data were obtained after administration of a Targretin® capsule formulation containing micronized bexarotene that was substantially more bioavailable than a formulation containing nonmicronized bexarotene. The following pharmacokinetic summary focuses on data obtained following administration of micronized bexarotene.

Peak plasma bexarotene concentrations were generally observed within 3 hours of dosing. The pharmacokinetics of bexarotene after a single oral dose were essentially dose-proportional over an 18 mg/m^2 to 800 mg/m^2 dose range, though there was high interpatient variability in both C_{max} and AUC_{0-6} parameters. Following multiple

dosing, mean repeat-dose C_{max} and AUC_{0-6} values were similar to respective single-dose values at most dose levels <230 mg/m^2 QD. For many patients, mean C_{max} and AUC_{0-6} values at dose levels ≥230 mg/m^2 QD were lower than respective values following single-dose administration, suggestive of an induction of bexarotene oral clearance at these higher dose levels. However, plasma concentrations in some patients at dose levels as high as 1000 mg/m^2 QD did not change with repeat dosing, indicating that there was not a clear relationship between the reduction in plasma concentrations and dose level.

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. Despite the apparent induction of oral clearance of bexarotene in some patients with multiple dosing, there was no detectable change in half-life values, possibly because the terminal elimination phase may not have been reached within the relatively short 6-hour sampling periods used in the studies.

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_{0-6} 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_{0-6} 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.

Oxidative metabolites (6- and 7-oxo-bexarotene and 6- and 7-hydroxy-bexarotene) were the major plasma metabolites of bexarotene following oral dosing. No bexarotene acyl glucuronide was observed in plasma. No bexarotene, 6- or 7-oxo-bexarotene or bexarotene acyl glucuronide were detectable in the urine samples. Only trace quantities of 6- or 7-hydroxy-bexarotene were observed in urine. Other minor bexarotene metabolites were detected in urine, 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.

Population analysis of the effect of concomitant administration of frequently coadministered medications (levothyroxine, atorvastatin and gemfibrozil) on plasma bexarotene concentrations following dosing with Targretin® capsules indicated that concomitant administration of gemfibrozil with bexarotene led to higher plasma bexarotene concentrations compared to bexarotene alone. In contrast, concomitant administration of levothyroxine or atorvastatin did not appear to affect plasma bexarotene concentrations. Individual patient plasma concentration data support

these observations from the population analysis. Additionally, based on limited data, CYP3A4 inhibitors (azole antifungal or macrolide antibiotics) did not appear to affect bexarotene concentrations when administered concomitantly.

6.3.3.3. Comparison of Systemic Bexarotene Concentrations Following Topical and Oral Dosing

The purpose of this section is to compare and contrast the pharmacokinetics of bexarotene following topical application of Targretin® gel to that observed following oral dosing with Targretin® capsules. The pharmacokinetics of Targretin® gel have previously been detailed in **Section 6.3.3.1.** and the pharmacokinetics of Targretin® capsules have been detailed in **Section 6.3.3.2.**

Systemic exposure to bexarotene following topical application is very low compared to exposure following oral dosing at recommended doses. Bexarotene concentrations were generally low following application of Targretin® gel. Of the post-dose blood samples that were collected and assayed for Targretin® gel 1%, 93.2% of the samples had plasma concentrations below 5 ng/mL. In contrast, at the dose (300 mg/m^2 QD) of Targretin® capsules recommended for treatment of patients with early or advanced stage CTCL, mean (±SD) C_{max} values were 1130 ng/mL ± 269 ng/mL following multiple dosing. This value is over 200-fold higher than the plasma concentrations generally observed following topical application.

The highest concentration observed across all Targretin® gel studies was measured in one patient in the Phase III study, who was believed to have applied an inordinately large amount of Targretin® gel 1% during the course of the study (90 tubes of gel dispensed to this patient at one visit, compared to a maximum of 17 tubes in other patients at any visit). Even 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 the short half-life of generally 1-3 hours observed following oral dosing, accumulation of bexarotene was minimal following topical application of Targretin® gel. 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 sporadic low (<5 ng/mL) plasma bexarotene concentrations.

6.3.3.4. Metabolism of Bexarotene

A series of in vitro studies and ex vivo studies following oral dosing with Targretin® capsules have been conducted to examine the human metabolism of bexarotene. The details of these studies and their study reports have previously been submitted in the NDA for Targretin® capsules (NDA 21-055) and are only summarized below. In all cases, [redacted] were used to determine [redacted] of bexarotene metabolites. [redacted]

Metabolite profiles generated during in vitro experiments with microsomes derived from human livers are presented. These data support the identification of the oxidative metabolites of bexarotene in plasma and indicate that glucuronidation of parent compound is a metabolic pathway for bexarotene.

Metabolite profiles in plasma samples obtained following single- and repeat-dose oral administration of bexarotene (Targretin® capsules) to patients with advanced cancers were generated. [redacted] indicated that the major plasma metabolites of bexarotene were 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene. The [redacted] of the hydroxy metabolites was not assessed. These metabolites were also observed in the plasma collected from rats and dogs, the species evaluated during toxicology studies. A summary of the retinoid receptor binding and transactivation profiles of the metabolites also is presented.

A series of experiments to identify the human P450 isozyme(s) responsible for the oxidative metabolism of bexarotene and to document the in vitro glucuronidation of bexarotene were conducted. CYP3A4 was the only isozyme identified that is responsible for production of the oxidative metabolites.

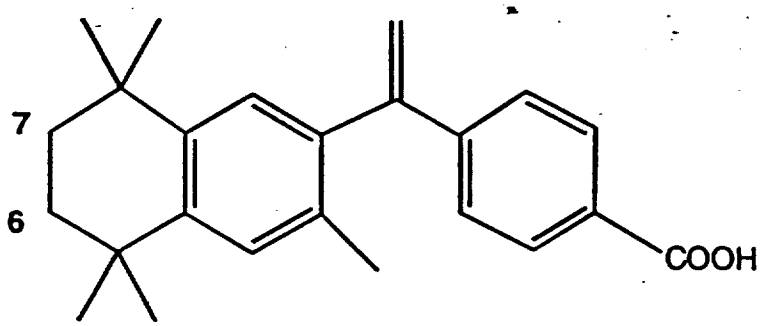
Based on the available metabolism data and assessments of drug interactions in clinical studies, a summary of the potential for P450-mediated drug interactions with bexarotene and the overall conclusions regarding bexarotene metabolism in humans is provided.

6.3.3.4.1. Identification of Human Metabolites of Bexarotene

Human bexarotene metabolites were examined using in vitro and ex vivo methods. Bexarotene was incubated with human liver microsomes under conditions supporting P450 oxidation or glucuronidation. The in the incubates were examined. Additionally, plasma samples from patients with advanced cancers collected before and after oral administration of bexarotene (Targretin® capsules) were evaluated. Human metabolites of bexarotene were identified by with previously identified and characterized rat metabolites (6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene and bexarotene acyl glucuronide). The structures of bexarotene metabolites formed in rats were determined using

(NDA 21-055, Section 5.3.0.8). In addition, reference standards of the oxidative metabolites were evaluated for with microsomal metabolites during The structure of bexarotene with relevant metabolic positions identified is presented in **Figure 6.3-Q.**

Figure 6.3-Q. Structure of Bexarotene Indicating Positions of Oxidative Metabolism (C-6 and C-7)



