

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:NDA 20-886**

**MEDICAL REVIEW(S)**

# MEDICAL OFFICER REVIEW

**NDA**                    **20-886**

**DRUG**                **PANRETIN (alitretinoin; 9-cis-retinoic acid) 0.1% gel**

**SPONSOR**           **Ligand Pharmaceuticals Inc.**  
**San Diego, CA 92121**

NDA dated May 26, 1998; arrived May 28, 1998 (@ HFD-150)

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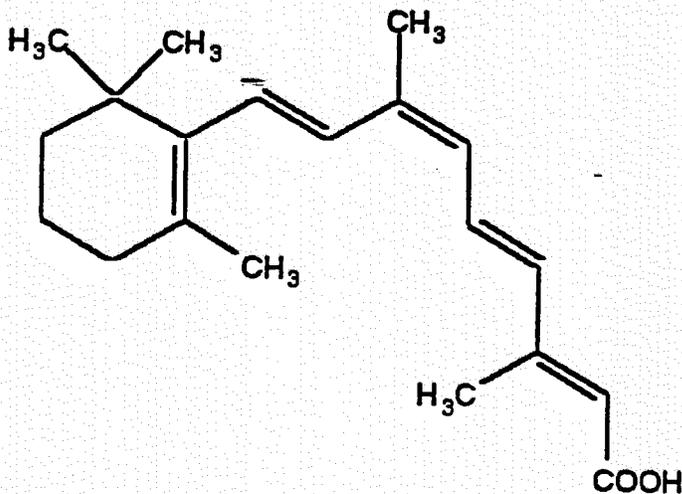
**FDA-LIGAND MEDICAL REVIEW INTERACTION**

<b>Query subject</b>	<b>Date FDA requested</b>	<b>Date Ligand responded</b>
Response criteria and progression criteria clarifications	June 12, 1998	June 16, 1998
Survival and OI data; Dr. Fleming's letter	June 12, 1998	July 9, 1998
Follow up global photographs on responders	June 12, 1998	July 17, 1998 (delay in arrival of complete global photographs package)  Received requested material in parts: July 1, 1998, July 30, 1998, Aug. 6, 1998
Total number of KS lesions and location @ baseline and F/U	June 12, 1998	June 25, 1998

Query subject	Date FDA requested	Date Ligand responded
MS ACCESS, lab data: missing pt. ID column	July 7, 1998	July 14, 1998
Pt. new lesions since baseline; total no. lesions (index & non-index) treated	July 7, 1998	July 10, 1998
Clarification on new lesions	July 10, 1998	July 23, 1998
Protease inhibitor clarifications	July 10, 1998	July 15, 1998
Study -31: 28 queries on 20 responders	Aug. 10, 1998	Aug. 17, 1998 Additional information: Oct. 9, 1998
Study -31: 13 queries on 11 responders	Sept. 1, 1998	Sept. 9, 1998 Additional information: Oct. 9, 1998
Electronic images of the global photographs submitted in hard copy: 7/1/98, 7/30/98, & 8/6/98	Sept. 1, 1998	Oct. 30, 1998
Study -503: 10 queries on 6 responders  Information on other treated lesions  Missing required CD4-counts on 10 pts.	Sept. 11, 1998	Oct. 15, 1998  Oct. 15, 1998  Oct. 15, 1998
Study -31: KS lesion ultrasound data & KS lesion serial biopsies	Sept. 22, 1998	Oct. 1, 1998
Study -503: all pt. #s, date entered, response	Oct. 5, 1998	Oct. 14, 1998

## 1. GENERAL INFORMATION

(2E,4E,6Z,8E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenoic acid; a common name is 9-*cis*-retinoic acid and the structural formula is as follows: molecular weight: 300; a molecular formula of C<sub>20</sub>H<sub>28</sub>O<sub>2</sub>.



1.1 Pharmacologic Category: retinoid

1.2 Proposed indication:

for first-line topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma.

## 2. PHARMACOLOGY

### 2.1 General

Panretin is a naturally occurring derivative of Vitamin A. It is a panagonist for six retinoid receptors (RAR<sup>1</sup>:  $\alpha$ ,  $\beta$ ,  $\gamma$ ; RXR<sup>2</sup>:  $\alpha$ ,  $\beta$ ,  $\gamma$ ). As a class of compounds, the retinoids have a role in normal development and physiology by modulating cell growth, division, reproduction, differentiation and immune function. In malignant cell lines, retinoids inhibit cell growth, induce differentiation, and induce apoptosis. The advantage of RXR agonism is the interaction with other nuclear receptors providing responsiveness to vitamin D, thyroid hormone and all-trans-retinoic acid (ATRA). Panretin has antiproliferative activity, in vitro, against cell lines derived from patients with Kaposi's sarcoma (KS).

