DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Henry Blissenbach
President and Chief Executive Officer
Ligand Pharmaceuticals Inc.
10275 Science Center Drive
San Diego, CA 92121

Re: BLA 103767 & NDA #21-055
ONTAK® (denileukin diftitox)
Targretin® (bexarotene) capsules
MACMIS # 14512

WARNING LETTER

Dear Mr. Blissenbach**:**

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional Cutaneous T-Cell Lymphoma Case Study [ONT212-LIG] for ONTAK® (denileukin diftitox) submitted by Ligand Pharmaceuticals Inc. [Ligand] under cover of Form FDA 2253. This promotional piece also includes claims for Ligand's Targretin® (bexarotene). DDMAC has concluded that the promotional piece is false or misleading because it omits and minimizes risks for Ontak and Targretin, overstates the effectiveness of Ontak and Targretin, and broadens the indication for both drugs. The case study thus misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & 321(n). In addition, it appears that the FDA approved product labeling (PI) for Targretin did not accompany the promotional piece, in violation of 21 CFR 201.100(d). This promotional material raises significant public health and safety concerns because it suggests that Ontak and Targretin are safer and more effective than has been demonstrated by substantial evidence or substantial clinical experience, and that Ontak is superior to other treatments for cutaneous T-cell lymphoma.

Background

Ontak (Denileukin Diftitox)

Ontak was approved under the Subpart E (accelerated approval) regulations in accordance with 21 CFR 601.41. According to the Indications section of the PI, "Ontak is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor. The safety and efficacy of denileukin diftitox in patients with CTCL whose malignant cells do not express the CD25 component of the IL-2 receptor have not been examined."

The PI for Ontak includes the following Boxed Warning:

BOXED WARNING

WARNING: Only physicians experienced in the use of antineoplastic therapy and management of patients with cancer should use ONTAK (denileukin diftitox). Patients treated with denileukin diftitox must be managed in a facility equipped and staffed for cardiopulmonary resuscitation and where the patient can be closely monitored for an appropriate period based on his or her health status.

The PI also states that Ontak is associated with the following risks outlined in the Warnings, Precautions and Adverse Events sections of the PI (in pertinent part):

WARNINGS

Acute Hypersensitivity-type Reactions: Acute hypersensitivity reactions were reported in 98 of 143 patients (69%) during or within 24 hours of ONTAK infusion; approximately half of the events occurred on the first day of dosing regardless of the treatment cycle. The constellation of symptoms included one or more of the following, defined as the incidence (%) in these 98 patients: hypotension (50%), back pain (30%), dyspnea (28%), vasodilation (28%), rash (25%), chest pain or tightness (24%), tachycardia (12%), dysphagia or laryngismus (5%), syncope (3%), allergic reaction (1%) or anaphylaxis (1%). These events were severe in 2% of patients. Death during infusion has been reported.

Vascular Leak Syndrome: This syndrome, characterized by 2 or more of the following 3 symptoms (hypotension, edema, hypoalbuminemia) was reported in 27% (38/143) of patients in the clinical studies. Six percent (8/143) of patients were hospitalized for the management of these symptoms. The onset of symptoms in patients with vascular leak syndrome was delayed, usually occurring within the first two weeks of infusion; symptoms may persist or worsen after the cessation of denileukin diftitox. Cases of vascular (capillary) leak with a fatal outcome have been reported. Special caution should be taken in patients with preexisting cardiovascular disease.

Visual Loss: Loss of visual acuity, usually with loss of color vision, with or without retinal pigment mottling has been reported following administration of ONTAK. Recovery was reported in some of the affected patients; however, most patients reported persistent visual impairment.

PRECAUTIONS

General: Patients should be monitored carefully for infection since patients with CTCL have a predisposition to cutaneous infection. Also, the binding of denileukin diftitox to activated lymphocytes and macrophages can lead to cell death and may impair immune function in patients.

Laboratory Tests: Eighty-three percent (118/143) of patients with lymphoma experienced hypoalbuminemia, which was considered moderate or severe in 17% (20/118) of the affected patients.

ADVERSE REACTIONS

The Ontak PI states, "All patients experienced one or more adverse events. Twenty-one percent (30/143) of patients required hospitalization for drug-related adverse events. . . . Five percent of clinical adverse reactions were severe or life-threatening."