6.3.3.4.1.1. In Vitro Assessments of Bexarotene Metabolism

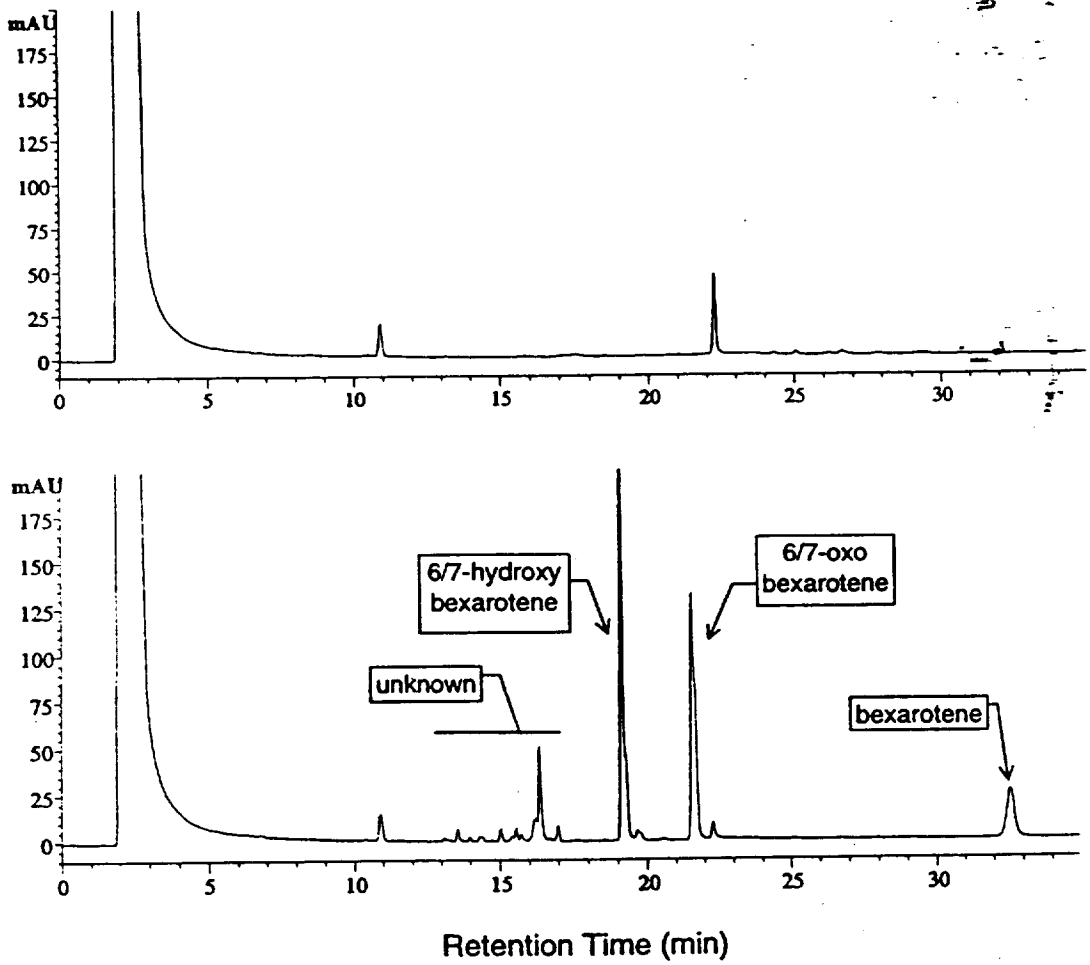
The metabolism of bexarotene in human hepatic microsome preparations was evaluated (**RR-845-98-002, NDA 21-055, Section 6.7.9**). Pooled (11 donors, male and female) human liver microsomes were incubated

bexarotene. For P450-mediated metabolism, incubation mixtures included an NADPH-generating system. For glucuronosyltransferase-mediated metabolism,

to promote glucuronosyltransferase activity; β-glucuronidase was inhibited with D-saccharic acid 1,4-lactone.

Under P450-supporting conditions, the predominant metabolites formed in human liver microsomes were 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene (**Figure 6.3-R**). The C-6 isomers of the hydroxy and oxo metabolites predominated over the respective C-7 isomers. Two enantiomers are possible for the C-6 and C-7 positional isomers of hydroxy-bexarotene. However, it was not possible to assign [redacted] of the 6- and 7-hydroxy-bexarotene metabolites with the [redacted] used. Minor unidentified metabolites were also observed in [redacted] Under incubation conditions that supported glucuronidation, human liver microsomes produced the acyl glucuronide of bexarotene.

Figure 6.3-R. Representative of an Extract of Control (No Drug) Human Liver Microsomes (Upper) and Human Liver Microsomes Incubated under Cytochrome P450-Supporting Conditions with Bexarotene for 4 Hours (Lower)



6.3.3.4.1.2. Ex Vivo Assessments of Bexarotene Metabolism

Bexarotene metabolite profiles were examined in plasma samples from patients with advanced cancers receiving 140 mg/m^2 to 400 mg/m^2 doses of Targretin® capsules (Study L1069-93-01 and Study L1069-93-02). Descriptions of the study designs and pharmacckinetic observations are presented in **Section 6.3.3.2.1.** Individual sample metabolite profiles were generated following both single-dose and repeat-dose administration of Targretin® capsules (**RR-845-98-002**). Consistent with the

observations with human hepatic microsome preparations, the primary plasma metabolites were 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene (**Figure 6.3-S** and **Figure 6.3-T**). No bexarotene acyl glucuronide was observed in the plasma [redacted] (retention time approximately 19.5 minutes). The single-dose and repeat-dose metabolite profiles were very similar, suggesting little alteration of the metabolite profile with repeat dosing. Additionally, metabolite [redacted] peak heights in repeat-dose predose samples were low, indicating there was minimal accumulation of the metabolites.

Figure 6.3-S. [redacted] of an Extract of Plasma from a Patient before and after a Single Oral Dose of Bexarotene (230 mg/m^2)

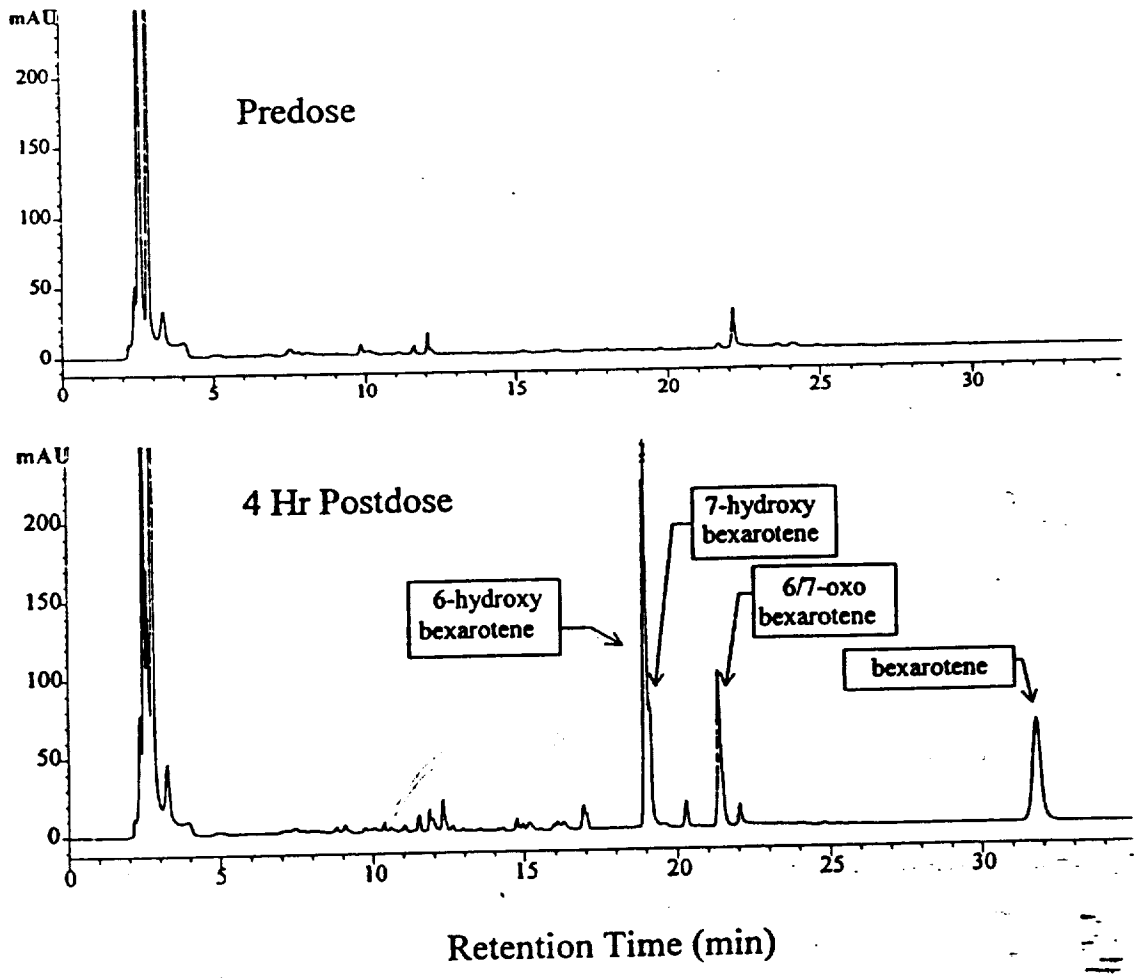
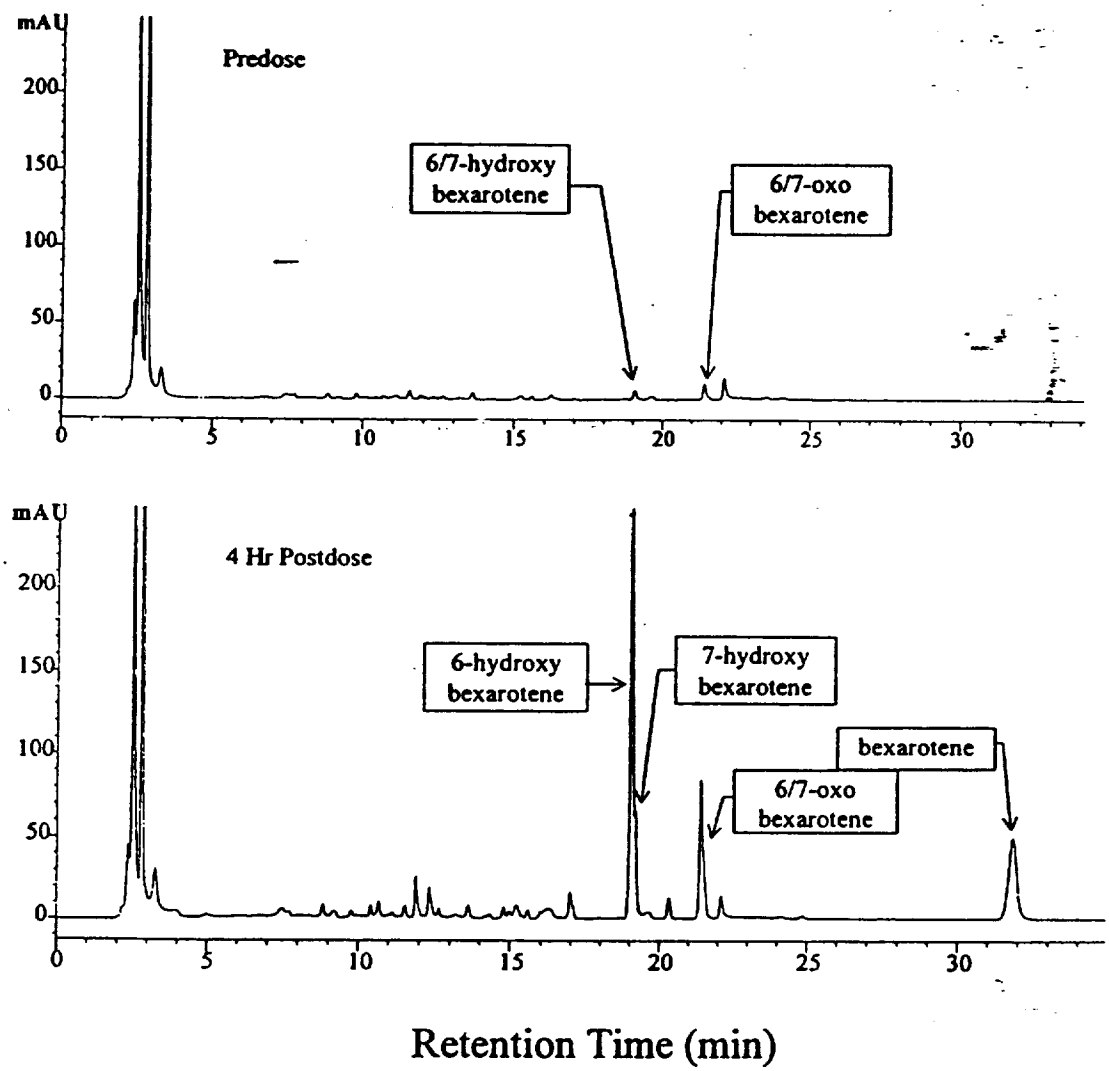


