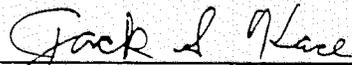


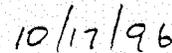
13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the persons responsible for preparation of the environmental assessment.

The undersigned official certifies that the information presented under item 1 through 15 of the environmental assessment and Appendices A through B contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR 1506.6



Jack S. Kace, Eng. Sc.D
Vice President and Director
Corporate Environmental and Safety Affairs



Date

14. REFERENCES

There are no published references cited in the environmental assessment for Xenical except the FDA's guidance document entitled, "Guidance for Industry: for the Submission of an Environmental Assessment in Human Drug Applications and Supplements" published by the Center for Drug Evaluation and Research (CDER), November 1995. All other references cited are to Hoffmann-La Roche internal reports which are included as confidential appendices in this Environmental Assessment.

15. APPENDICES

- A. Physical - Chemical Property Data and Material Safety Data Sheet (MSDS) for Orlistat.
- B. Compliance Statements signed by a High Ranking Official from various Companies.

- C. List of Chemical Substances along with CAS No. associated with manufacture of Drug Substance and copies of available MSDSs (confidential).
- D. List of Chemical Substances along with CAS No associated with manufacture of Drug Product and copies of available MSDSs (confidential).
- E. The maximum Projected Annual Production and Energy Utilization Data (confidential).
- F. Calculation of Expected Introduction Concentration (EIC), Maximum Expected Environmental Concentrations (MEEC) and Expected Environmental Concentrations (EEC) (confidential).
- G. Orlistat (Ro 18-0647): Update on Summary of ADME Data of Orlistat in Humans and Experimental Animals (confidential).
- H. Test Report Ro 18-0647: Acute Toxicity to the Water Fleas Daphnia magna under static conditions (confidential).
- I. Test Report Ro 18-0647: Acute Toxicity to Rainbow Trout, Oncorhynchus mykiss, under Static Conditions (confidential).
- J. Test Report Ro 18-0647: Microbial Growth Inhibition (confidential).
- K. Test Report Ro 18-0647: Activated Sludge Respiration Inhibition Test (confidential).
- L. Test Report Ro 18-0647: Aerobic Biodegradation in Water (confidential).
- M. Test Report Ro 18-0647: Toxicity to the Freshwater Green Alga, Selenastrum capricornutum, under Static Test Conditions (confidential).
- N. Test Report Ro 18-0647: Determination of Soil Adsorption/Desorption (confidential).
- O. Test Report Ro 18-0647: Earthworm Subacute Toxicity Study (confidential).

APPENDIX A

PHYSICAL - CHEMICAL PROPERTY DATA

AND

MATERIAL SAFETY DATA SHEET

(MSDS)

FOR

ORLISTAT

Material Name: Orlistat
MSDS Number .: m-003673.asc

Page: 1
Approved: 05/26/94

ROCHE LABORATORIES
a division of Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

Emergency: (201) 235-6660
Chemtrec: (800)-424-9300
Information: (800) 526-6367

MATERIAL SAFETY DATA SHEET

SECTION 1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Material Name: Orlistat
RO #: 18-0647/000
CAS Number: 96829-58-2
Synonyms: [2S-[2alpha(R*),3beta]]-N-formyl-L-leucine 1-[(3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester
(S)-1-[[2S,3S)-3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl
(S)-2-formamido-4-methylvalerate
N-formyl-L-leucine (S)-1[[2S,3S)-3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester tetrahydrolipstatin
THL
TSCA Status: FDA Exemption - Not on Inventory; R&D Exemption - Not on Inventory.
Chemical Family: Ester
Therapeutic Category: Antiobesity agent
Formulations Used In: XENICAL(TM)

SECTION 2. COMPOSITION/INFORMATION ON INGREDIENTS

Ingredient Name	CAS Number	Concentration %
Orlistat	96829-58-2	>97

SECTION 3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW

Physical State: Powder.
Color: White to off-white
Odor: Odorless

Severe dust explosion hazard.

POTENTIAL HEALTH EFFECTS

Relevant Routes of
Exposure: Inhalation, Ingestion.
Target Organs: Gastrointestinal System.

Acute Effects

General: May cause headaches. May cause gastrointestinal effects such as nausea, vomiting, diarrhea, constipation, cramps, and loss of appetite.

Chronic Effects: No adverse effects known.

Material Name: Orlistat
MSDS Number .: m-003673.asc

Page: 2
Approved: 05/26/94

SECTION 3. HAZARDS IDENTIFICATION (Continued. . .)

Carcinogenicity: Not listed by NTP, IARC, or OSHA.

SECTION 4. FIRST AID MEASURES

Inhalation: Remove to fresh air. If discomfort occurs or persists, get medical attention.
Skin Contact: Wash area with soap and plenty of water.
Eye Contact: Immediately flush eyes with plenty of water. If irritation occurs or persists, get medical attention.
Ingestion: If large quantities of this material are swallowed, get medical attention immediately. Do not induce vomiting unless directed by medical personnel. Never give anything by mouth to an unconscious person.

SECTION 5. FIRE FIGHTING MEASURES

Flash Point: Not Applicable
Extinguishing Media : Water, Carbon Dioxide, Dry Chemical, Foam.
Unusual Fire and
Explosion Hazards . .: Severe dust explosion hazard.
Fire Fighting
Instructions: Wear NIOSH/MSHA approved positive pressure, self contained breathing apparatus and full protective turn out gear. Use caution in approaching fire. Use water to keep fire exposed containers cool.
ST number: 2, Hartmann Tube.

