CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21055

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

Submission: NDA 21-055
Submission Date: June 22, 1999
Drug Name: Targretin® (bexarotene)
Dosage Form: 75 mg soft gelatin capsule
Applicant: Ligand Pharmaceuticals, Inc.
Submission Type: 1P
Reviewer: Gene M. Williams, Ph.D.

This review is performed to determine if the Clinical Pharmacology and Biopharmaceutics data submitted in NDA 21-055 allows Targretin® to be dosed to provide effective and safe therapy.

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I. Synopsis and regulatory recommendations

I.A. Synopsis

The applicant seeks approval for Targretin® (bexarotene) 75 mg soft gealtin capsules for the treatment of patients with cutaneous T-cell lymphoma (CTCL IA-IVB).

There are no bioequivalence issues with this application. Release rate data (dissolution) has been included in the submission and the applicant proposes the following dissolution specification:

	Tier 1	Tier 2
Apparatus Type	Type 2	Type 2
Media		
Volume		
Speed of rotation		
Sampling Times		
Description of Analytical Method		
Recommended Dissolution Specification		

HDTMA = hexadecyltrimethylammonium bromide

Since all lots of drug tested for dissolution in the past 3 years have passed the following specification at the time of manufacture, we recommend the following specification:

	Tier 1	Tier 2
Apparatus Type	Type 2	Type 2
Media		
Volume		
Speed of rotation		
Sampling Times		
Description of Analytical Method		
Recommended Dissolution Specification		

HDTMA = hexadecyltrimethylammonium bromide

The applicant has not performed Mass Balance, Dose Proportionality, Special Population or Drug Drug Interaction studies. Although the elimination of bexarotene is not well-described, the best available evidence suggests that the drug is a CYP 3A4 substrate and is eliminated and excreted through hepato-biliary mechanisms.

We are requesting the following Phase IV commitments of the applicant:

1. Please commit to conducting a Phase IV drug-drug interaction study, in patients or healthy subjects (sampling of sufficient frequency to describe potential multi-exponential pharmacokinetics and of sufficient duration to describe elimination half-life), characterizing the pharmacokinetics of bexarotene when ketoconazole is co-adminstered with Targretin®.

2. Please commit to conducting Phase IV *in vitro* studies to determine the inhibition potential of bexarotene on cytochrome enzymes. The results of these studies may indicate that it is necessary to perform subsequent *in vivo* drug interaction studies. The applicant need agree to perform these *in vivo* studies if CDER review of the *in vitro* data indicates that such studies are essential.

We are requesting significant alterations to the package insert – see I.C. below.

We have made a number of recommendations for further study to the applicant – see I.D. below.

I.B. Dissolution specification

	Tier 1	Tier 2
Apparatus Type	Type 2	Type 2
Media		
Volume		
Speed of rotation		
Sampling Times		
Description of Analytical Method		
Recommended Dissolution Specification		
HDTMA = hexadecyltrimethylammonium bromide		

I.C. Phase IV commitments

1. Please commit to conducting a Phase IV drug-drug interaction study, in patients or healthy subjects (sampling of sufficient frequency to describe potential multi-exponential pharmacokinetics and of sufficient duration to describe elimination half-life), characterizing the pharmacokinetics of bexarotene when ketoconazole is co-adminstered with Targretin®.

2. Please commit to conducting Phase IV *in vitro* studies to determine the inhibition potential of bexarotene on cytochrome enzymes. The results of these studies may indicate that it is necessary to perform subsequent *in vivo* drug interaction studies. The applicant need agree to perform these *in vivo* studies if CDER review of the *in vitro* data indicates that such studies are essential.

I.D. Package insert alterations

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pages of trade

secret and/or

confidential

commercial

information

Draft Labeling pgs 6-8

I.C. General Comments

Fulfillment of the recommendations listed below would allow the package insert to be revised to provide suitable information to prescribers.

1. We recommend that the applicant perform a formal study (sampling of sufficient frequency to describe potential multi-exponential pharmacokinetics and of sufficient duration to describe elimination half-life) to describe the pharmacokinetics of Targretin® when dosed to steady state at doses from 300-650 mg/m^2/day to CTCL patients. If the 650 mg/m^2/day dose is too toxic, a reasonable upper limit would be substituted.

2. We recommend that the applicant perform a formal study (sampling of sufficient frequency to describe potential multi-exponential pharmacokinetics and of sufficient duration to describe elimination half-life) to describe the metabolic profile of Targretin® when when dosed to steady state at doses from 300-650 mg/m^2/day to CTCL patients. The relative contribution of the metabolites identifed to the efficacy and safety observed upon Targretin® administration should be assessed.

3. We recommend that the applicant perform a studies to describe the plasma proteins to which bexarotene binds, the ability of bexarotene to displace drugs bound to plasma proteins and the ability of drugs to displace bexarotene binding.

4. We recommend that the applicant perform a formal study (sampling of sufficient frequency to describe potential multi-exponential pharmacokinetics and of sufficient duration to describe elimination half-life) to describe any differences in bexarotene pharmacokinetics between elderly and non-elderly.

5. We recommend that the applicant perform a formal study (sampling of sufficient frequency to describe potential multi-exponential pharmacokinetics and of sufficient duration to describe elimination half-life) to describe any differences in bexarotene pharmacokinetics between men and women.

5. We recommend that the applicant perform a formal study (sampling of sufficient frequency to describe potential multi-exponential pharmacokinetics and of sufficient duration to describe elimination half-life) to describe any differences in bexarotene pharmacokinetics between individuals of different ethnic origins.

6. We recommend that the applicant perform a formal study (sampling of sufficient frequency to describe potential multi-exponential pharmacokinetics and of sufficient duration to describe elimination half-life) to describe any differences in bexarotene pharmacokinetics that accompany moderate-severe renal insufficiency. We recommend that free bexarotene concentrations be measured.

7. We recommend that the applicant perform a formal study (sampling of sufficient frequency to describe potential multi-exponential pharmacokinetics and of sufficient duration to describe elimination half-life) to describe any differences in bexarotene pharmacokinetics that accompany moderate-severe hepatic insufficiency.

I.D. **Approval/non-approval recommendation**

Although the submission has met the current absolute minimum requirements of the Office of Clinical Pharmacology and Biopharmaceutics, it does not provide dosing guidelines for patients receiving certain concomittant therapies. The Office of Clinical Pharmacology and Biopharmaceutics finds the application approvable if the dissolution specification is changed as recommended, the applicant agrees to perform the studies listed under Phase IV commitments, and the recommended package insert alterations are made.

/S/ 12/22/99
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