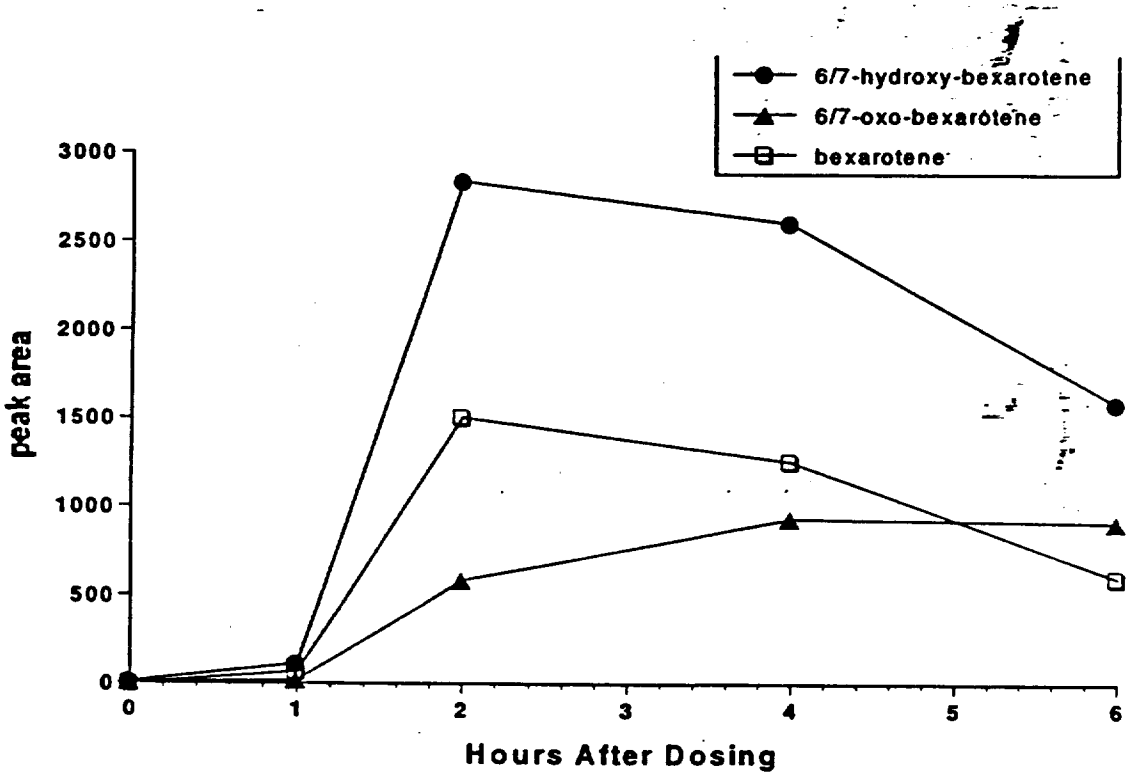
Figure 6.3-T. [redacted] of an Extract of Plasma from a Patient 4 Hours after Dosing on Day 16 of Daily Oral Dosing with Bexarotene (230 mg/m^2)

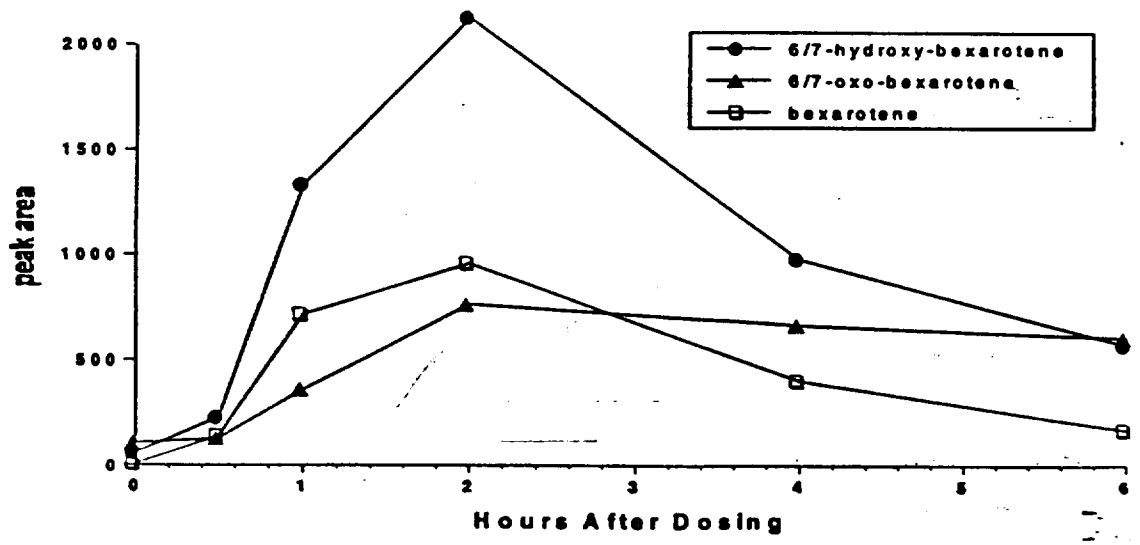


Absolute concentrations of the metabolites in the plasma samples were not quantified. However, the [redacted] peak areas [redacted] of metabolites and parent in serial plasma samples obtained following single- and repeat-dose administration of Targretin® capsules were determined (Figure 6.3-U). At respective sample collection times, single-dose and repeat-dose metabolite profiles were similar. After single and multiple doses, the AUC for the [redacted] peak area for the peak representing 6- and 7-hydroxy-bexarotene (primarily 6-hydroxy-bexarotene) was greater than that of parent drug. The AUC for the [redacted] peak area for the peak representing 6- and 7-oxo-bexarotene was similar to that of parent. Metabolite [redacted] peak heights in repeat-dose predose samples were low, indicating there was minimal accumulation of the metabolites.

