5.3.4 FDA ASSESSMENT OF SAFETY

The following safety assessment is from the Ligand MS ACCESS database (panel ADVERSE).

SEVERE SKIN ADVERSE EVENTS

Severe Skin Adverse events	International Phase 3 Study (ALRT1057-503)	
	Panretin Gel N=36 Pts.	Vehicle Gel N=46 Pts.
Severe, General 1st 12 wks	4 (11%)	2 (4%)
Severe At treatment site 1st 12 wks	2 (6%)	0 (0%)
Severe, General, Entire study	-	-
Severe At treatment site Entire study	-	-

ADVERSE EVENTS WITH AN INCIDENCE OF AT LEAST 5% AT THE APPLICATION SITE IN PATIENTS RECEIVING PANRETIN GEL IN BLINDED PHASE

Adverse event	International Phase 3 Study (ALRT1057-503)	
	Panretin Gel N=36 Pts. %	Vehicle Gel N=46 Pts. %
Rash	25	4
Pain	0	4
Pruritus	8	4
Exfoliative dermatitis	3	0
Skin disorder	0	0
Paresthesia	22	7
Edema	3	0

ADVERSE EVENTS WITH AN INCIDENCE OF AT LEAST 5% IN THE SKIN OF PATIENTS (APPLICATION SITE AND/OR NON-APPLICATION SITE) RECEIVING PANRETIN GEL IN BLINDED PHASE

Adverse event	International Phase 3 Study (ALRT1057-503)	
	Panretin Gel N=36 Pts.	Vehicle Gel N=46 Pts.
Rash	15 (42%)	6 (13%)
Pain	5 (14%)	8 (17%)
Pruritus	5 (14%)	2 (4%)
Exfoliative dermatitis	4 (11%)	0 (0%)
Skin disorder	3 (8%)	0 (0%)
Paresthesia	9 (25%)	5 (11%)
Edema	1 (3%)	8 (17%)
Infection	2 (6%)	2 (4%)

In addition, the following analyses were done.

Similar to Study -31, most of the adverse events, which were determined to be clinically significant, occurred at the site of application of the topical agent. In Study -503, study drug was applied to lesions twice a day in contrast to Study -31 in which study drug was applied four times a day. Forty-two percent (42%) of the panretin patients and 9% (4/46) vehicle patients had dose adjustments or discontinuations. Only 14% (5/36) of the panretin patients dose adjusted or discontinued therapy due to an adverse event in comparison to 7% (3/46) of the vehicle patients. Twenty-five percent (9/46) of the panretin patients and 4% (2/46) of the vehicle patients discontinued therapy due to personal reasons.

6. NON-PIVOTAL CLINICAL TRIALS: Kaposi's Sarcoma Trials (the results are taken from Ligand's meeting package dated 4/23/97).

STUDY #	# PTS AGE RANGE (MEAN) M/F	RESULTS PANRETIN (P) VEHICLE (V)	SAFETY
L1057-94-01T[68,69,70]	24 (40) 12/0	P 8/24 (33%) V 4/24 (17%)	See pooled results below
L1057-94-02T	16 (37) 8/0	P 8/16 (50%) V 2/16 (13%)	See pooled results below
L1057-94-04T	7 (35) 4/0	P 2/7 (29%) V 1/7 (14%)	See pooled results below
L1057-94-07T	2 27 1/0	P 0/2 V 0/2	See pooled results below
L1057T-21	32 (39) 16/0	P 3/32 (9%) V 3/32 (9%)	See pooled results below
L1057T-22	26 (39) 13/0	P 7/26 (27%) V 5/26 (19%)	See pooled results below
L1057T-24	3 38 1/0	P 2/3 (67%) V 1/3 (33%)	See pooled results below
L1057T-25	1 52 1/0	P 0/1 V 0/1	See pooled results below
L1057T-30	4 (41)	P 2/4 (50%) V 1/4	See pooled results below

[68] Phase I/II intrapatient control for this study and all the others in this table.
[69] US trial for this study and all the others in this table.
[70] Random:panretin, 0.05% v 0.1% bid, for this study and all the others in this table.

