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APPLICATION NUMBER: NDA 20-886

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-886

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Drug Name: Panretin Gel (LGD1057, ALRT1057)
Formulation: Topical, gel
Applicant: Ligand Pharmaceuticals, Inc.
10275 Science Center Drive
San Diego, CA 92121
Reviewer: Z. John Duan, Ph.D.
Type of Submission: NDA

I. SYNOPSIS

PANRETIN™ Gel contains the active ingredient: LGD1057. LGD 1057 is a naturally-occurring retinoic acid isomer 9-cis-retinoic acid, an endogenous substance in humans. The proposed indication of panretin (alitretinoin) gel in this NDA is for the first-line topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma.

In the NDA, pharmacokinetic data from Phase 1-2 studies conducted by the applicant are presented. Based on agreements reached at the End of Phase 2 Meeting between FDA and the applicant (11/20/95), no pharmacokinetic data were collected in the pivotal Phase 3 studies of PANRETIN™ Gel in patients with KS.

Additional Phase 1-2 studies with PANRETIN™ Gel have been conducted in patients with cutaneous T-cell lymphoma (CTCL). Supportive pharmacokinetic data from these studies are included in this NDA.

An oral soft gelatin capsule dosage form of LGD1057 (PANRETIN™ Capsules) is also being evaluated for possible development as an oral agent for the systemic treatment of Kaposi's sarcoma and for the treatment of other cancers and dermatologic diseases. Pharmacokinetic data from Phase 1-2 studies of PANRETIN™ Capsules are described in the NDA. In addition, the pharmacokinetics of orally administered 9-cis-retinoic acid have been assessed in healthy male subjects and in patients with solid tumors. Data from these studies are also summarized in this NDA. However, these data were considered only as supportive material to those of topical gel, not as the data for independent oral formulations.

As an endogenous substance in humans, 9-cis-Retinoic acid has been shown to be present at concentrations _____ ng/mL in up to _____ % of fasting patients prior to therapy.

A mean peak concentration of 2.7 ng/mL has been observed in healthy individuals ingesting a vitamin A-rich meal.

Plasma concentration monitoring of 9-cis-retinoic acid and metabolites was conducted during studies assessing the safety, tolerance and efficacy of PANRETIN™ Gel applied topically on patients with Kaposi's sarcoma (KS) lesions and patients with cutaneous T-cell lymphoma (CTCL) lesions. The single-time point samples were analyzed using one of three validated analytical methods.

The very low or undetectable 9-cis-retinoic acid concentrations found after topical application of 9-cis-retinoic acid in patients is consistent with the rapid elimination and lack of accumulation observed following repeat oral administration of 9-cis-retinoic acid. The pharmacokinetics of orally administered 9-cis-retinoic acid have been evaluated following single- and repeat-dose administration to healthy volunteers, patients with advanced cancer, and patients with severe plaque psoriasis. C_{max} values at the lower oral dose levels (5 mg/m²) were approximately 10 fold greater than the highest observed 9-cis-retinoic acid concentration in patients applying PANRETIN™ Gel for the treatment of cutaneous KS. The single oral dose pharmacokinetics are approximately dose-proportional over a 5 mg/m² to 50 mg/m² dose range. C_{max} values occurred within one to three hours following dosing. Across studies, terminal elimination phase half-life values were 10 to 20 hours. No demographic groups having altered 9-cis-retinoic acid pharmacokinetics were identified. Following repeat once-daily oral dose administration of lower doses of 9-cis-retinoic acid (5 mg/m²), repeat dose C_{max} and AUC values were similar to Day 1 values. A dose-related apparent induction of oral clearance of 9-cis-retinoic acid was observed in most studies at higher total daily dose

levels (mg/m²). Following repeat twice-daily oral dose administration, the extent of induction appeared to be related to the total daily dose administered. In all studies, repeat dose terminal elimination half-life values were similar to values observed following single dose administration. Pre-dose concentrations in patients receiving repeat doses were generally less than % of C_{max} values and were routinely observed only at dose levels mg/m², indicating that there is minimal accumulation of drug on a repeat once-daily or twice-daily dose regimen. 4-oxo-9-cis-Retinoic acid has been identified as a major circulating metabolite of 9-cis-retinoic acid and was quantitated in many of the studies. Following both single-dose and multiple-dose administration, plasma concentrations of this metabolite ranged from being approximately one-half the concentration of parent compound to being equivalent to the concentrations of parent compound. Little isomerization of 9-cis-retinoic acid to all-trans-retinoic acid (ATRA), 13-cis-retinoic acid or 9,13-di-cis-retinoic acid was observed. Low oral dose (mg) administration of 9-cis-retinoic acid did not appear to affect the total body retinoid pool as assessed by plasma retinol concentrations. Administration of higher oral doses (mg) of 9-cis-retinoic acid resulted in dose-related decreases in plasma retinol concentrations of up to %.

Based on *in vivo* and *in vitro* studies, metabolism of 9-cis-retinoic acid occurs through oxidation to 4-hydroxy and 4-oxo metabolites; isomerization to ATRA, 9,13-di-cis-retinoic acid and 13-cis-retinoic acid; and glucuronidation of parent compound, 4-oxo-9-cis-retinoic acid and possibly other aglycones. The oxidative metabolites are capable of binding to and activating retinoid receptors; however, they are less potent and efficacious than 9-cis-retinoic acid. This metabolite profile is qualitatively very similar to that observed for 9-cis-retinoic acid in preclinical models. Based on three *in vitro* methods, ¹⁴C-1A1, ¹⁴C-1A2, ¹⁴C-2C9, and ¹⁴C-3A4 appear to be involved in the human oxidative metabolism of 9-cis-retinoic acid.