APPEARS THIS WAY
ON ORIGINAL

Figure 6.3-U. [redacted] Peak Area Versus Time Profile of Bexarotene and Metabolites Following Single Dose and Repeat Daily Dose Administration of 230 mg/m^2 Targretin® Capsules





6.3.3.4.1.3. Retinoid Receptor Binding and Activity of Bexarotene Metabolites

In vitro studies were conducted to assess the retinoid receptor binding affinity and retinoid receptor transactivation activity of synthetic oxidative metabolites of bexarotene (RR-845-98-002). Racemic mixtures of synthetic 6- and 7-hydroxy-bexarotene were tested.

The binding of synthetic bexarotene metabolites to RARs was very weak (**Table 6.3-R**). Although the metabolites were capable of binding to the RXRs, the binding affinity was much less than that of bexarotene. The most abundant human plasma metabolite, 6-hydroxy-bexarotene, displayed the weakest binding at RXR (binding affinity >3 μM).

Table 6.3-R. In Vitro Binding of Bexarotene and Bexarotene Metabolites to Retinoic Acid Receptors and Retinoid X Receptors

Compound	Ki (nM) (mean±SE)[1]					
	RARα	RARβ	RARγ	RXRα	RXRβ	RXRγ
Bexarotene	>10,000	>10,000	>10,000	34	78	78
6-Hydroxy-bexarotene	8171[2]	>10,000	>10,000	3464±474	4205±1003	4831±1354
6-Oxo-bexarotene	7901[2]	>10,000	>10,000	1324±253	2265±634	1702±797
7-Hydroxy-bexarotene	8364[2]	>10,000	>10,000	2483±225	4386±871	2761±750
7-Oxo-bexarotene	7037[2]	>10,000	>10,000	288±92	508±168	236±15

[1] For bexarotene, N=2; for metabolites, N=3.
[2] Two values were >10,000, one was less than 10,000.

The ability of bexarotene and the synthetic oxidative metabolites of bexarotene to transactivate the retinoid receptors was assessed (**Table 6.3-S**) (**RR-845-98-002**). Efficacy of transactivation was determined relative to LG100351, a reference activator of the six retinoid receptors. EC_{50}, the concentration at which half-maximal activation occurs, was also determined. Similar to bexarotene, the metabolites of bexarotene exerted little activity at RAR, exhibiting low efficacy values and high EC_{50}

values. Although bexarotene and the oxidative metabolites had similar RXR efficacy values, the oxidative metabolites were 4 to 20 times less potent than bexarotene at transactivating the RXR receptors.

Table 6.3-S. Activity of Bexarotene and Bexarotene Metabolites at RAR and RXR in the

Compound	RARα		RARβ		RARγ	
	Efficacy (%)	EC_{50} (nM)	Efficacy (%)	EC_{50} (nM)	Efficacy (%)	EC_{50} (nM)
Bexarotene	7±1	7013±2987	57±17	292±19	64±31	1366±560
6-Hydroxy bexarotene	16±6	4414±1800	20±5	2121±152	18±5	1092±527
6-Oxo bexarotene	22±11	4199±1852	31±6	1462±328	34±8	2043±277
7-Hydroxy bexarotene	14±4	5133±2176	12±3	2590±419	18±9	4377±1889
7-Oxo bexarotene	13±5	4179±1851	15±3	602±259	7±3	5165±2792

Compound	RXRα		RXRβ		RXRγ	
	Efficacy (%)	EC_{50} (nM)	Efficacy (%)	EC_{50} (nM)	Efficacy (%)	EC_{50} (nM)
Bexarotene	77±7	25±9	148±11	41±13	82±9	25±7
6-Hydroxy bexarotene	43±8	413±29	99±17	462±137	49±10	385±90
6-Oxo bexarotene	69±11	398±35	139±14	356±49	87±10	420±59
7-Hydroxy bexarotene	50±6	447±26	131±28	558±71	66±6	520±50
7-Oxo bexarotene	56±6	102±11	148±25	169±31	72±8	103±22

Note: Values are mean ± SE of 3-6 replicates for bexarotene and six replicates for metabolites.
Efficacy of compounds calculated relative to LGD100351, a reference pan-agonist.

Based on the low plasma concentrations of bexarotene following topical application of Targretin® gel compared to oral administration, the very low binding affinity of the oxidative metabolites to retinoid receptors, the relatively low to very low transactivation activity of the oxidative metabolites, and the low amounts of metabolites expected in plasma after topical application, it can be concluded that the oxidative metabolites of bexarotene do not contribute substantially to the in vivo retinoid receptor activity of bexarotene.

6.3.3.4.2. Identification of Human P450 Isozymes Responsible for Bexarotene Metabolism

In vitro studies were conducted to identify the human P450 isozymes capable of metabolizing bexarotene to its oxidative metabolites. The techniques employed were: 1) testing the effect of isozyme-selective inhibitors on the rate of metabolism of the drug in pooled human liver microsomes; 2) analyzing the correlation between the rate of drug metabolism and isozyme activities in liver microsomes from a panel of human subjects; and 3) testing the ability of cDNA-expressed isozymes to metabolize the drug. Quantification of bexarotene metabolites was achieved using the [redacted] described in **Section 6.3.8.5.** Because 6/7-oxo-bexarotene is presumably formed via 6/7-hydroxylation of bexarotene, the sum of the production of all four of these metabolites was used to monitor the oxidative metabolism of bexarotene. Results of the individual techniques and an overall summary are provided. CYP3A4 was the only isozyme identified that is responsible for the oxidative metabolism of bexarotene.

6.3.3.4.2.1. Specific Inhibitors of P450 Metabolism of Bexarotene

The effect of specific P450 inhibitors on the in vitro rate of metabolism of bexarotene was assessed (RR-845-98-003, **NDA 21-055, Section 6.7.10**). Incubation of a drug with liver microsomes in the presence or absence of selective P450 inhibitors can provide evidence for the role of particular P450 isozymes in that drug's metabolism. Three types of P450 isozyme-selective inhibitors were employed: 1) competitive

substrates, which inhibit by competing with drug for access to a specific isozyme; 2) non-competitive, mechanism-based substrates, which are metabolized to products that strongly and specifically bind to P450; and 3) an inhibitory antibody.

Bexarotene was incubated with pooled (11 donors, male and female) human liver microsomes for 15 minutes. For each type of inhibitor, control incubations (no inhibitor added) were also conducted. The rate of bexarotene metabolism in the presence of inhibitor was compared to that in the absence of inhibitor.

The effects of the selective P450 isozyme inhibitors on the metabolism of bexarotene in human liver microsomes are presented in **Table 6.3-T** Of the evaluated inhibitors, only troleandomycin, an inhibitor of CYP3A4, caused a marked inhibition of bexarotene metabolism. Consistent, slight decreases in the rate of bexarotene oxidation after treatment with coumarin (CYP2A6 inhibitor) and S-mephenytoin (CYP2C19 inhibitor) were also seen. The magnitude of inhibition achieved with these latter agents was not biologically relevant. In contrast, the 25% decrease in metabolism of bexarotene in microsomes treated with troleandomycin does indicate that human CYP3A4 is involved in the metabolism of bexarotene.

Table 6.3-T. Effect of Selective Inhibitors of P450 Isozymes on the Metabolism of Bexarotene in Human Liver Microsomes

Inhibitor	Isozyme Inhibited	Replicates	Metabolism Rate (nmol/mg protein/min)[1]	Percent of Control Rate
Competitive inhibitor control	none	5	0.334±0.003	100
Coumarin	CYP2A6	5	0.320±0.004	96±1[2]
Sulfaphenazole	CYP2C9	5	0.335±0.004	100±1
S-Mephenytoin	CYP2C19	5	0.316±0.005	94±1[2]
Quinidine	CYP2D6	4	0.332±0.002	99±1
4-Methylpyrazole	CYP2E1	5	0.339±0.003	102±1
Mechanism-based control	none	5	0.319±0.008	100
Acetanilide	CYP1A2	5	0.297±0.008	93±3
Orphenadrine	CYP2B6	4	0.316±0.009	99±3
Troleandomycin	CYP3A4	5	0.239±0.016	75±5[2]
Antibody control	none	1	0.110	100
CYP4A Antibody	CYP4A	1	0.111	101

[1] Mean ± SD, as measured by the appearance of 6/7-hydroxy- and 6/7-oxo-bexarotene.
[2] $p < 0.001$, using one-way analysis of variance.