<sup>1</sup> RAR = retinoic acid receptor

<sup>2</sup> RXR = retinoic X receptor

## 2.2 Local pathology and absorption of panretin

Application of panretin (0.01%, 0.05%, or 0.5%) to the skin of rats and guinea pigs resulted in erythema, epidermal thickening, scaling, loosening of the stratum corneum, and increased trans-epidermal water loss. Rats treated for up to 28 consecutive days and after a 14-day recovery had histopathology performed. The findings revealed epidermal hyperplasia, crust, ulceration and dermal fibrosis at all doses. Hematological effects seen at the 0.5% dose level may be due to the severity of the skin irritation. The alteration in the skin with chronic application of panretin represented disruption of the skin's barrier function; this may account for an observed increase in day 28 vs day 1 plasma concentrations of panretin. However, in 2 of 3 human Kaposi's sarcoma trials (i.e., L1057-94 & L1057T-21), patients treated with topical panretin plasma retinoid concentrations were no different than untreated controls; in one trial (i.e., L1057T-22) 26 of 153 samples (17%) had measurable 9-cis-retinoic acid (CRA) @ concentrations of ng/ml or 10 of 22 patients (45%) had quantifiable 9-CRA plasma concentrations at least once.

## 2.3 Information derived from the oral formulation of panretin

In rats and dogs, prolonged oral administration resulted in reduced exposure, i.e., increased clearance; in the rat this was not accompanied by a reduction in plasma half-life. There was no evidence of either accumulation or induction of metabolism at the doses studied. In the dog daily doses up to 50 mg/kg x 28 days resulted in a reduction in  $C_{max}$  and AUC over time. In a human oral study (L1057-93-01 & L1057-93-02), single doses of panretin resulted in  $C_{max}$  and AUC increased dose-proportionally; at doses  $\geq 140$  mg/m<sup>2</sup> &  $\geq 83$  mg/m<sup>2</sup>, respectively, there was evidence of induction of clearance. In general, at high oral doses, 9-cis-retinoic acid can result in a dose-related decrease in plasma retinol pools by as high as 30%.

The terminal elimination  $t_{1/2}$  of oral panretin in humans was 1-2 hrs.

Panretin binding to plasma protein as tested at concentrations of \_\_\_\_\_ ng/ml) were as follows:

Rat, 92%

Dog, 95%

In human plasma, the free fraction of 9-cis-retinoic acid was determined by ultrafiltration. The fraction of radiolabel present in plasma ultrafiltrate was < 3%.

Radioactivity peaked in 4 hours post-injection of tritiated-panretin injected into rat; the greatest tissue/plasma ratios were in the liver and fat. Radioactivity was greater than plasma @ 8 hr and 24 hr in the liver; radioactivity was greater than plasma @ 48 hr in liver, adrenals, fat, kidneys, ovaries, mesenteric lymph node, lungs and skin.

Panretin metabolites were predominantly excreted in the feces. In male rats 68% of the drug was excreted in the feces over 48 hr; in female rats 48% was excreted in the feces. In the urine 5.6% and 11.7% of the drug appeared in male and female rats, respectively.

Metabolism of panretin in the rat and dog was via hydroxylation and ketone formation at carbon-4, isomerization to all-trans-, 13-cis- and (9Z, 13Z)-RA, reduction to 13, 14-dihydro-9-cis-retinoic acid, and glucuronidation. Except for the reduction product, metabolism of panretin was similar to ATRA and 13-cis-retinoic acid. In humans 4-oxo-9-cis-retinoic acid was the major circulating metabolite. The oxidative products bound and activated retinoid receptors but they were less potent than 9-cis-retinoic acid. Cytochrome P450 isozymes 1A1, 1A2, 2C9, and 3A4 appeared responsible for human oxidative metabolism of this drug.

Teratogenic effects of retinoids as a class of compounds were of concern. In an oral rabbit study, a daily dose of 1.5 mg/kg clearly produced teratology (Cmax for 9-cis-retinoic acid 96.6 ng/ml). Also in the rabbit, at a daily dose of 0.5 mg/kg, no gross teratogenic abnormalities were seen (Cmax for 9-cis-retinoic acid 39.7 ng/ml); there was increased incidence of fused sternebrae. With regard to human risk, Ligand estimated that their product exposed the patient to the equivalent of 0.04 mg/kg/d; the highest plasma concentration of 9-cis-retinoic acid after topical exposure was 0.638 ng/ml. This estimated exposure and 9-cis-retinoic acid exposure appeared to have a reduced risk for teratogenesis.