The *in vitro* free fraction of 9-cis-retinoic acid in human plasma was determined using ultrafiltration methods. A high degree of non-specific binding (31.9%) to the ultrafiltration apparatus precluded accurate determination of the free fraction; however, the fraction of radiolabel present in plasma ultrafiltrate was less than %, suggesting that the binding of 9-cis-retinoic acid to human plasma proteins is very high.

In this NDA, the applicant made a request for biowaiver of the *in vitro* performance test. Although some preliminary experiments for the development of an *in vitro* performance assay were conducted, no method proved suitable for soluble PANRETIN™ Gel, and therefore, no such assay has been implemented.

II. RECOMMENDATIONS

The pharmacokinetic studies provide an understanding to the systemic exposure of 9-cis-retinoic acid and support a recommendation for the approval of this NDA from the Clinical Pharmacology and Biopharmaceutics standpoint. The General Comments and the Labeling Comments should be conveyed to the sponsor.

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IV. SUMMARY

A. Overview of the analytical methods

B. Formulations Used during PANRETIN™ Gel Development

Alcohol-based gelled solutions containing 0.01%, 0.05% and 0.1% LGD1057 were developed for use in Phase 1-2 studies. A 0.5% LGD1057 gel was also developed for evaluation of the pharmacokinetics and toxicity in rats following topical application. A 0.1% gel formulation was the only formulation used during the Phase 3 studies in patients with cutaneous KS (L1057T-31, ALRT1057-503/504). The PANRETIN™ Gel formulation applied in Phase 3 studies was modified relative to the formulations applied in the Phase 1-2 studies to eliminate two of the three antioxidants which were found to be unnecessary for adequate stability. The minor differences in the clinical formulations between Phase 1-2 and Phase 3 would not be expected to affect the dermal absorption of 9-*cis*-retinoic acid. Table 1 provides the composition of the various PANRETIN™ Gel formulations, and the clinical studies in which they were used.

TABLE 1. Composition of Formulations Used during PANRETIN™ Gel Development

Ingredients (%w/w)	Toxicology Studies			Clinical Studies			
	0.01% Gel	0.05% Gel	0.5% Gel	Phase 1-2			Phase 3
				0.01% Gel	0.05% Gel	0.1% Gel	0.1% Gel
LGD1057 ^a							
Dehydrated Alcohol, USP							
Polyethylene glycol 400, USP							
Hydroxypropyl cellulose, NF							
Butylated hydroxytoluene, NF							

^a LGD1057 quantities include a 5% overage until consistent manufacturing was demonstrated.

^b 1% overage allowed for evaporative loss during manufacturing.

Phase 1-2 Studies: L1057-94-01T, L1057-94-02T, L1057-94-03T, L1057-94-04T, L1057-94-05T, L1057-94-07T, L1057T-21, L1057T-22, L1057T-24, L1057T-25, and L1057T-30.

Phase 3 Studies: L1057T-31, ALRT1057-503/504.

C. Pharmacokinetic summary

1. Endogenous 9-*cis*-Retinoic Acid Concentrations

9-*cis*-retinoic acid is an endogenous substance formed *in vivo* from dietary or nutritional sources of vitamin A. The development of a sensitive assay for quantitation of 9-*cis*-retinoic acid in human plasma permitted determination of the endogenous systemic exposure to 9-*cis*-retinoic acid (from dietary or nutritional supplement sources) in plasma samples from fasting patients with severe plaque psoriasis prior to receiving therapy. Plasma samples were assayed using this method with a LLQ of ng/mL. 9-*cis*-Retinoic acid was present at concentrations ng/mL in 13 of 45 (29%) patients with evaluable pre-therapy samples. The highest observed pre-therapy concentration was ng/mL. Thus, in this study, 29% of evaluable predose samples from fasting patients had plasma 9-*cis*-retinoic acid concentrations ng/mL prior to receiving therapy.

Measurable concentrations of 9-*cis*-retinoic acid also were observed in a study which evaluated the effect of dietary liver administration on plasma concentrations of 9-*cis*-retinoic acid and other retinoids. Plasma concentrations of 9-*cis*-retinoic acid and other retinoids were determined following ingestion of fried turkey liver (2 g raw weight/kg body weight, equivalent to approximately 3300 IU vitamin A) by ten healthy male volunteers. Plasma samples were obtained prior to and at eight time points over 24 hours following liver ingestion and analyzed by to determine concentrations of retinoid isomers and metabolites. Fasting endogenous 9-*cis*-retinoic acid concentrations were less than ng/mL in all volunteers, increased to a mean (\pm SD) of 2.7 ng/mL \pm 1.1 ng/mL within four hours following liver ingestion and decreased to less than quantifiable concentrations ng/mL) by hours (Table 2). All-*trans*-retinoic acid (ATRA), 13-*cis*-retinoic acid and 4-oxo-13-*cis*-retinoic acid were all quantifiable in endogenous fasting samples and also increased following liver ingestion. Thus, dietary ingestion of foods containing vitamin A and its derivatives can lead to quantifiable systemic exposure to 9-*cis*-retinoic acid. This non-therapy-related exposure to 9-*cis*-retinoic acid may be expected to contribute to the overall systemic exposure to 9-*cis*-retinoic acid following therapeutic application of PANRETIN™ Gel.