6.3.3.4.2.2. Correlation of P450 Isozyme Activity and Bexarotene Metabolism

Using a panel of human liver microsome preparations, the rate of bexarotene metabolism was correlated to P450 isozyme activities (RR-845-98-003). Correlation analysis, which takes into account the naturally-occurring interpatient variability in P450 isozyme activities, involves measurement of the rate of a drug's metabolism by liver microsomes from a panel of individuals in which the relative activities of the various P450 isozymes are known. A positive correlation between the rate of metabolism and the relative activity of a particular isozyme provides evidence for that isozyme being involved in the metabolism of the drug.

Bexarotene was incubated with a panel of individual-donor human liver microsome preparations (N=14). The rate of formation of the sum of 6- and 7-hydroxy-bexarotene plus 6- and 7-oxo-bexarotene was compared to the relative activity of each P450 isozyme. Based on the correlation coefficients and the slopes of the regression lines, the extent of involvement of each isozyme in the metabolism of bexarotene was determined.

The rate of bexarotene oxidation was positively correlated with the levels of CYP2C9 and CYP3A4, suggesting that both isozymes may be involved in the metabolism of bexarotene in human liver **(Table 6.3-U)**. However, the apparent correlation of CYP2C9 activity with the metabolism of bexarotene may be an artifact of the high correlation of CYP2C9 and CYP3A4 activity in the study samples. Supporting this hypothesis, the microsomal preparation with the highest rate of bexarotene metabolism had very high CYP3A4 activity, but very low CYP2C9 activity **(Figure 6.3-V)**. The failure of sulfaphenazole to inhibit the metabolism of bexarotene **(Section 6.3.3.4.2.1.)** and the failure of recombinant CYP2C9 to metabolize bexarotene **(Section 6.3.3.4.2.3.)** further support the conclusion that CYP2C9 is not involved in the metabolism of bexarotene in humans.

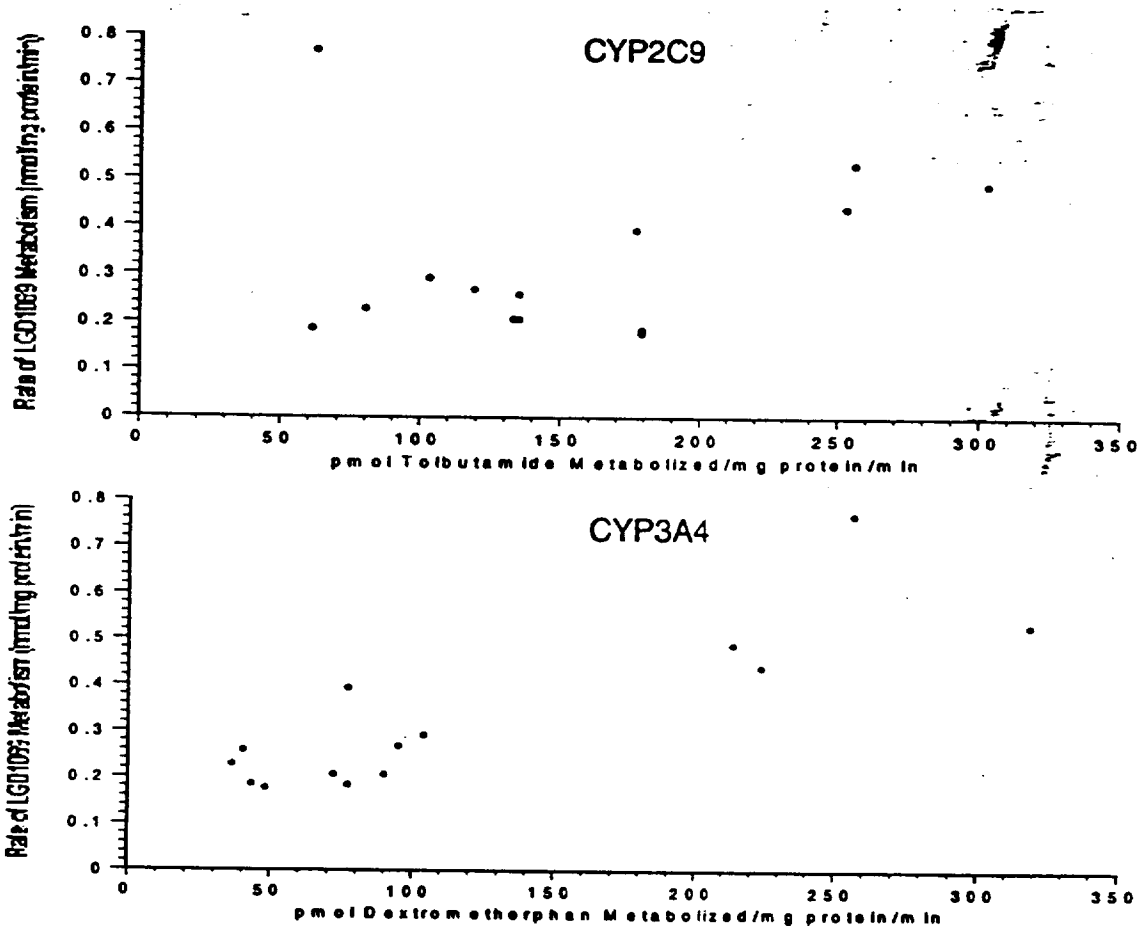
Table 6.3-U. Correlation Between P450 Isozyme Activities and the Rate of Bexarotene Metabolism in Human Liver Microsomes (N=5)

Cytochrome P450 Isozyme	Slope of Regression Line Describing the Relationship of Rate of Bexarotene Metabolism and Isozyme Activity[1]	Correlation Between Metabolism of Bexarotene and Isozyme Activities (Correlation Coefficient)
1A2	-0.024	0.120
2A6	4.002	0.572
2C9	0.375	0.809
2C19	0.191	0.362
2D6	0.357	0.512
2E1	-0.838	0.117
3A4	0.576	0.873
4A9/11	-0.124	0.084

[1] (nmol bexarotene metabolized/min/mg protein)/(nmol marker substrate metabolized/min/mg protein).

APPEARS THIS WAY
ON ORIGINAL

Figure 6.3-V. Correlation Between the Rate of Bexarotene Metabolism by a Panel of Human Liver Microsomes and the Activity of CYP2C9 and CYP3A4 in those Microsomes



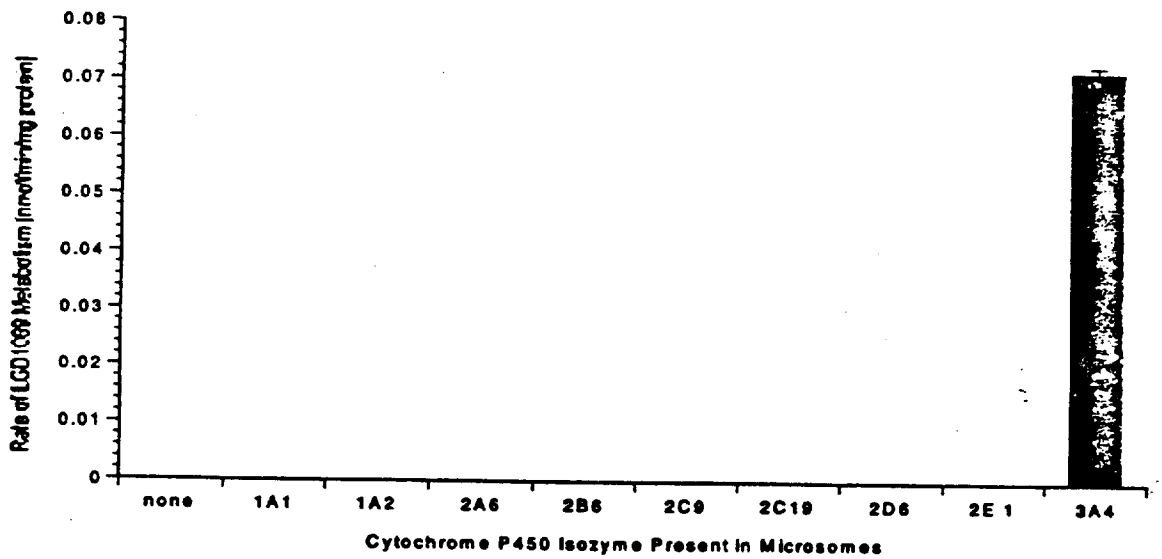
6.3.3.4.2.3. Bexarotene Metabolism by Microsomes from Individual Isozyme-Expressing Cells

The metabolism of bexarotene by microsome preparations of individually-expressed P450 isozymes was assessed (**RR-845-98-003**). Use of cloned, expressed human P450 isozymes allows evaluation of the activity of individual isozymes without the potentially confounding presence of other P450 isozymes.