The most commonly reported adverse events associated with the use of Ontak therapy include chills/fever (81%), asthenia (66%), infection (48%), pain (48%), hypotension (36%), nausea/vomiting (64%), anorexia (36%), hypoalbuminemia (83%), transaminase increase (61%), edema (47%), and rash (34%). In addition, the Adverse Reactions section of the Ontak PI describes infectious complications (in 48% [69/143] of the study population, of which 23% [16/69] were considered severe), infusion-associated reactions which included an acute hypersensitivity-type symptom complex (experienced by 69% of patients) and a flu-like symptom complex (experienced by 91% of patients), as well as gastrointestinal, rash, and cardiovascular system adverse events. Finally, patients reported the following hematologic and lymphatic adverse events (All grades/grade 3 and 4): anemia (18%/6%), thrombocytopenia (8%/2%), and leukopenia (6%/3%).

Targretin (Bexarotene)

The case study also includes claims for Targretin (bexarotene) capsules. According to the approved product labeling, Targretin is indicated "for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy."

Treatment with Targretin is also associated with the following risks outlined in the Boxed Warning, Warnings, Precautions and Adverse Events sections of the PI (in pertinent part):

BOXED WARNING

> 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.

CONTRAINDICATIONS

Pregnancy: Category X: Targretin (bexarotene) capsules may cause fetal harm when administered to a pregnant woman. Targretin capsules must not be given to a pregnant woman or a woman who intends to become pregnant. If a woman becomes pregnant while taking Targretin capsules, Targretin capsules must be stopped immediately and the woman given appropriate counseling.

WARNINGS

Lipid abnormalities: Targretin capsules induce major lipid abnormalities in most patients. These must be monitored and treated during long term therapy. About 70% of patients with CTCL who received an initial dose of ≥300 mg/m^2/day of Targretin capsules had fasting triglyceride levels greater than 2.5 times the upper limit of normal. About 55% had values over 800 mg/dL with a median of about 1200 mg/dL in those patients. Cholesterol elevations above 300 mg/dL occurred in

approximately 60% and 75% of patients with CTCL who received an initial dose of 300 mg/m^2/day or greater than 300 mg/m^2/day, respectively. Decreases in high density lipoprotein (HDL) cholesterol to less than 25 mg/dL were seen in about 55% and 90% of patients receiving an initial dose of 300 mg/m^2/day or greater than 300 mg/m^2/day, respectively, of Targretin capsules. The effects on triglycerides, HDL cholesterol, and total cholesterol were reversible with cessation of therapy, and could generally be mitigated by dose reduction or concomitant antilipemic therapy.

Pancreatitis: Acute pancreatitis has been reported in four patients with CTCL and in six patients with non-CTCL cancers treated with Targretin capsules; the cases were associated with marked elevations of fasting serum triglycerides. . . . One patient with advanced non-CTCL cancer died of pancreatitis.

Liver function test abnormalities: For patients with CTCL receiving an initial dose of 300 mg/m^2/day of Targretin capsules, elevations in liver function tests (LFTs) have been observed in 5% (SGOT/AST), 2% (SGPT/ALT), and 0% (bilirubin). In contrast, with an initial dose greater than 300 mg/m^2/day of Targretin capsules, the incidence of LFT elevations was higher at 7% (SGOT/AST), 9% (SGPT/ALT), and 6% (bilirubin). Two patients developed cholestasis, including one patient who died of liver failure.

Thyroid axis alterations: Targretin capsules induce biochemical evidence of or clinical hypothyroidism in about half of all patients treated, causing a reversible reduction in thyroid hormone (total thyroxin [total T4]) and thyroid-stimulating hormone (TSH) levels.

Leukopenia: A total of 18% of patients with CTCL receiving an initial dose of 300 mg/m^2/day of Targretin capsules had reversible leukopenia in the range of 1000 to <3000 WBC/m^3. Patients receiving an initial dose greater than 300 mg/m^2/day of Targretin capsules had an incidence of leukopenia of 43%.

PRECAUTIONS

Drug-Drug Interactions: Concomitant administration of Targretin capsules and gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene . . . Concomitant administration of gemfibrozil with Targretin capsules is not recommended.

ADVERSE REACTIONS

The most commonly reported adverse events associated with the use of Targretin therapy include hyperlipemia, hypercholesteremia, headache, asthenia, hypothyroidism, leukopenia and diarrhea. In addition, the Adverse Reactions section of the Targretin PI describes hypertriglyceridemia, pruritus, headache, peripheral edema, leukopenia, rash and hypercholesteremia as moderately severe (NCI grade 3) and severe (NCI grade 4) adverse events.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made in the materials or with respect to the consequences that may result from the use of the drug as recommended or suggested in the materials. The promotional material presents several

treatment options for a patient portrayed in a hypothetical case study. Citing support from polled attendants at a Ligand advisory board meeting, the promotional piece indicates that 77% of physicians polled would treat the case study patient with Ontak. The case study does not discuss outcome details following treatment. The piece presents the following effectiveness and safety claims for Ontak and Targretin:

- Denileukin diftitox (DAB_{389}IL-2, ONTAK®) is approved by the FDA for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor.
- A phase III study of denileukin diftitox was completed in patients with CTCL, whose tumors expressed the IL-2R as determined by immunohistochemical staining. . . . The overall response rate was 30%, with CR occurring at both dose levels. A slightly higher response rate was seen in patients who received the higher dose.
- Oral bexarotene (Targretin®) has been approved by the FDA for use in all stages of refractory mycosis fungoides and has a response rate of 45% in patients with CTCL.

