CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020766

CHEMISTRY REVIEW(S)

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

N.A. # 20-766 CHEM. REVIEW #: #2 REVIEW DATE: 5-5-97

SUBMISSION TYPE	DOCUMENT DATE	CDEV DATE	ASSIGNED DATE
Original	11-26-96	11-27-96	12-5-96
Amendment	4-28-97	4-28-97	4-29-97

NAME & ADDRESS OF APPLICANT: Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110

DRUG PRODUCT NAME:
Proprietary: Xenical
Non-proprietary/USAN: Orlistat Capsules
Code Name/Number: Tetrahydrolipstatin
Ro 18-0647/002 unmilled substance
Ro 18-0647/008 milled substance
Chem. Type/Ther. Class: 1 P

DNA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL. CATEGORY/INDICATION: Treatment of obesity

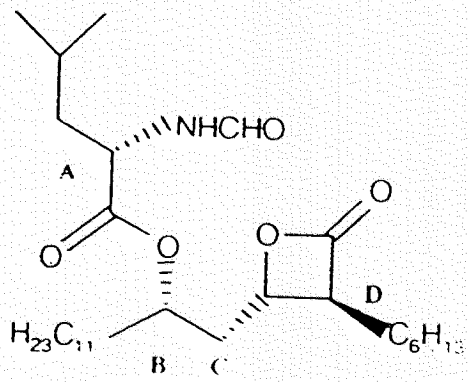
DOSAGE FORM: Capsules

STRENGTHS: 120 mg/capsule

ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

(S)-2-Formylamino-4-methyl-pentanoic acid (S)-1-[(2S,3S)-3-hexyl-4-oxo-oxetan-2-ylmethyl]-dodecylester



Molecular Formula: $C_{29}H_{53}NO_5$
Molecular Weight: 495.75

N.A.# 20-766 Hoffmann-La Roche Xenical

SUPPORTING DOCUMENTS: IND [redacted]

RELATED DOCUMENTS: None

CONSULTS: None

REMARKS/COMMENTS: See next page.

CONCLUSIONS & RECOMMENDATIONS:
The CMC information for the drug substance and drug product for this NDA is being reviewed separately. This review pertains only to the drug substance. [redacted] Application is approved from chemistry viewpoint provided the deficiencies pertaining to the deficiencies pertaining to the drug product are also properly answered [redacted]

cc:
Orig. NDA #20-766
HFD-510/Division File
HFD-510/CHNiu/5/5/97
HFD-510/MHess
HFD-510/D.-G. Wu/SMoore
R/D init. by:

/S/ [redacted]

Chien-Hua Niu, Ph.D.
Review Chemist
filename: Disc #2/NDA/NDA20766.002

/S/ [redacted]

5/5/97

MAY - 5 1997

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-766 **DATE REVIEWED:** 5-May-97

CHEMISTRY REVIEW #: 2 **REVIEWER:** Martin Haber, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	26-NOV-96	27-NOV-96	5-DEC-96
AMENDMENT	28-APR-97		

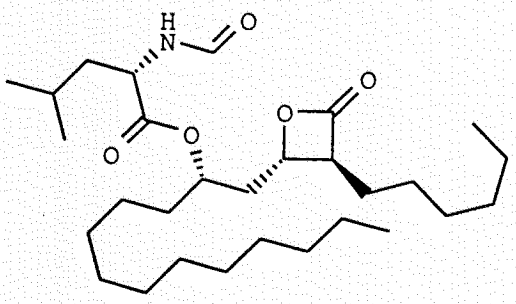
NAME & ADDRESS OF SPONSOR:
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110
(201) 812-3550 Ms. Virginia A. Pate (CMC only)

DRUG PRODUCT NAME:

Proprietary:	Xenical
Nonproprietary:	Orlistat, Tetrahydrolipstatin
Code Name/#:	Ro 18-0647
Chem.Type/Therapeutic.Class:	Type 1, NME/ Class P

PHARMACOL. CATEGORY/INDICATION: Treatment of Obesity
DOSAGE FORM: Capsules
STRENGTHS: 120 mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: X
Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(S)-2-Formylamino-4-methyl-pentanoic acid (S)-1-[[(2S,3S-3hexyl-4-oxo-oxetan-2-yl]methyl]-dodecyl ester
CAS #: , $C_{29}H_{53}NO_5$, mol. wt. 495.75



REMARKS:
Xenical specificly inhibits gastric and pancreatic lipases in the stomach and small intestine. Recommended dose is 120 mg three times a day. For specific chemistry comments, see Review notes.

CONCLUSIONS & RECOMMENDATIONS:
The CMC information for the drug substance and product are being reviewed separately. This review pertains only to the drug product. Chemistry review for the drug substance is being done by Dr. C-H. Niu, see his reviews. The sponsor has responded adequately to the FDA request for additional chemistry information for the drug product. From a chemistry viewpoint, the application can be approved, pending an acceptable GMP status for the facilities listed on the EER's dated 12/10/96 and 1/9/97.