STUDY #	# PTS AGE RANGE (MEAN) M/F	RESULTS PANRETIN (P) VEHICLE (V)	SAFETY
Pooled safety data from above nine trials	2/0	(25%)	Median time on study: P 98 days (5-674) V 77 days (1-362) Rx limiting toxicity (dermal) P grade 2: 9/115 (8%) Grade 3: 13/115 (11%)[71] Grade 4: 1/115 Rash 84% Skin disorder 21% Skin dry 10% Skin ulceration 10%) Pruritus 8% Pain 25% Infection 11% Fever 9%

[71] Comparable to treatment limiting toxicity in Study -31

7. NON-PIVOTAL CLINICAL TRIALS IN OTHER CANCERS

STUDY #	RX	# PT AGE RANGE (Median) M/F	RESULTS	
L1057-94-05T and -03T[72,73] Mycosis fungoides	0.05% changed to 0.01%	7 - (67) 5/2	PR: 43% (3/7) by Physician's Global Assessment	5 pts: #6 episodes of grade 3 dermal irritation

APPEARS THIS WAY
ON ORIGINAL

[72] U.S. trial
[73] Phase 1-2 design

8. NON-PIVOTAL CLINICAL TRIALS[74] IN KAPOSI'S SARCOMA WITH **ORAL** PANRETIN

STUDY #	RX	# PT AGE RANGE (MEAN) M/F	RESULTS	
L1057-28	60 then 100 mg/m2/d	57 (40) 57/0	RR by ACTG on index lesions: 46% (12/26)	Adverse events: headache, dry skin, hyperlipids, alopecia, rash arthralgia, vasodilatation
AMC #002	60 then 100 mg/m2/d	66 (39) 66/0	RR by ACTG on index lesions: 36% (18/50)	Adverse events: 11 pts withdrew due to toxicity Grade 3-4:26% headache; inc. 13% triglycerides; alopecia, desquamation, & nail changes

APPEARS THIS WAY
ON ORIGINAL

[74] U.S. trials; Phase 2 design

9. SUMMARY

The following table summarizes the efficacy results in L1057T-31.

RESPONSE EFFICACY IN STUDY -31

DURING THE INITIAL BLINDED PHASE (12 WEEKS)

	PANRETIN	PLACEBO
Ligand Modified ACTG Response (6 index lesions)	47/134 (35%) 1 CR	24/134 (18%) p = 0.002
FDA Modified ACTG Response (6 index lesions)	46/134 (34%) 1 CR	22/134 (16%) p= 0.0012
Ligand Physician's Global Assessment (all rxed lesions)	26/134 (19%)	5/134 (4%) p = 0.00014
FDA Beneficial Response Photographs (index lesions only)	20/134 (15%)	5/134 (4%) p =0.0026
FDA *Beneficial Response Photographs (index lesions only)	23/134 (17%)	Not Applicable
Ligand *Patient's Overall Satisfaction with KS Lesion Drug Effect (all rxed lesions)	P=.0001 Favoring Panretin	

*Entire Study both Blinded Phase and Post Blinded Phase

The following table summarizes the efficacy results in ALRT 1057-503.

RESPONSE EFFICACY IN STUDY -503

DURING INITIAL BLINDED PHASE (12 WEEKS) INTERIM ANALYSIS

	PANRETIN	PLACEBO
Ligand Modified ACTG Response (index lesions only)	41.7% (15/36) 1 CR	6.5% (3/46) p=0.00027
FDA Modified ACTG Response Analysis (index lesions only)	39% (14/36) 0 CR	6.5% (3/46) (p=0.00062)
Ligand Physician's Subjective Assessment (all rxed lesions)	47% (17/36)	11% 5/46 (p=0.0003)
FDA Beneficial Response Photographs (index lesions only)	19% (7/36)	2.2% (1/46) (p=0.019)
Ligand Patient's Subjective Assessment (all rxed lesions)	47% (17/36)	11% (5/46)

The following tables summarize the safety results in pivotal trials L1057T-31 and ALRT 1057-503.

SEVERE SKIN ADVERSE EVENTS

Severe Skin Adverse events	North American Phase 3 Study (L1057-31)		International Phase 3 Study (ALRT1057-503)	
	Panretin Gel N=134 Pts.	Vehicle Gel N=134 Pts.	Panretin Gel N=36 Pts.	Vehicle Gel N=46 Pts.
Severe, General 1st 12 wks	16 (12%)	1 (1%)	4 (11%)	2 (4%)
Severe At treatment site 1st 12 wks	14 (10%)	0 (0%)	2 (6%)	0 (0%)
Severe, General, Entire study	19 (14%)	-	-	-
Severe At treatment site Entire study	18 (13%)	-	-	-

