DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

JUN 28 2000

Howard T. Holden, Ph.D.
Vice President
Regulatory Affairs and Compliance
Ligand Pharmaceuticals, Inc.
10275 Science Center Drive
San Diego, CA 92121-1117

RE: NDA 21-055
Targretin® (bexarotene) capsules
MACMIS ID# 9044

Dear Dr. Holden:

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified certain promotional materials for Targretin by Ligand Pharmaceuticals (Ligand) that are in violation of the Federal Food, Drug, and Cosmetic Act (the Act). Specifically, we refer to Ligand's convention panels for Targretin that were used at the 36th Annual American Society of Clinical Oncology (ASCO) Meeting in New Orleans on May 20-23, 2000. These panels (TAR123A-LIG) were submitted under cover of Form FDA 2253 on June 9, 2000.

Misleading Efficacy Claims

These convention panels display before/after photos of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL), as well as headers that claim "all-stage efficacy" and "proven tumor regression at all stages of CTCL." All of the photos depict patients who had favorable responses to Targretin. However, given the 1.6% complete response and 30% partial response of the 62 patients in the clinical studies, the photos and claims are misleading since many patients did not achieve such favorable results. Targretin therapy produces various individual responses on cutaneous lesions; while one lesion may improve, others may worsen. The overwhelming impression that all lesions will improve is misleading because it implies greater effectiveness than demonstrated by substantial evidence. In addition, your presentation of text about tumor response rates does not overcome the misleading impression created by the photos and claims.

Lack of Fair Balance

Promotional materials are lacking in fair balance if they fail to present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug, taking into account all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis. The convention panels lack fair balance because efficacy information is prominently presented with colors, photos, and enlarged fonts while risk information is presented as paragraphed text at the bottom of the panel.

Failure to Comply with 314.81(b)(3)(i)

Since the convention panels were not submitted on Form FDA 2253 at the time of initial dissemination, Ligand has violated the post-marketing reporting requirements of the Act.

Conclusions and Requested Actions

We acknowledge your letter that accompanied the aforementioned Form FDA 2253 submission, which stated that Ligand has discontinued use of the convention panels and does not intend to use them again. Ligand should immediately cease dissemination of all other promotional materials that contain these or similar claims. Ligand should submit in writing, on or before July 12, 2000, a description of the steps that will be taken to comply with the above request. Ligand should also include a list of all similarly violative materials being discontinued, as well as the date of discontinuation.

Ligand should direct its response to me by facsimile at (301) 594-6771, or by written communication at the Food and Drug Administration; Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS ID# 9044 and NDA 21-055.

Sincerely,

/S/

Jean-Ah Choi, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

AN INNOVATION FOR PATIENTS
WITH CUTANEOUS T-CELL LYMPHOMA (CTCL)
REFRACTORY TO PRIOR SYSTEMIC THERAPY

Targretin®
(bexarotene) capsules

Please see full prescribing information available at Targretin.com

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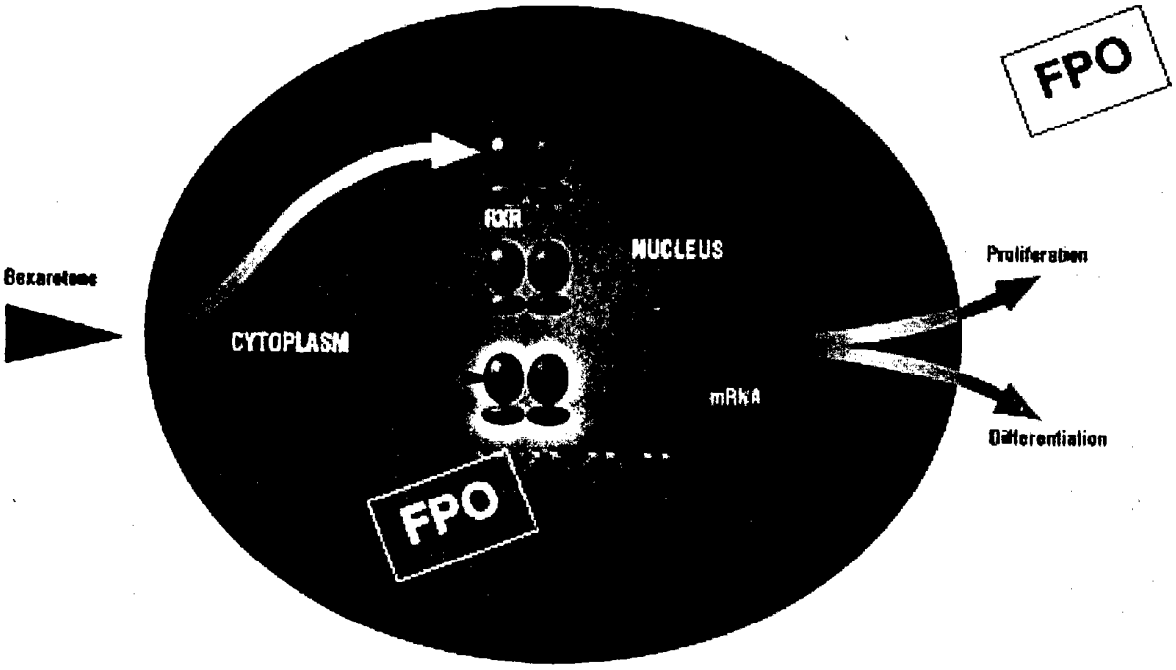
LIGAND®