Bexarotene was incubated with microsomes prepared from human B-lymphoblasts expressing a single recombinant P450 isozyme. Control incubations contained microsomes from human B-lymphoblasts that had not been transfected with any P450 isozyme. The rate of formation of the sum of 6- and 7-hydroxy-bexarotene plus 6- and 7-oxo-bexarotene was determined.

Microsomes containing CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or no recombinant P450 (control) failed to metabolize bexarotene (**Figure 6.3-W**). However, microsomes containing CYP3A4 formed the oxidative metabolites of bexarotene. These data indicate that only CYP3A4 is involved in the oxidative metabolism of bexarotene in humans.

Figure 6.3-W. Rate of Bexarotene Metabolism by Microsomes Containing Single Recombinant Human P450 Isozymes (Mean ± SD, N=5)



APPEARS THIS WAY
ON ORIGINAL

6.3.3.4.2.4. Summary of Bexarotene Metabolism by Cytochrome P450

Based on the results of the three individual techniques, an overall assessment of the isozymes responsible for the oxidative metabolism of bexarotene was conducted (Table 6.3-V). All three techniques indicated that CYP3A4 was involved in the oxidative metabolism of bexarotene. Although individual techniques suggested CYP2A6, CYP2C9, or CYP2C19 may be involved in bexarotene metabolism, a role for these isozymes in bexarotene metabolism was not supported by the other techniques. Therefore, of all the evaluated isozymes, only CYP3A4 is involved in the oxidative metabolism of bexarotene.

Table 6.3-V. Summary of Experiments Conducted to Determine the Human Liver P450 Isozymes Involved in the Metabolism of Bexarotene

P450 Isozyme	Experimental Approach			Conclusion
	Inhibitor Study	Correlation Analysis	Isolated Isozymes	
CYP1A1	not involved	not tested	not involved	not involved
CYP1A2	not involved	not involved	not involved	not involved
CYP2A6	not involved[1]	not involved	not involved	not involved
CYP2B6	not involved	not tested	not involved	not involved
CYP2C9	not involved	involved[2]	not involved	not involved
CYP2C19	not involved[1]	not involved	not involved	not involved
CYP2D6	not involved	not involved	not involved	not involved
CYP2E1	not involved	not involved	not involved	not involved
CYP3A4	involved	involved	involved	involved
CYP4A	not involved	not involved	not tested	not involved

(1) Although metabolism rate in the presence of the inhibitor was statistically different from that in control microsomes, the magnitude of the decrease was minor (~5%).

(2) The apparent correlation of CYP2C9 activity and bexarotene metabolism was likely due to a confounding correlation between CYP2C9 and CYP3A4 activity in the panel of microsomes.

6.3.3.4.3. Assessment of the Potential for P450-Mediated Bexarotene Drug Interactions in Studies with Targretin® Gel and Targretin® capsules

Because oxidative metabolism of bexarotene appears to be via CYP3A4, the effects of concomitant administration of CYP3A4 inhibitors and/or inducers were assessed in population analyses of the clinical studies utilizing Targretin® gel, and separately in population evaluations of data obtained from studies of Targretin® capsules. Population analysis of data from the Targretin® gel studies did not identify drug

interactions with CYP3A4 inducers (carbamazepine, dexamethasone, nevirapine, phenytoin, rifabutin, or troglitazone) or inhibitors (clarithromycin, dronabinol, erythromycin, fluconazole, fluoxetine, indinavir, itraconazole, ketoconazole, metronidazole, nefazodone, nelfinavir, omeprazole, paroxetine, ritonavir, saquinavir, sertraline). In the studies of Targretin® capsules, based on few data, CYP3A4 inhibitors (azole antifungals and macrolide antibiotics) did not alter plasma bexarotene concentrations (**Section 6.3.7.**). Although no evidence for a drug interaction with CYP3A4 inhibitors was observed during either the topical or oral clinical studies, inhibitors could theoretically lead to an increase in plasma bexarotene concentrations.

6.3.3.4.4. Overall Summary of Bexarotene Metabolism

The human metabolism of bexarotene was assessed using in vitro and ex vivo methods. Bexarotene is metabolized in humans to 6- and 7-oxo-bexarotene, 6- and 7-hydroxy-bexarotene and bexarotene acyl glucuronide. 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. Bexarotene acyl glucuronide was only observed in human liver microsome preparations. All of these metabolites have been observed in the toxicology species (**Table 6.3-W** and **Section 5.3., NDA 21-055**). Because of their low affinity for retinoid receptors and their low activity in retinoid receptor assays, the oxidative metabolites are not expected to contribute significantly to the clinical retinoid receptor activity of bexarotene. Urine metabolite ( ) also identified a number of minor urinary bexarotene metabolites that do not represent a significant fraction of the administered dose of bexarotene (**Section 6.3.5.2.2.**).

Table 6.3-W. Species in which Identified Human Bexarotene Metabolites were Observed

Metabolite	Species In Which Observed		
	Human	Rat	Dog
6-hydroxy-bexarotene	X	X	X
7-hydroxy-bexarotene	X	X	X
6-oxo-bexarotene	X	X	X
7-oxo-bexarotene	X	X	X
bexarotene acyl glucuronide	X	X	X

Formation of the oxidative metabolites was mediated by CYP3A4.

The effects of concomitant administration of CYP3A4 inhibitors and/or inducers were assessed in population analyses of the clinical studies utilizing Targretin® gel, and separately in population evaluations of data obtained from studies of Targretin® capsules. Population analysis of data from the Targretin® gel studies did not identify drug interactions with CYP3A4 inducers or inhibitors. Additionally, based on limited data, CYP3A4 inhibitors (azole antifungals and macrolide antibiotics) did not effect bexarotene concentrations in the Targretin® capsule studies.

6.3.3.5. Elimination of Bexarotene

The elimination of bexarotene was evaluated through an assessment of the urinary excretion of bexarotene and its metabolites following oral administration of Targretin® capsules to patients with Type II diabetes mellitus. The metabolite profile of bexarotene in urine was determined using [redacted] and urine bexarotene concentrations were evaluated using an [redacted] Metabolism data relevant to the elimination of bexarotene were presented in **Section 6.3.3.4.1.** Bexarotene is metabolized to 6- and 7-hydroxy-bexarotene, 6- and 7-oxo-bexarotene and bexarotene acyl glucuronide. Despite their presence in the systemic circulation, no detectable bexarotene or 6- or 7-oxo-bexarotene are excreted in urine. Only trace quantities of 6- or 7-hydroxy-bexarotene were excreted in urine. Bexarotene acyl glucuronide is not detectable in plasma or urine. Only minor amounts of other unidentified bexarotene metabolites are excreted in urine.

Therefore, urinary excretion of bexarotene and its oxidative metabolites is a minor pathway for the elimination of bexarotene. Although fecal excretion of bexarotene and metabolites has not been evaluated, the available metabolism and elimination data suggest that bexarotene elimination is primarily through hepatobiliary mechanisms.

This conclusion is supported by preclinical observations with bexarotene. In rats, only 0.244% of an intravenous dose was excreted in urine within 49.5 hours of dosing (**NDA 21-055, Section 5.3.0.9.1.**). 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene were substantial bexarotene metabolites in both rat and dog plasma. In addition, although bexarotene acyl glucuronide was a major metabolite in incubations with rat and dog liver slices and in bile samples collected from rats and dogs dosed with bexarotene, it was not a major plasma metabolite in either species (**NDA 21-055, Sections 5.3.0.8.3** and **5.3.0.8.4**).