ADVERSE EVENTS WITH AN INCIDENCE OF AT LEAST 5% AT THE APPLICATION SITE IN PATIENTS RECEIVING PANRETIN GEL IN BLINDED PHASE OF EITHER PHASE 3 STUDY

Adverse event	North American Phase 3 Study (L1057-31)		International Phase 3 Study (ALRT1057-503)	
	Panretin Gel N=134 Pts. %	Vehicle Gel N=134 Pts. %	Panretin Gel N=36 Pts. %	Vehicle Gel N=46 Pts. %
Rash	77	17	25	4
Pain	34	7	0	4
Pruritus	11	4	8	4
Exfoliative dermatitis	9	2	3	0
Skin disorder	8	1	0	0
Paresthesia	3	0	22	7
Edema	8	3	3	0

ADVERSE EVENTS WITH AN INCIDENCE OF AT LEAST 5% IN THE SKIN OF PATIENTS (APPLICATION SITE AND/OR NON-APPLICATION SITE) RECEIVING PANRETIN GEL IN BLINDED PHASE OF EITHER PHASE 3 STUDY

Adverse event	North American Phase 3 Study (L1057-31)		International Phase 3 Study (ALRT1057-503)	
	Panretin Gel N=134 Pts.	Vehicle Gel N=134 Pts.	Panretin Gel N=36 Pts.	Vehicle Gel N=46 Pts.
Rash	105 (78%)	31 (23%)	15 (42%)	6 (13%)
Pain	59 (44%)	26 (19%)	5 (14%)	8 (17%)
Pruritus	17 (13%)	7 (5%)	5 (14%)	2 (4%)
Exfoliative dermatitis	13 (10%)	4 (3%)	4 (11%)	0 (0%)
Skin disorder	14 (10%)	4 (3%)	3 (8%)	0 (0%)
Paresthesia	8 (6%)	3 (2%)	9 (25%)	5 (11%)
Edema	25 (19%)	20 (15%)	1 (3%)	8 (17%)
Infection	8 (6%)	3 (2%)	2 (6%)	2 (4%)

The expected study population at the FDA-Ligand end of Phase 2 meeting was early KS with a small number of cutaneous lesions not severe enough to merit systemic chemotherapy. The actual population in the two pivotal randomized controlled trials has extensive KS and some patients have had prior systemic chemotherapy.

The NDA has complete information on only the marker lesions in each patient, although other lesions could be treated if desired.

The response rates with topical panretin are not comparable to the response rates produced with systemic therapy for a number of reasons. First, for systemic therapy, all lesions (or lesions in a selected region of the body) are counted and evaluated. For topical therapy, only a minimum of 6 lesions was required as index lesions—for evaluation of height and area

reductions.

Second, with systemic therapy, the appearance of new lesions often prevents a response from being declared, confirmed, or prolonged. New lesions are not considered progressive disease with topical therapy. In Study -31, in the total population of patients accrued, 131 patients (49%) developed new lesions since baseline. For the panretin responders, at least 22 (47%) developed new lesions during the trial. In contrast, in trials with systemic therapy, new lesions would have interfered with the declaration, confirmation, or prolongation of a response.

Progressive disease was scored only in the treated index lesions for panretin. Also, if nearly all the index lesions are raised at baseline, progressive disease by flat lesions becoming raised can not occur in trials of topical therapy

Fourth, in the panretin pivotal trials, progressive disease in the treated lesions was required to be confirmed in 4 weeks; systemic therapy for KS, approved by the FDA, did not have this requirement for progressive disease.

Overall, the response rate for panretin topical therapy is inflated when compared to the response rates for systemic therapy.

The tumor responses claimed by the Applicant in the two randomized controlled trials using Modified ACTG criteria are generally confirmed by the FDA based on the assessments of the index lesions recorded by the study Investigators. However, many of the responses, including some of the best responses (e.g., complete disappearance of lesions or decrease in area in addition to flattening), are not clear on the photographs. Any improvement in the KS lesions is sometimes obscured by the accompanying inflammation and edema induced by the panretin, which are far more unsightly than the initial KS lesion. When the inflammation and edema subside, the KS lesion may again be visible. It is difficult to score tumor response using photographs alone, but at the very least the failure of some of the best claimed tumor responses to be apparent on the photographs raises questions about whether some of the claimed tumor responses are beneficial to the patient.