Orig. NDA #20-766
cc: HFD-510/Division file/D-G.Wu/C-H.Niu/M.Haber/M.Hess
ONDC/ODEII/J.Gibbs
R/D Init by: Dr. Stephen Moore, Team Leader Chemist

/S/ [redacted]

/S/ [redacted]
5/5/97

Martin Haber, Ph.D.
Review Chemist

MAR 20 1997

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

N.A. # 20-766 CHEM. REVIEW #: 1 REVIEW DATE: 2-10-97

SUBMISSION TYPE	DOCUMENT DATE	CDEV DATE	ASSIGNED DATE
Original	11-26-96	11-27-96	12-5-96
Amendment	2/3/97	2/4/97	2/5/97

NAME & ADDRESS OF APPLICANT: Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110

DRUG PRODUCT NAME:
Proprietary: Xenical
Non-proprietary/USAN: Orlistat Capsules
Code Name/Number: Tetrahydrolipstatin
Ro 18-0647/002 unmilled substance
Ro 18-0647/008 milled substance

Chem. Type/Ther. Class: 1 P

DNA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL. CATEGORY/INDICATION: Treatment of obesity

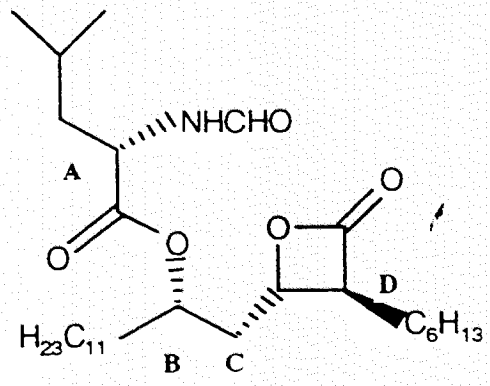
DOSAGE FORM: Capsules

STRENGTHS: 120 mg/capsule

ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

(S)-2-Formylamino-4-methyl-pentanoic acid (S)-1-[(2S,3S)-3-hexyl-4-oxo-oxetan-2-ylmethyl]-dodecylester



Molecular Formula: $C_{29}H_{53}NO_5$
Molecular Weight: 495.75

N.A.# 20-766 Hoffmann-La Roche Xenical

SUPPORTING DOCUMENTS: IND [redacted]

RELATED DOCUMENTS:

CONSULTS: Environmental assessment (EA) was sent for review on April 25, 1995.

REMARKS/COMMENTS:

1. Orlistat inhibits absorption of dietary fat by inhibition of the gastrointestinal lipases. The mode of action of orlistat is non-systemic, meaning that it reduces the digestion and subsequently the absorption of dietary fat by about 30% by acting locally in the gastrointestinal tract.

2. [redacted]

3. This review only deals with the chemistry, manufacturing and controls of the drug substance. For the drug product, it should refer to the chemistry review written by Dr. Martin Haber.

4. [redacted]

CONCLUSIONS & RECOMMENDATIONS:

Sufficient information on chemistry and manufacturing controls of the drug substance has been submitted for the NDA. Application can be approved from chemistry viewpoint provided the deficiencies listed in the draft letter are properly answered.

cc:
Orig. NDA #20-766
HFD-510/Division File
HFD-510/CHNiu/2/10/97
HFD-510/RHedin
HFD-510/D.-G. Wu/SMoore
R/D init. by:

/S/ [redacted]

Chien-Hua Niu, Ph.D.
Review Chemist
filename: Disc #2/NDA/NDA20766.001

/S/ [redacted]

3/20/97

APPEARS THIS WAY ON ORIGINAL

HESS

MAR 20 1997

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-766 **DATE REVIEWED:** 20-March-97

CHEMISTRY REVIEW #: 1 **REVIEWER:** Martin Haber, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	26-NOV-96	27-NOV-96	5-DEC-96

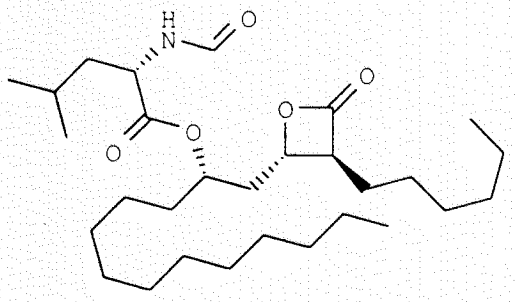
NAME & ADDRESS OF SPONSOR: Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110
(201) 812-3550 Ms. Virginia A. Pate (CMC only)

DRUG PRODUCT NAME:

Proprietary:	Xenical
Nonproprietary:	Orlistat, Tetrahydrolipstatin
Code Name/#:	Ro 18-0647
Chem.Type/Therapeutic.Class:	Type 1, NME/ Class P

PHARMACOL. CATEGORY/INDICATION: Treatment of Obesity
DOSAGE FORM: Capsules
STRENGTHS: 120 mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: X
Rx ___ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(S)-2-Formylamino-4-methyl-pentanoic acid (S)-1-[[(2S,3S-3hexyl-4-oxo-oxetan-2-yl]methyl]-dodecyl ester
CAS #: 96829-58-2, $C_{29}H_{53}NO_5$, mol. wt. 495.75



REMARKS:

Xenical specificly inhibits gastric and pancreatic lipases in the stomach and small intestine by forming a covalent bond with the active site serine. Therefore, triglyceride (fat) is not hydrolyzed into absorbable free fatty acid and monoglyceride. The lost of absorbed fat from the diet leads to a caloric deficit resulting in eventual weight loss. The drug is not absorbed. Recommended dose is 120 mg three times a day (taken with each meal). For specific chemistry comments, see Review notes.

CONCLUSIONS & RECOMMENDATIONS:

From a chemistry viewpoint the application is approvable. The sponsor should provide additional chemistry information [redacted]

Orig. NDA #20-766
cc: HFD-510/Division file/D-G.Wu/C-H.Niu/S.Moore/M.Haber/M.Hess
ONDC/ODEII/J.Gibbs
R/D Init by: Dr. S. Moore, Team Leader Chemist

/S/ [redacted]
Martin Haber, Ph.D.
Review Chemist

/S/ [redacted]
3/20/97