6.3.3.5.1. Urinary Bexarotene Metabolite Profiles

The urinary excretion of bexarotene and its metabolites was assessed in patients with Type II diabetes mellitus (**RR-845-99-001**). A complete description of the study design and patient demographic data are presented in **Section 6.3.3.2.2.** Total urinary output was collected over a 12-hour period prior to and over the 24-hour period following a 75-mg to 300-mg dose of Targretin® capsules. The metabolite profile in urine samples from three patients was assessed using a [redacted]

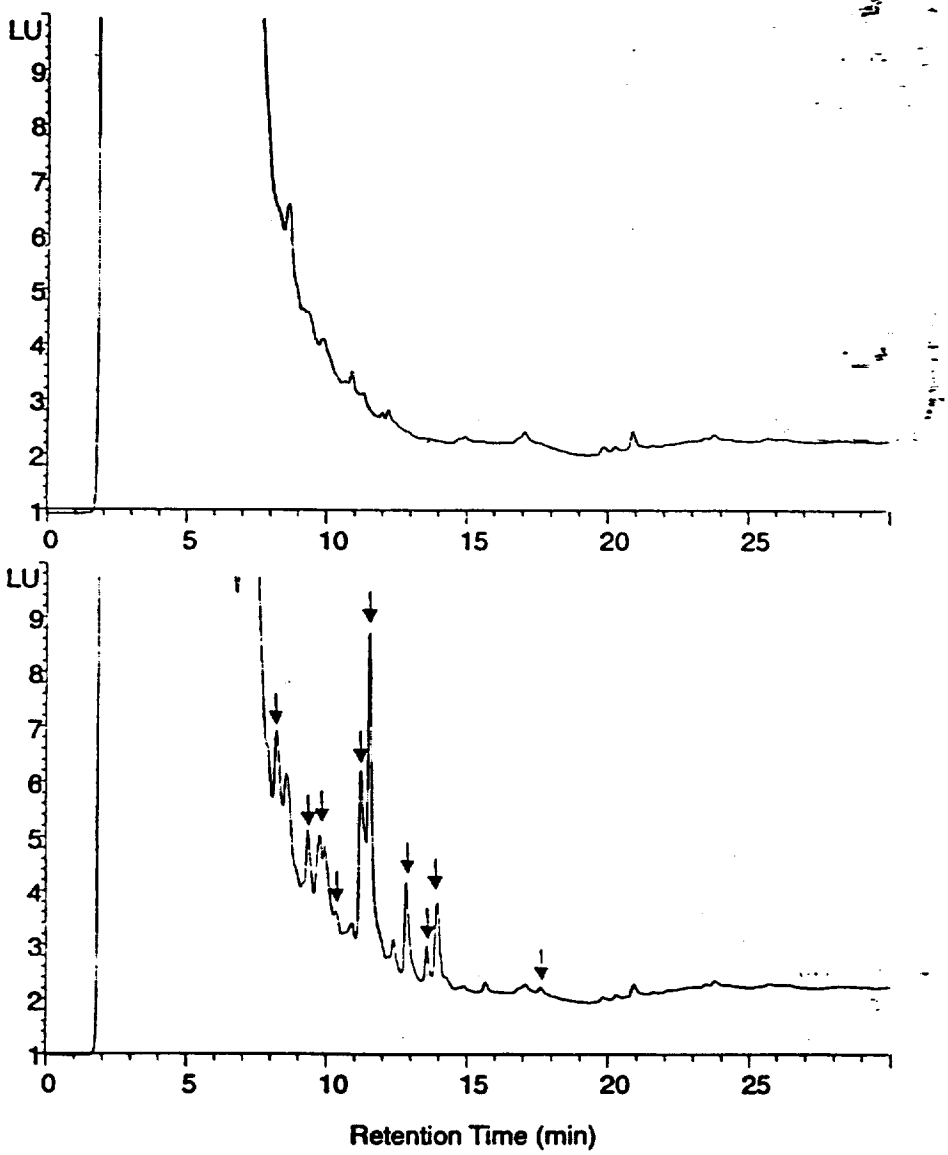
Predose and postdose urine samples from three patients receiving a 300 mg dose of Targretin® capsules were treated with an equal volume of 1 M potassium phosphate buffer (pH 4.0) to stabilize any acyl glucuronide that might have been present. Aliquots were analyzed using a [redacted] procedure, that had been used to profile the metabolites of bexarotene in other biological matrices (**Section 6.3.8.5**).

[redacted] which proved to be more sensitive than [redacted] for analysis of metabolites, was used for these analyses.

Representative predose and postdose [redacted] are shown in **Figure 6.3-X**. Metabolite profiles were very similar in the postdose urine samples of all three patients. No [redacted] peaks at the elution times of bexarotene (27.7 minutes), bexarotene acyl glucuronide (18.2 minutes) or 6- or 7-oxo-bexarotene metabolite peaks (19.8 minutes) were observed. Only a very small [redacted] peak was observed at the elution time of 6- or 7-hydroxy-bexarotene (17.6 minutes). Due to minor [redacted] changes, these retention times are slightly sooner than retention times observed during metabolism experiments (**Section 6.3.3.4.1.**). A number of minor peaks were observed in postdose urine samples that were not evident in predose urine samples. Although the identity of these metabolites was not confirmed, the largest metabolite peaks eluted at relative retention times similar to those of the ether glucuronide and hydroxy acyl glucuronide metabolites of bexarotene that were also formed in rats and dogs. The minor peaks were not quantified; however, they were not thought to represent significant elimination of administered drug.

APPEARS THIS WAY
ON ORIGINAL

Figure 6.3-X. [redacted] of Urine Collected from a Patient before (Upper) and 0 to 24 Hours after (Lower) a Single Oral Dose of Bexarotene (300 mg)



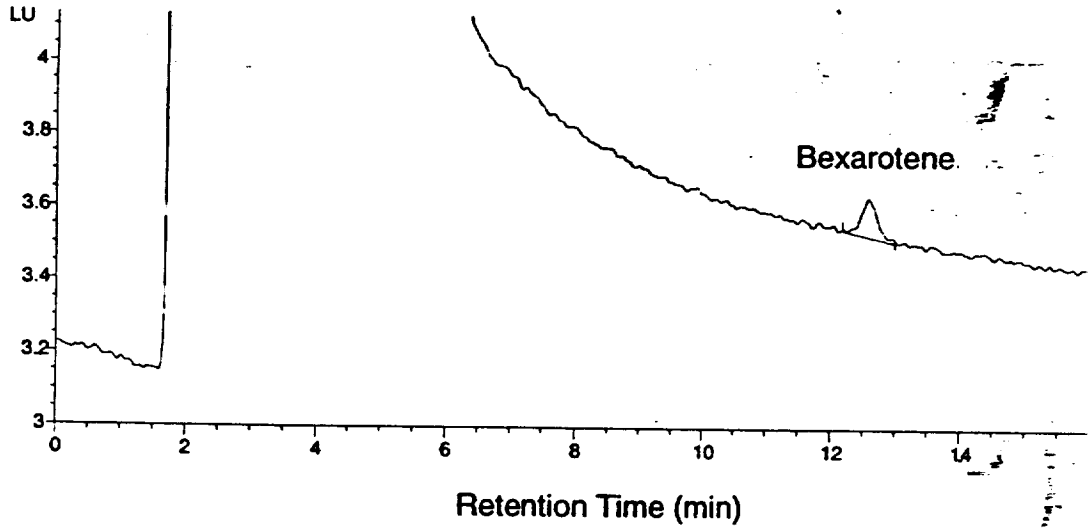
If present, bexarotene would elute at 27.7 minutes, bexarotene acyl glucuronide at 18.2 minutes and bexarotene oxidative metabolite peaks at 17.6 and 19.8 minutes. Arrows indicate 6/7-hydroxy-bexarotene (17.6 minutes) and unknown peaks not present in predose urine.

6.3.3.5.2. Urinary Excretion of Bexarotene

The urine metabolite [redacted] profiles from three patients indicated that essentially no bexarotene, bexarotene acyl glucuronide or known bexarotene oxidative metabolites were excreted in urine (**Section 6.3.3.5.1.**). The lack of renal excretion of unchanged bexarotene was verified using urine samples collected prior to and following single-dose administration of Targretin® capsules to patients with Type II diabetes mellitus (**RR-845-99-001**). A description of the study design and patient demographic data are presented in **Section 6.3.3.2.2.** Total urinary outputs were collected over a 12-hour period prior to and over the 24-hour period following a 75 mg to 300 mg dose of Targretin® capsules. Predose and 0- to 24-hour postdose urine samples were analyzed for bexarotene using an [redacted] with [redacted] (**Section 6.3.8.5**). Given the lack of detectable bexarotene in the metabolite profiles, the goal of method development was to establish a reproducible assay [redacted] The lowest concentration of bexarotene that consistently yielded a detectable peak (signal-to-noise ratio >3) was 10 ng/mL (28 nM). A representative [redacted] is illustrated in **Figure 6.3-Y.**

APPEARS THIS WAY
ON ORIGINAL

Figure 6.3-Y. Representative [redacted] of Predose Human Urine Standard Containing 10 ng/mL Bexarotene