#### 2.4 Selection of the concentration of panretin gel

In the Phase 1-2 trial program in KS, three concentrations of panretin gel (0.1%, 0.05%, and 0.01%) were tested. Although the studies were not designed to select a concentration, there was no relationship between patient overall response and the gel concentration applied. However, the three patients who achieved a complete response were treated with the 0.1% concentration. The 0.1% concentration of panretin gel was selected for the pivotal trials.

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### 3. BACKGROUND: KAPOSI'S SARCOMA

#### 3.1 General

In recent years, approximately 2700 new cases of Kaposi's Sarcoma (KS) were diagnosed annually in the U.S. The prevalence of KS in the U.S. was approximately 18,000 to 20,000.

AIDS-related KS was first reported in the late 1970's as an explosive disorder in homosexual or bisexual men in New York and California. KS appeared to be an early manifestation of AIDS, occurring in the absence of any detectable clinical immune dysfunction. The disease presented fulminantly as widespread disseminated mucocutaneous lesions often progressing to lymph node and visceral organ involvement (e.g., GI tract and lungs). With time or as the immune system deteriorated as a function of HIV infection, other manifestations of AIDS manifested (e.g., pneumocystis, cryptococcus, toxoplasmosis) and contributed to morbidity and mortality in these patients. In the late 1970's, the frequency of KS was about 20% in AIDS patients. Today, KS was the AIDS-defining illness in about 10% of patients. This percentage may be higher in the subgroup of patients positive for human herpesvirus 8 antibodies. The downward change in frequency in KS may be due to improvement in antiretroviral therapies.

KS associated with AIDS appeared to be identical histopathologically to the clinical models of the disease previously described, but a more aggressive type of the same disease in the milieu of near absence of a cellular immune system<sup>3</sup>.

Kaposi's sarcoma (KS) is a tumor of vascular origin<sup>4</sup>. There are four varieties of KS with similar histopathology but markedly different natural histories. They include classic KS, African KS, immunosuppression related KS, and acquired immunodeficiency syndrome (AIDS) related KS.

Moritz Kaposi first described classic KS in 1872. This disease was described as a painless eruption of nonpruritic nodules on the feet and distal lower extremities. The disease occurs in

<sup>3</sup> Krigel and Friedman-Kien; A Chachoua, R Krigel, F Lafleur et al. Prognostic factors and staging classification of patients with epidemic Kaposi's sarcoma. J Clin Onc 7:774-780, 1989

<sup>4</sup> RJ Biggar. Cancer in acquired immunodeficiency syndrome: an epidemiological assessment. Sem Onc 17:251-260, 1990

elderly (50-70 years) men of Mediterranean origin. The disease progresses slowly with visceral and lymph node involvement occurring late. Typically the disease runs an indolent course with gradual enlargement of primary lesions and development of new lesions. The course of the disease is one of increase in size, coalescing, fungating, and ulcerating and eventual venous blockage and lymphedema in the lower extremity. The course of this disease commonly stretches over 8-15 years. It is of note that one-third of these patients developed a second cancer, i.e., non-Hodgkin's lymphoma<sup>5</sup>.

African KS was first described as a common malignancy in equatorial Africa in the 1950's. In young adult African males (age 25-40 years) the disease manifested as the classic KS (57%) with localized nodular lesions and followed an indolent course or as a more aggressive fungating disease or a disease invasive to underlying bone (38%) with a more progressive course. This form of the disease was usually fatal in 5-8 years. Another form of KS developed in children (age 2-13 years). This disease manifested as generalized lymphadenopathy with subsequent involvement of the viscera. The disease course was rapidly progressive and fatal within 2-3 years. Although a more aggressive form of KS was appearing in these same regions of Africa (e.g., Zambia and Uganda) associated with AIDS, retrospective analysis of stored sera from KS patient's as far back as 1960 failed to link AIDS to KS<sup>6</sup>.

Immunosuppression related KS was first being reported in the setting of organ transplantation in the early 1970's. This malignancy occurred in patients after renal transplantation and other organ allograft recipients and in patients under chronic immunosuppression for autoimmune diseases.