However, the piece fails to include any risk information for Ontak, and the most serious and frequently occurring risks for Targretin, including risks from the Boxed Warnings, Warnings, Precautions, and Adverse Reactions sections of the PIs. Therefore, the case study misleadingly suggests that Ontak and Targretin are safer than has been demonstrated by substantial evidence or substantial clinical experience.

Not only does the piece fail to communicate any risks associated with Ontak therapy, but it also presents claims that minimize the risks associated with Ontak use. For example, the case study states, "For this patient, denileukin diftitox was chosen particularly for its lack of myelosuppression…," and "Denileukin diftitox is generally well tolerated. . . ." This first claim is particularly problematic as myelosuppression is a type of hematologic adverse event, and Table 2 in the Adverse Reactions section of the PI provides the following information for hematologic and lymphatic risks for all grades (n [%]) and grades 3 and 4 (n [%]), respectively: anemia (26 [18%], 9 [6%]), thrombocytopenia (12 [8%], 3 [2%]), and leukopenia (9 [6%], 4 [3%]). Moreover, the term "generally well tolerated" is not appropriate for drugs associated with frequent and serious adverse events, such as this product. As outlined in the background section above, the PI for Ontak includes a boxed warning as well as numerous other serious warnings, including acute hypersensitivity-type reactions, vascular leak syndrome, and visual loss. The PI also outlines precautions for impaired immune function, and hypoalbuminemia, and adverse events that occur in a very high proportion of patients (e.g., hypoalbuminemia (83%), chills/fever (81%), asthenia (66%), nausea/vomiting (64%), transaminase increase (61%), infection (48%), pain (48%), edema (47%), hypotension (36%), anorexia (36%), and rash (34%)). Of note, twenty-one percent of patients required hospitalization following a drug-related adverse event, and five percent of all adverse reactions were severe or life-threatening. The Ontak PI states that "All patients experienced one or more adverse events." Given these risks associated with therapy, the claims of a "lack of myelosuppression," and that the drug is "generally well tolerated," are misleading.

Similarly, the promotional piece limits the risk presentation for Targretin to the following, "Hypertriglyceridemia, the most common adverse event, occurs in 80% of treated patients. . . . Targretin at a dose of 300 mg/m^2/day is likely to increase her triglycerides. If there were time to control her triglycerides with a statin, then Targretin would be an option. This patient, however, is in need of treatment immediately since her symptoms are significant enough to keep her home bound."

As outlined in the background section above, the labeling for Targretin includes a boxed warning and contraindication for use in pregnant women. The drug is also associated with a number of other serious risks, and its labeling includes warnings and precautions related to lipid abnormalities (triglyceride and total cholesterol elevations, HDL cholesterol decreases), pancreatitis, liver function test abnormalities, thyroid axis alterations, leukopenia and drug-drug interactions with concomitant administration of gemfibrozil.

Overstatement of Effectiveness

The piece overstates the demonstrated effectiveness of Ontak therapy. Specifically, the piece claims, "Symptomatic relief is seen in about 60% of patients." The reference[1] cited, however, does not demonstrate that 60% of patients studied experienced symptomatic relief. First, the reference cited, which presents data from an open-label, two-arm, parallel, dose comparison study, does not include any study endpoint assessing "symptomatic relief." The only possible measure of symptomatic relief was a secondary endpoint of patient-assessed severity of pruritus. An improvement in pruritus cannot be equated with overall "symptomatic relief," as it is not the only symptom. Second, even if improvement in pruritus could be equated with symptomatic relief, in the referenced study, only 51% of patients receiving Ontak therapy demonstrated an improvement in patient-reported pruritus (36/71). Eighteen patients (25%) had no change in pruritus, as they did not have significant baseline symptoms of pruritus. The remaining 17 patients (24%) continued to have persistent significant pruritus. Thus, the cited reference does not substantiate the claim that, "Symptomatic relief is seen in about 60% of patients." If you have data to substantiate this claim, please submit them to FDA for review.