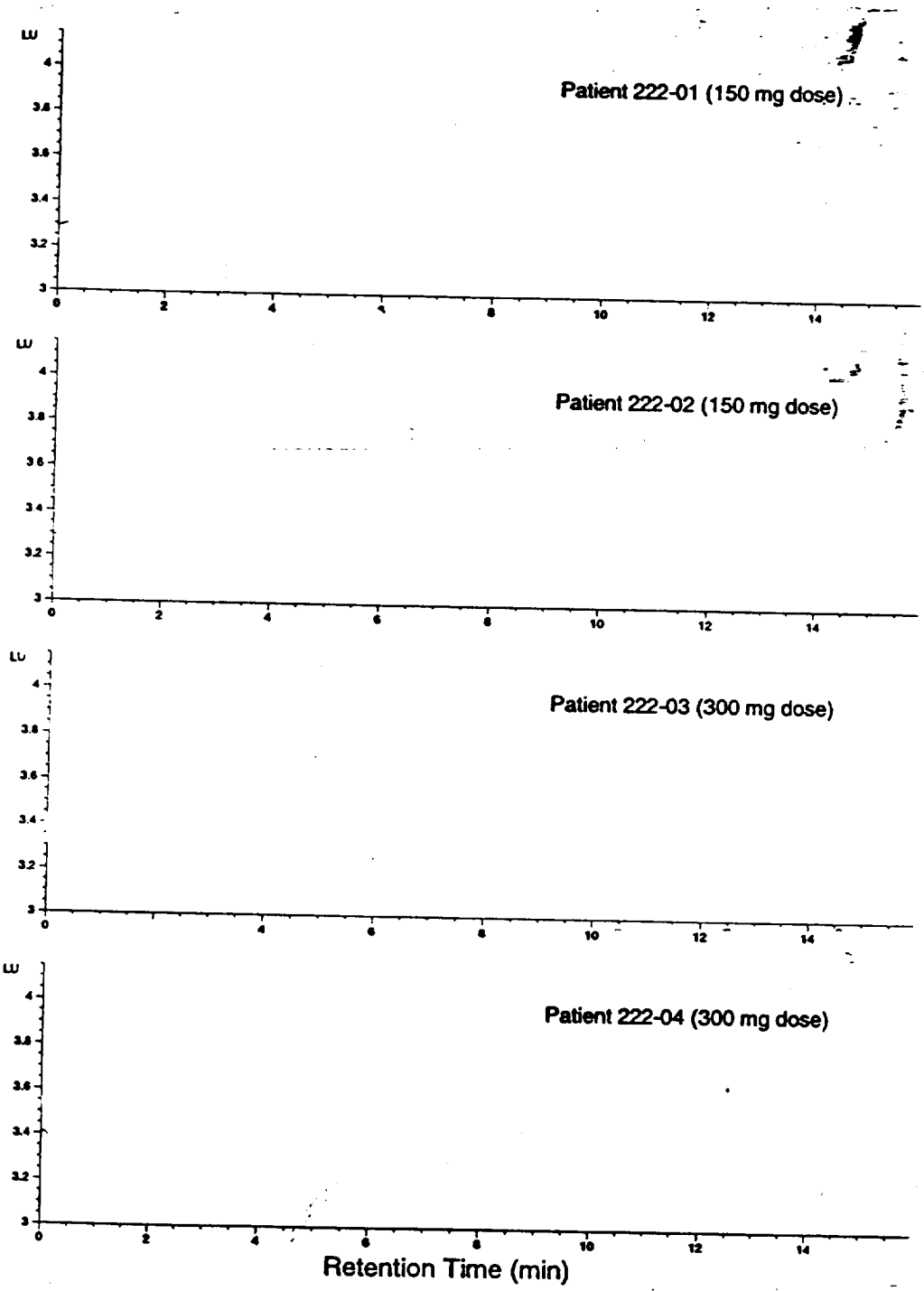


All samples were analyzed on two separate occasions. Representative [redacted] of the urine samples collected 0 to 24 hours after an oral dose of bexarotene are presented in **Figure 6.3-Z.** No bexarotene peak was discernable in any [redacted] These data indicate that the concentration of bexarotene in the urine samples from all 14 patients was less than 10 ng/mL.

Based on the limit of detection and individual patient urine volumes, the maximum theoretical amount of bexarotene excreted unchanged in the urine (Ae) after oral administration was less than 0.04% of the administered dose. Additionally, based on plasma $AUC_{0\text{-}24}$ values and the maximum theoretical Ae, CL_r of bexarotene was less than 1 mL/minute. These data indicate that renal excretion is a negligible pathway for the elimination of bexarotene.

The lack of renal elimination of bexarotene in humans is consistent with observations in rats in which less than 1% of an intravenous administered dose of radiolabeled bexarotene was recovered in urine **(Section 6.3.2.2.2.)**.

Figure 6.3-Z. Representative [redacted] of 0- to 24-Hour Postdose Urine Samples Collected from Patients With Type II Diabetes Mellitus Following Oral Administration of Targretin® Capsules (Study-L1069DM-01)



Bexarotene, if detectable, would elute at approximately 12.5 minutes.

6.3.3.5.3. Summary of Bexarotene Elimination

The elimination of bexarotene was evaluated through an assessment of the urinary excretion of bexarotene and its metabolites following oral administration of Targretin® capsules to patients with Type II diabetes mellitus. The metabolite profile of bexarotene in urine was determined using a [redacted] and urine bexarotene concentrations were evaluated using [redacted]. Metabolism data relevant to the elimination of bexarotene were presented in **Section 6.3.3.4.1.** Bexarotene is metabolized to 6- and 7-hydroxy-bexarotene, 6- and 7-oxo-bexarotene and bexarotene acyl glucuronide. Despite their presence in the systemic circulation, no detectable bexarotene or 6- or 7-oxo-bexarotene are excreted in urine. Only trace quantities of 6- or 7-hydroxy-bexarotene were excreted in urine. Bexarotene acyl glucuronide is not detectable in plasma or urine. Only minor amounts of other unidentified bexarotene metabolites are excreted in urine. Therefore, urinary excretion of bexarotene and its oxidative metabolites is a minor pathway for the elimination of bexarotene. Although fecal excretion of bexarotene and metabolites has not been evaluated, the available metabolism and elimination data suggest that bexarotene elimination is primarily through hepatobiliary mechanisms.

This conclusion is supported by preclinical observations with bexarotene. In rats, only 0.244% of an intravenous dose was excreted in urine within 49.5 hours of dosing **(NDA 21-055, Section 5.3.0.9.1.)**. 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene were substantial bexarotene metabolites in both rat and dog plasma. In addition, although bexarotene acyl glucuronide was a major metabolite in incubations with rat and dog liver slices and in bile samples collected from rats and dogs dosed with bexarotene, it was not a major plasma metabolite in either species **(NDA 21-055, Sections 5.3.0.8.3 and 5.3.0.8.4)**.

6.3.4. Binding of Bexarotene to Plasma Proteins

An in vitro study was conducted to assess the binding of ^{3}H-bexarotene to human plasma proteins (**RR-845-99-002, NDA 21-055, Section 6.7.8.**). These data have previously been submitted in the NDA for Targretin® capsules (NDA 21-055) and are only summarized below.

Although all systems evaluated showed some degree of nonspecific binding, preliminary experiments indicated that nonspecific binding of ^{3}H-bexarotene was minimized with [redacted] using [redacted] Drug-free plasma (heparin anticoagulant) was obtained from three fasted healthy male and female volunteers and pooled. The pooled human plasma was pre-warmed to 37°C in a water bath and pH was adjusted to 7.4. Plasma samples were spiked with ^{3}H-bexarotene to achieve concentrations of 5, 10, 100, 1000, and 5000 ng/mL. In the clinical studies of Targretin® gel, bexarotene plasma concentrations were rarely greater than 5 ng/mL, the lowest concentration used in this in vitro study (**Section 6.3.3.1.3.4.**). After a 15-minute incubation, plasma and Dulbecco's phosphate buffered saline (dialysate) were added to respective sides of the [redacted] cells, and [redacted] was placed in a 37°C water bath for 4 hours. Preliminary experiments indicated that binding was maximized within the 4-hour [redacted] period. Limiting [redacted] to this time interval also minimized nonspecific binding to the [redacted] apparatus. Over an 8-hour [redacted] period, non-specific binding of ^{3}H-bexarotene to the [redacted] apparatus was potentially as high as 18%. At 4 hours, aliquots of plasma and [redacted] were removed and analyzed for [redacted] and calculation of protein binding.

Binding of ^{3}H-bexarotene to human plasma proteins was very high (**Table 6.3-X**). Mean free fractions ranged from 0.12% to 0.18% and were independent of bexarotene concentration.