The immunosuppressive agents most often implicated were prednisone and azathioprine. The time from start of immunosuppressive drugs to onset of KS was 15-24 months. The course of the disease could be localized to skin and followed an indolent course or disseminated with visceral organ involvement; a rapid progressive fatal course followed. It was most

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<sup>5</sup>RL Krigel and AE Friedman-Kien. Sem Onc 17:350-360, 1990; PA Volberding. Non-HIV Kaposi's sarcoma: classic KS and KS associated with immunosuppression. In The AIDS Knowledge Base, edited by PT Cohen, MA Sande, PA Volberding, The Medical Publishing Group, Waltham, MA, 1990. p 7.1.3.1-2

<sup>6</sup>Krigel and Friedman-Kien; PA Volberding, JO Kahn, DM Heyer. Non-HIV Kaposi's sarcoma: African KS. In The AIDS Knowledge Base. p7.1.1.1-3; RJ Biggar. Cancer in acquired immunodeficiency syndrome: an epidemiological assessment. Sem Onc 17:251-260, 1990

interesting that as many of 50% of KS patients in this setting could have complete remission of their tumors after discontinuing immunosuppressive agents.

### 3.2. "A disease within a disease"

Dr. Susan Knowlton has often stated that Kaposi's sarcoma was "a disease within a disease."<sup>7</sup> The evaluation of the AIDS-patient with KS should be taken in the context of antiretroviral therapy. Significant suppression of HIV viral load by combination anti-HIV agents has resulted in a small subset of KS patients having responses. This should not be surprising that improvement in immune function resulted in regression of KS in view of the experience of regression of KS lesions in transplant patients when immunosuppression was withdrawn. Long term remission of KS has also been reported with foscarnet<sup>8</sup> (in panretin pivotal trial -31, seven patients received foscarnet--4 panretin and 3 controls; none of these were responders).

The following table describes the literature available on the interaction of protease inhibitors in Kaposi's sarcoma.

Authors Journal	# of pts	Protease inhibitor	time to response type of response	duration of response	Comments
Conant, Opp, Poretz, Mills  AIDS 1997, 11: 1300-1301)	5	Ritonovir	in one case improvement noted in 18 days  flattening, resolution, no new lesions (during double blind Rx with placebo: new lesions)	recurrence 6 wks post d/c PI	CD4 at baseline: 21-76  immune restituti- on: $\geq 3$ x increase in CD4

<sup>7</sup> Knowlton SE. The Little et al article reviewed. Oncology 1998; 12:883-884.

<sup>8</sup> Murphy, Armstrong, Sepkowitz, Ahkami, Myskowski. AIDS 1997, 11: 261-262.

Authors Journal	# of pts	Protease inhibitor	time to response type of response	duration of response	Comments
Murphy, Armstrong, Sepkowitz, Ahkami, Myskowski  AIDS 1997, 11: 261- 262	1	Indinavir	Fading in 4 wks; complete resolution by 12 wks	At least 7 mos.	CD4 increase from 15 to 53
Blum, Pellet, Agbalika, Blanchard, Morel, Calvo, Lebbe  AIDS 1997, 11: 1653-1654	1	Indinavir	no new lesions, partial desinfiltration of previous lesions @ 2 months  complete desinfiltration @ 4 mos. (bx proven @ 7 mos.)	at least 11 months	HHV-8 load decreased starting @ 2 mos.; HIV viral RNA load decreased to undetectable  CD4 from 38 to 160 @ 10 mos.
Burdick, Carmichael, Rady, Tyring, Badiavas  J Amer Acad Dermatol 1997, 37:648-649	1	Ritonavir	@ 1 mo. lesions smaller  @ 4 mo. lesions flat  @ 6 mo. soft lesion gone		CD4 from 46 to 177 @ 1 mo.  decrease viral load  HHV-8 DNA gone from regressed lesion
Aboulafia  Mayo Clin Proc 1998, 73: 439-443	1	Indinavir	@ 2 mos. CXR improving & Sxs improving	@ least 18 mos.	CD4 from 35 to 135
Krischer, Rutschmann, Hirschel, Vollenweider-Roten, Saurat, Pechere  J Amer Acad Dermatol 1998, 38:594-8	9	Saquinavir, ritonavir, saquinavir	in 6 pts.: onset 4-8 wks  no new lesions, flattening		undetected viremia after PI  mean increase in CD4 = 49

From the foregoing table, it appeared that the response of KS to protease inhibitors occurred as early as 18 days and as late as 2 months. The authors of the articles suggested that the KS responses may be due to inhibition of HIV replication, decrease in viral load, increase and restoration of immune function, or inhibition of KS-associated herpesvirus protease.