TAR1334-UC

FOR CUTANEOUS MANIFESTATIONS
OF CUTANEOUS T-CELL LYMPHOMA (CTCL) IN PATIENTS
REFRACTORY TO AT LEAST 1 PRIOR SYSTEMIC THERAPY

ALL-STAGE REXINOID

SELECTIVELY BINDS AND ACTIVATES RXR SUBTYPES



Blood lipid determinations should be done before starting therapy, weekly until the lipid response is established (usually 2–4 weeks), and at 8-week intervals thereafter. Fasting triglycerides should be normal prior to initiating therapy with TARGRETIN Capsules. A white blood cell count with differential should be obtained at baseline and periodically during treatment; liver function tests should be performed at baseline, after weeks 1, 2, and 4, and, if stable, at 8-week intervals thereafter. Baseline thyroid function tests should be obtained and then monitored during treatment. Treatment with thyroid supplements should be considered in patients with laboratory evidence of hypothyroidism. TARGRETIN Capsules should be used only with great caution in patients with hepatic insufficiency. Bexarotene is metabolized by cytochrome P450 3A4 (please see prescribing information for precaution). Lopid®†(gemfibrozil) should not be administered with TARGRETIN.

Targretin® capsules are a member of the retinoid class of drugs that is associated with birth defects in humans. Targretin® capsules also caused birth defects when administered orally to pregnant rats. Targretin® capsules must not be administered to a pregnant woman. See CONTRAINDICATIONS.

Please see full prescribing information available at this exhibit

†Lopid® is a registered trademark of Parke-Davis, a division of Warner-Lambert

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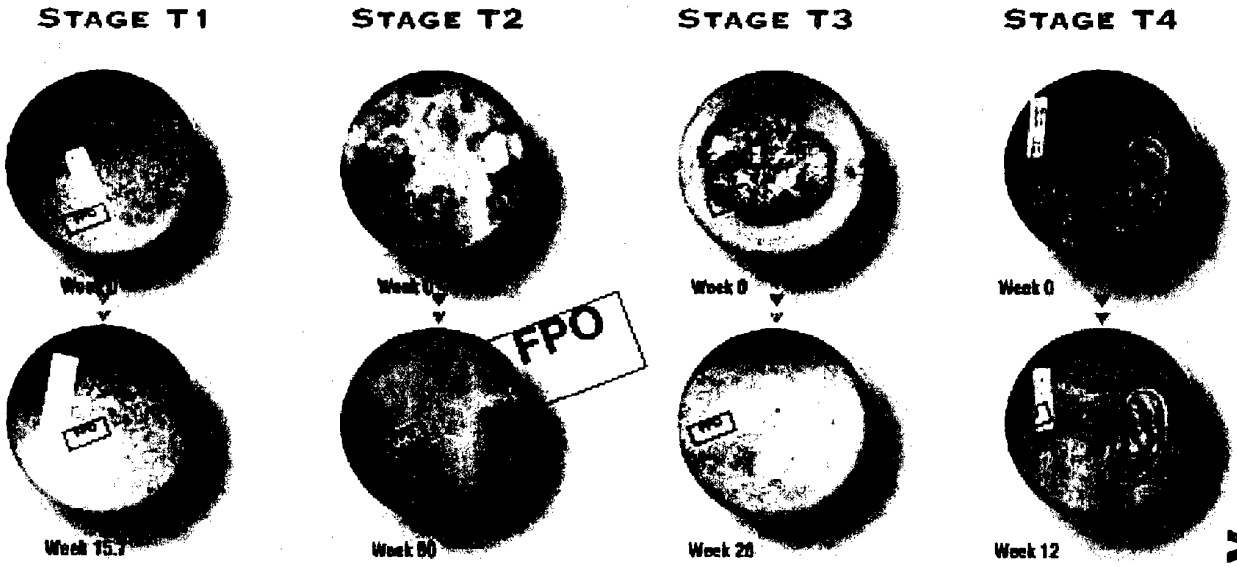
LIGAND® PHARMACEUTICALS

TAR123A-LIG

BEST POSSIBLE COPY

FOR CUTANEOUS MANIFESTATIONS
OF CUTANEOUS T-CELL LYMPHOMA (CTCL) IN PATIENTS
REFRACTORY TO AT LEAST 1 PRIOR SYSTEMIC THERAPY

ALL-STAGE EFFICACY



PROVEN TUMOR REGRESSION AT ALL STAGES OF CTCL

- Extensively evaluated in 2 international, multicenter trials of 152 CTCL patients at every stage of CTCL—62 patients received 300 mg/m²/day and had CTCL refractory to at least 1 prior systemic therapy
- 30% (19/62) of patients had a partial tumor response, and 2% (1/62) of patients had a complete clinical response according to Composite Assessment of Index Lesion Disease Severity
- Responses were seen as early as 4 weeks, and new responses continued to be seen at later visits

The safety of TARGRETIN was evaluated in 152 CTCL patients who received TARGRETIN for up to 97 weeks. The most commonly observed adverse reactions in patients receiving the recommended dose of TARGRETIN were hypertriglyceridemia (78.6%), hypercholesterolemia (32.1%), headache (29.8%), hypothyroidism (28.6%), and asthenia (20.2%). Pancreatitis associated with marked elevations of fasting serum triglycerides (≥770 mg/dL) was reported in 4 patients with CTCL and in 6 patients with advanced non-CTCL cancer. Reversible leukopenia (mostly neutropenia) was seen in 18% of CTCL patients.

Please see full prescribing information outside of this ad.

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LIGAND PHARMACEUTICALS

TAR123AA1G

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