The piece also overstates the demonstrated effectiveness of Targretin, claiming Targretin "has a response rate of 45% in patients with CTCL." No reference is cited in support of this claim. However, the PI states, "At the initial dose of 300 mg/m^2/day, 1/62 (1.6%) of patients had a complete clinical tumor response and 19/62 (30%) of patients had a partial tumor response." DDMAC is not aware of substantial evidence to support a response rate of 45%. If you have data supporting this response rate, please submit it to FDA for review.

Broadening of Indication

The case study fails to present a major limitation to the use of Ontak—that it is only indicated for patients whose malignant cells express the CD-25 component of the IL-2 receptor—suggesting it is safe and effective for use in a broader population of patients. The "CASE" description states, "A 53-year-old woman has recently moved into your area and seeks your opinion regarding further treatment options for cutaneous T-cell lymphoma. Two years ago she was diagnosed with Sézary syndrome (SS)." Laboratory findings for the patient include, "lymphocytes to be 90% CD4 positive, 3% CD7 positive." The presentation fails to indicate whether the patient's malignant cells express the CD25 component of the IL-2 receptor. Only a subset of patients with CTCL express the CD25 component of the IL-2 receptor, and patients with SS—a form of CTCL—are no more likely than other patients with manifestations of CTCL to exhibit the CD25 component of the IL-2 receptor. For the physician to determine the appropriateness of Ontak therapy, the patient would require immunophenotyping to confirm the presence of CD25 components on the IL-2 receptor. The labeling specifically points out

[1] Olsen et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol*. 2001;19 (2): 376-388.

that "[t]he safety and efficacy of denileukin diftitox in patients with CTCL whose malignant cells do not express the CD25 component of the IL-2 receptor have not been examined."

The piece also misleadingly implies that Targretin is safe and effective for use in a broader population and under broader conditions than have been demonstrated by substantial evidence. The piece claims, "Oral bexarotene (Targretin) has been approved by the FDA for use in **all stages** of refractory mycosis fungoides and has a response rate of 45% in patients with CTCL" (emphasis added). This presentation misleadingly broadens the indication for Targretin by failing to communicate important limitations in the approved indication. As stated in the Indications and Usage section of the PI, Targretin is "…indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory **to at least one prior systemic therapy**" (emphasis added). Patients with earlier stages of mycosis fungoides are often treated with non-systemic therapies such as topical corticosteroids, topical retinoids, and locally applied topical chemotherapy such as mechlorethamine. Therefore, not all prior therapies constitute systemic therapies, which are the only therapies that render patients appropriate for Targretin treatment. By failing to adequately communicate Targretin's approved indication, the case study misleadingly broadens Targretin's indication.

Misleading Treatment Selection Presentation

Of additional concern, the promotional piece includes the following physician response table and summary claim.

- RESPONSES FROM OTHER COMMUNITY AND ACADEMIC HEMATOLOGISTS / ONCOLOGISTS

CHOP	8%
Total body electron Beam radiotherapy	15%
Pentostatin	0%
Diphtheria-IL2 fusion toxin (ONTAK)	77%
Methotrexate	0%
Other	0%

- Seventy-seven percent of community and academic hematologists and oncologists participating in a recent review of this case study selected denileukin diftitox (DAB_{389}IL-2, ONTAK®) as the treatment they would most likely administer to this patient.

According to the promotional piece, these data arose from physician treatment selections that were generated in response to "a recent review of this case study" (page 4). As detailed in the letter, the hypothetical case study presented in the promotional piece is misleading for multiple reasons, notably in failing to present evidence that the tumor cells expressed the CD-25 component of the IL-2 receptor. Without this information, selection of Ontak as the treatment of choice by physicians is uninformed.

Conclusion and Requested Action

For the reasons discussed above, the promotional piece is false or misleading in that it omits and minimizes risks for Ontak and Targretin, overstates the effectiveness of Ontak and Targretin, and broadens the indication for both drugs. Therefore, it misbrands the drug in violation of the Act. See

§§ 21 U.S.C. 352(a) & 321(n). Furthermore, it appears that the PI for Targretin did not accompany the booklet, as required by 21 CFR 201.100(d).

DDMAC requests that Ligand immediately cease the dissemination of violative promotional material for Ontak and Targretin such as that described above. Please submit a written response to this letter on or before November 6, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Ontak and Targretin such as that described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-796-9877. In all future correspondence regarding this matter, please refer to MACMIS ID # 14512 in addition to the BLA and NDA numbers. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Ontak and Targretin comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, RPh, MBA
Director
Division of Drug, Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams

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