In patients who enter a clinical trial on stable antiretroviral medication and respond, concomitant antiretroviral medications may not be a problem. It may become an issue for patients who have their antiretroviral medication changed or adjusted shortly before entry on the trial or during the trial. Little and co-authors<sup>9</sup> suggested monitoring anti-HIV regimens, viral loads, and CD4 counts in patients entered on KS trials. In Study -503, patients were allowed to participate on other investigational treatments for AIDS/HIV was allowed but the treatment should have been stable for the previous 3 months if possible (vol. 1.91, p. 005). This appears to be reasonable in view of a meeting with Ligand in July 1998. Their pivotal trial for oral panretin capsules required patients to be on stable antiretroviral therapy for a least three months prior to entry on study and that there should not be a change in antiretroviral therapy during the time of study drug administration. From the discussion with the three KS consultants brought to the meeting by Ligand, deviation from this requirement may disqualify the patient as a responder.

### 3.3 Retinoid therapy

There were no responses in six patients with AIDS-related KS treated with oral isotretinoin (13-cis-retinoic acid) (2 mg/kg/d for four weeks. Patients developed new lesions during therapy<sup>10</sup>. In another trial with 13-cis-retinoic acid, fifteen men with HIV-associated Kaposi's sarcoma and poor risk disease according to the TIS staging were enrolled in a phase II trial of oral 13-cis-retinoic acid. The median CD4 cell count was 95 cells/microl (range 7-260) and 6 had prior AIDS-defining opportunistic infections. One patient was withdrawn on account of cutaneous toxicity. Evaluation was by AIDS Clinical Trials Group assessment. One patient achieved a partial response. The overall response rate is 7% (95% confidence interval 0-23%); 5 patients

<sup>9</sup>Little RF, Pluda JM, Feigal E, Yarchoan R. The challenge of designing clinical trials for AIDS-related Kaposi's sarcoma. *Oncology* 1998; 12:871-883.

<sup>10</sup>Ziegler JL, Volberding PA, Itri LM. Failure of isotretinoin in Kaposi's sarcoma [letter]. *Lancet* 1984 Sep 15;2(8403):641.

had stable disease (38%: 95% confidence interval 7-64%). The authors concluded that the overall low activity, considerable toxicity and limited cosmetic benefit even in responding patients limited the value of this approach in KS<sup>11</sup>.

The following table illustrates trials of ATRA in patients with AIDS-related KS.

**Oral ATRA trials in AIDS-related KS**

Dose	Results
2 mg/kg/d (divided)	6 of 7 pts. Clinical response (2 PRs, 1 significant, regression)
175 mg/m2/d	5 of 6 pts. rapid PD
100 mg/m2/d	2 of 8 pts. Stable
45 mg/m2/d escalating to 150 mg/m2/d	17% (4/24) PRs
40 mg/m2/d escalating to 100 mg/m2/d + interferon	N=13 1 PR to combination 0 responses to ATRA alone

In a trial of eight AIDS-related KS patients, 1% ATRA topically treated TID x 3 months resulted in at least 50% reduction in area in seven patients; no responses occurred in the vehicle alone lesions and untreated control lesions.

**3.4 Early Kaposi's sarcoma**

KS in early stages is not life-threatening. Nevertheless, these cutaneous lesions can be painful and associated with edema. The lesions serve as a visible social stigma and a constant reminder of the patient's HIV disease. The goal of therapy is to decrease lesion height, area, and/or color; these changes are reported to result in an improvement in the quality of the patient's life. The potential advantages of topical therapy included limited side effects, noninvasiveness, and self-administration by the patient.

Several authors recommend for patients with a few lesions that are cosmetically or psychologically unacceptable a variety of local therapies (e.g., cosmetic makeup, surgical excision, cryotherapy, local injection of cytotoxics, laser therapy)<sup>12</sup>.

<sup>11</sup> Bower M, Fife K, Landau D, Gracie F, Phillips RH, Gazzard BG. Phase II trial of 13-cis-retinoic acid for poor risk HIV-associated Kaposi's sarcoma. Int J STD AIDS 1997 Aug;8(8):518-21.

<sup>12</sup> Levine AM. AIDS-related malignancies: the emerging epidemic. JNCI. 1993;85:1382-1397; Little RF, Pluda JM, Feigal E, Yarchoan R. The challenge