CHEMISTRY REVIEW(S)
DIVISION OF ONCOLOGY DRUG PRODUCTS
Original NDA Review of Chemistry, Manufacturing, and Controls

NDA #: 21-055   CHEMISTRY REVIEW #: 2   REVIEW DATE: December 23, 1999

SUBMISSION TYPE   DOC. DATE   CDER DATE   ASSIGNED DATE
Original           June 22, 1999   June 23, 1999   June 30, 1999
Amendment (BC)    December 8, 1999   December 9, 1999   December 14, 1999
Amendments (BC)   December 21, 1999   December 22, 1999   December 22, 1999

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

DRUG PRODUCT NAME:
Proprietary: Targretin® Capsule
Nonproprietary/USAN: Bexarotene (This name was adopted by the USAN Council, correspondence of 3/25/98)
Code Name/Number: LGD1069, LG100069
Chem. Type/Ther. Class: IP
Activation of three retinoid X receptors (RXRa, β, γ)/ Cutaneous T-cell lymphoma (CTCL)
Soft Gelatin Capsule
75mg/capsule
Oral
Rx
OTC

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

CAS Name: 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl] benzoic acid (see attached USAN publication)
Other Chemical Name: p-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl 2-naphthylvinyl]-benzoic acid
Common Name: Not available
CAS Number: 153559-49-0
Code Number: LGD1069, LG100069
M.F.: C29H26O2
M.W.: 348.48

SUPPORTING DOCUMENTS:
INDs: X

DMFs:

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<th>DMF No.</th>
<th>Holder Name</th>
<th>LOA date</th>
<th>Subject</th>
<th>Status</th>
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<td>DMF</td>
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<td>1/29/99</td>
<td>Tamper-evident, foil innersel M-1</td>
<td>Adequate</td>
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<td>5/13/99</td>
<td>Preparation of gelatin mass used for the</td>
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Trademark consultation was requested under IND on 11/16/77. Targetine® was found acceptable on 2/18/98.
Biopharm consultation was initiated on 10/1/99 concerning dissolution specifications and its method. Acceptable on 12/16/99 with change of the paddle speed from

Micro consultation, not applicable
Environmental assessment, Exemption is requested. Granted.
Stability data consultation, Not needed.
Method validation, Pending for initiation.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:
All CMC deficiencies were addressed satisfactorily in these amendments. Approval of this NDA is recommended from the standpoint of CMC. An expiration dating period of 12 months for the drug product manufactured from both sources is granted at this time.

The following CMC comments should be included in an action letter to be prepared:
1) An expiration dating period of 12 months for the drug product manufactured from both sources of the drug substance is granted at this time.
2) We remind your commitment to report a validation report concerning indene impurity within 6 months from the date of approval.
3) An approved paddle speed for the regulatory dissolution methods is 50rpm.
4) Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Orig. NDA 21-055
HFD-150/Division File
HFD-150/AChapman
HFD-150/ SKim
HFD-150/LWood
HFD-810/HPatel
HFD-810/Simmons
R/D Init. by: __________

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

/S/
12-23-99
DIVISION OF ONCOLOGY DRUG PRODUCTS
Original NDA Review of Chemistry, Manufacturing, and Controls

NDA #: 21-055
SUBMISSION TYPE
 original
Amendment (NC) July 12, 1999
Amendment (NC) September 16, 1999

CHEMISTRY REVIEW #:
DOC. DATE
Original June 22, 1999
Amendment (NC) July 12, 1999
Amendment (NC) September 16, 1999

REVIEW DATE: November 26, 1999
CDER DATE June 23, 1999
ASSIGNED DATE June 30, 1999
July 14, 1999 July 23, 1999
September 17, 1999 September 21, 1999

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

DRUG PRODUCT NAME:
Proprietary:
Nonproprietary/USAN:

Code Name/Number:
Chem. Type/Ther. Class:
Targretin® Capsule
Bexarotene (This name was adopted by the USAN
Council, correspondence of 3/25/98)
LGD1069, LG100069

1P

PHARMACOL. CATEGORY/INDICATION:
Activation of three retinoid X receptors (RXRα, β, γ)
Cutaneous T-cell lymphoma (CTCL)
Soft Gelatin Capsule
75mg/capsule
Oral

x Rx ____ OTC

DOSAGE FORM:

STRENGTHS:

ROUTE OF ADMINISTRATION:

DISPENSED:

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

CAS Name: 4-[1-(3,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalenyl)vinyl]benzenecarboxylic acid
Other Chemical Name: 4-[1-(3,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]-benzoic acid
Common Name: Not available
CAS Number: 153559-49-0
Code Number: LGD1069, LG100069
M.F.: C_{24}H_{28}O_{2}
M.W.: 348.48

SUPPORTING DOCUMENTS:
INDs: IND

DMFs:

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REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:
CMC deficiencies were noted in this application. This NDA is approvable pending for satisfactory response to the deficiencies indicated in the draft letter.

cc:
Orig. NDA 21-055
HFD-150/Division File
HFD-150/AChapman
HFD-150/SKim
HFD-150/RWood
HFD-810/HPatel
HFD-810/JSimmons
R/D Init. by: S 11-29-99

filename: N21055.org
(1st draft 11/12/99, revised 11/26/99)