In the randomized controlled trial 1057T-31 in the initial blinded phase on the panretin arm 47 responders are reported by

the Modified ACTG criteria. However, the Investigator's Global Response Assessment reports 26 responders which is in closer agreement with the FDA assessment of the photographs where 23 patients were found to have a cosmetically beneficial response at sometime during their panretin treatment. Although in Study -31, cosmetically beneficial response was 17%, grade 3 skin toxicity was 16% on panretin. A similar assessment based on photographs in the randomized controlled 1057-503 trial is more difficult because the quality of photographs for this study is poorer. Similarly, in Study -503, cosmetically beneficial response was 19% and severe skin toxicity was 11% on panretin.

Although an attempt was made to blind the two randomized controlled trial, panretin topical gel induces an erythematous area where it contacts the skin, frustrating the efforts at blinding. In Study 1057T-31, this may explain why only two of 38 patients who were randomized to panretin crossed-over to blinded vehicle in comparison to 15 of 32 patients who were randomized to vehicle crossed-over to blinded panretin.

10. The Results of the Oncology Drugs Advisory Committee

November 16, 1998

QUESTIONS TO THE COMMITTEE

1. Is Panretin Gel effective for first-line topical treatment of cutaneous lesions in patients with AIDS-related Kaposis sarcoma?

The Committee advised removing the words "first-line" from the proposed indication, due to concerns that this topical treatment might be automatically chosen when a systemic therapy would be more appropriate. The re-worded question was:

> 1. Is Panretin Gel effective for topical treatment of cutaneous lesions in patients with AIDS-related Kaposis sarcoma?

The vote was:

Yes - 8 No - 1

2. Is the safety of Panretin Gel acceptable in view of its efficacy and in view of available alternative treatments?

The vote was:

Yes - 8 No - 1

3. Is this Panretin Gel NDA approvable?

The Committee agreed with the Open Public Hearing speakers that the psychological and aesthetic considerations were important and felt that there is a niche for this drug when the patient is adverse to the cytotoxicity of a systemic therapy, or in conjunction with systemic therapy. The Committee recommended that the labeling be explicit in stating that Panretin lacks systemic absorption and effects, and is not a treatment for visceral disease.

The vote was:

Yes - 8 No - 1

4. If so, should the Cosmetically Beneficial Response rate based on photographs be included in the package insert?

The Committee would like to see the cosmetically beneficial rate tables included in the package insert so that each patient and doctor may make an informed decision in the use of this drug.

The vote was:

Yes - 9 No - 0

APPEARS THIS WAY
ON ORIGINAL

11. RECOMMENDATION

Two well-controlled, double-blind, randomized trials, demonstrating the efficacy and safety of Panretin gel (0.1%) for topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma have been submitted and reviewed. Based on this review, NDA 20-886 is clinically approvable for treatment of cutaneous lesions in AIDS-related Kaposi's sarcoma for whom systemic therapy is not indicated, conditional on inclusion of the cosmetically beneficial response assessment in the labeling, as unanimously recommended by the Advisory Committee. Tumor assessment by other criteria exaggerates the benefit of the drug. For example, the Physician's Global assessment and the Physician's Subjective Assessment focus only on the KS lesions and ignore the often considerable skin toxicity adjacent to the KS lesions. Approval is also conditional on satisfactory resolution of Chemistry and Manufacturing Deficiencies and satisfactory resolution of labeling issues from chemistry, pharmacology/toxicology, biopharmaceutics, biometrics, and medical disciplines.

/S/

ROBERT M. WHITE, JR., MD, FACP
November 24, 1998

/S/ 11-24-98

CC:
NDA #20-886
HFD-150/DIV FILE
HFD-150/RWHITE
HFD-150/A CHAPMAN CSO
HFD-340
HFD-150

MEDICAL OFFICER REVIEW

120-DAY SAFETY UPDATE
Received Sept. 25, 1998

NDA 20-886

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

SPONSOR Ligand Pharmaceuticals Inc.
San Diego, CA 92121

The safety update covers patients treated in panretin trials through 7/6/98. The NDA provided safety data from 435 patients in 11 clinical trials. The Safety Update provides additional follow up of patients from Study -31 and Study -503. Safety data, from 151 new patients in clinical trials not included in the NDA (i.e., Studies -503 and -504), was also provided. The incidence of the adverse events is similar to the information provided in the NDA submission and does not appear different than the already reviewed safety profile for panretin except for a higher incidence of rash, pain, and pruritus at the application site in Study -503. The information in the Safety Update does not reveal any new kinds of adverse events when compared to the data reviewed in the NDA.

/S/

ROBERT M. WHITE, JR., MD, FACP
November 24, 1998

/S/ 11-24-98

CC:
NDA #20-886
HFD-150/DIV FILE
HFD-150/RWHITE
HFD-150/A CHAPMAN CSO
HFD-340
HFD-150

DIVISION OF ONCOLOGY DRUG PRODUCTS
Original NDA Review of Chemistry, Manufacturing, and Controls

NDA #: 20-886 CHEMISTRY. REVIEW #: 4 REVIEW DATE: January 19, 1999

SUBMISSION TYPE	DOC. DATE	CDER DATE	ASSIGNED DATE
Original	May 26, 1998	May 27, 1998	June 3, 1998
Amendment (BC)	December 21, 1998	December 22, 1998	January 4, 1999
Amendment (BL)	January 11, 1999	January 12, 1999	January 14, 1999
Amendment (BC)— Fax	January 11, 1999		January 12, 1999
Amendment (BC)— Fax	January 13, 1999		January 14, 1999

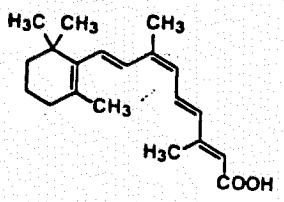
NAME & ADDRESS OF APPLICANT: Ligand Pharmaceuticals Inc.
10275 Science Center Drive
San Diego, CA 92121-1117

DRUG PRODUCT NAME:
Proprietary: Panretin® (Alitretinoin) Gel 0.1%
Nonproprietary/USAN: Alitretinoin (This name was adopted by the USAN Council, see a copy dated 3/25/98 attached)
Common Name: 9-cis-Retinoic acid
Code Name/Number: ALRT1057, LGD1057, LG100057, AGN192013
Chem. Type/Ther. Class: 1P

PHARMACOL. CATEGORY/INDICATION: AIDS-related Kaposi's Sarcoma
DOSAGE FORM: Topical Gel
STRENGTHS: 0.1%
ROUTE OF ADMINISTRATION: Topical Only
DISPENSED: _x_ Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

CAS Name: 9-cis-Retinoic acid
IUPAC Name: (2E, 4E, 6Z, 8E)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid
Common Name: 9-cis-Retinoic acid
CAS Number: 5300-03-8
Code Number: ALRT 1057, LGD 1057, LG100057, AGN 192013, NSC 659772
M.F.: $C_{20}H_{28}O_2$
M.W.: 300.44



SUPPORTING DOCUMENTS:
INDs: IND

DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Notes
		11/4/98	USP amber glass bottles (Soda Lime Amber Glass Containers)	Adequate	6/9/93 (HFD-635)	Found acceptable for USP Type & molded glass vials.
		11/5/98	Green Urea Screw Cap lined with	Adequate	1/19/99 (HFD-150)	Urea-formaldehyde resin is compliant with 21CFR 177.1900.
		2/11/98	Collapsible aluminum tubes lined with	Adequate	3/22/95 and 10/4/96 (HFD-540)	Internal coating is epoxy material (lacquer) which complies with 21CFR 175.300 resinous and polymeric coatings

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Notes
		11/6/98	White screw cap with spike made from polypropylene resin	Adequate	1/23/95 (HFD-643), 4/15/96 (HFD-170)	Certificate states that screw cap lot# 27390 complies with the current closure specifications for Polypropylene is compliant with 21CFR 177.1520 Olefin Polymers

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:

EER for **submitted on acceptable for , acceptable for , acceptable for , acceptable for**

Trademark "Panretin" consultation **on 7/15/98, Acceptable with some concerns (E-mail dated 11/16/98)**

Micro consultation, **not applicable**

Environmental assessment, **exemption is requested. Granted.**

Stability data consultation, **initiated on 10/1/98, completed on 11/4/98, 2nd request on 11/18/98, Completed on 12/7/98 and 12/21/98.**

Method validation **will be initiated after satisfactory response to deficiencies regarding method validation.**

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

Responses submitted in the minor amendments of 12/21/98, 1/11/99, and 1/13/99 were found to be adequate. Approval of this NDA 20-886 is recommended from CMC standpoints. Please include the CMC comments on the last page of this review in an approval letter to be prepared.

/S/

Sung K. Kim, Ph.D.,
Review Chemist, HFD-150

cc:
Orig. NDA 20-886
HFD-150/Division File
HFD-150/CSO/AChapman
HFD-150/SKim
HFD-150/RWood
R/D Init. by: /S/ 1-19-99

filename: N20886.or3