SECTION 6. ACCIDENTAL RELEASE MEASURES

Spill Clean Up
Procedures: Review Section 3-Hazards Identification, and Section 8-Exposure Controls/Personal Protection before proceeding with the clean up. Shut off the source of the spill or leak if it is safe to do so. Eliminate possible ignition sources. Follow appropriate grounding procedures. Scoop or shovel spilled material into a suitable labeled open head drum. Secure the drum cover and move the container to a safe holding area. Wash spill area thoroughly with soapy water.
Treatment and
Disposal: Dispose of in accordance with recommendations in Section 13 Disposal Considerations.
Reporting
Requirements: The United States Environmental Protection Agency (USEPA) has not established a Reportable Quantity (RQ) for releases of this material. In New Jersey, report all releases which are likely to endanger the public health, harm the environment or cause a complaint to the NJDEPE Hotline (1-609-292-5560) and to local officials. State and local regulations vary and may impose additional reporting requirements.

Material Name: Orlistat
MSDS Number .: m-003673.asc

Page: 3
Approved: 05/26/94

SECTION 7. HANDLING AND STORAGE

Special Sensitivity : Heat. Moisture.

Handling & Storage

Precautions: Do not generate dust or expose to ignition sources.
Ground and bond all transfer equipment.
Eliminate potential ignition sources.
Use with adequate ventilation.
Avoid breathing dust.
When handling, use proper personal protective equipment specified in section 8.
Wash thoroughly after handling.
Keep container tightly closed when not in use.
Store in a cool, dry area.
Store under inert atmosphere.

SECTION 8. EXPOSURE CONTROLS / PERSONAL PROTECTION

ENGINEERING CONTROLS

Ventilation: General room ventilation is adequate unless the process generates airborne dust or fume.

PERSONAL PROTECTION

Respirator Type(s) .: Half Face, Negative Pressure Air Purifying, Nontoxic Dust/Mist Filter.

Conditions for Use .: Under normal conditions of use, respiratory protection is not expected to be necessary. Respiratory protection is recommended under excessively dusty conditions. OSHA considers effective engineering controls to be the primary means to control worker exposure. Respiratory protection should not substitute for feasible engineering controls. Whenever respiratory protection is used, a complete respirator program should be developed in accordance with OSHA Subpart I (29CFR1910.134) requirements.

Glove Materials .: Any plastic or rubber glove.

Conditions for Use .: Gloves are recommended if there is a potential for skin contact.

Skin Protection .: None required under normal and foreseeable conditions of use.

Eye Protection .: Safety Glasses Required, Safety Goggles Recommended.

OTHER CONTROL MEASURES

Additional

Protective Measures : Prevent the accumulation of dust in the work area by thorough periodic cleaning of the area.

EXPOSURE LIMITS

There are no exposure limits specified either for this material or for any of its ingredients.

Material Name: Orlistat
MSDS Number :: m-003673.asc

Page: 4
Approved: 05/26/94

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Physical State: Powder.
Color: White to off-white
Odor: Odorless
Molecular Weight: 495.75
Chemical Formula: C₂₉H₅₃NO₅
Pure/Mixture: Pure.
Melting Point: 44.0 C
H₂O Solubility: Negligibly Soluble (<0.1% by weight).
Solubility - Other ..: Soluble in diethyl ether, ethanol (absolute),
chloroform.

SECTION 10. STABILITY AND REACTIVITY

Stability: Normally stable but may become unstable at elevated
temperatures or reacts with water, releasing some
energy but not violently.
Conditions to Avoid : Dust Accumulation
Airborne Dust
Sources of Ignition
Decomposition
Products: Carbon monoxide, carbon dioxide, oxides of nitrogen
Polymerization: No
Conditions of
Polymerization: Will not occur.

SECTION 11. TOXICOLOGICAL INFORMATION

Orlistat

Acute Oral, Single Dose, Rat: >5000 mg/kg
Summary: Acute oral LD₅₀ (rat) is greater than 5000 mg/kg body weight at 14 days (limit test) under the study conditions utilized. No deaths occurred and no clinical symptoms of toxicity were observed during the 14 day period.

Mutagenicity

Summary: No evidence of mutagenicity was found in the Ames assay with or without metabolic activation and in the mouse micronucleus assay, the HGPRT test, the unscheduled DNA synthesis assay, and the chromosomal aberration assay using human lymphocytes, under the study conditions utilized.

Reproductive Rat

Summary: No effect was observed when doses up to 400 mg/kg/day body weight were administered to male rats before and during mating and to female rats before and during the mating, gestation, and lactation periods, under the study conditions utilized.

Teratogenicity Oral, Rabbit

Summary: No evidence of embryotoxicity in pregnant rabbits or of birth defects in offspring was observed at oral doses up to 800 mg/kg body weight under the study conditions utilized.

Teratogenicity Oral, Rat

Summary: No evidence of embryotoxicity in pregnant rats or of birth

Material Name: Orlistat
MSDS Number .: m-003673.asc

Page: 5
Approved: 05/26/94

SECTION 11. TOXICOLOGICAL INFORMATION (Continued. . .)

defects in offspring was observed at oral doses up to 800 mg/kg body weight, under the study conditions utilized.

SECTION 12. ECOLOGICAL INFORMATION

No ecological data available on this material.

SECTION 13. DISPOSAL CONSIDERATIONS

Disposal

Recommendations: This material is suitable for incineration. These recommendations are based on the product as shipped. Use, processing, alteration or contamination may affect these disposal recommendations. State, local or site restrictions affecting the available proper disposal options may vary.

RCRA Waste #: Not regulated under RCRA

Empty Containers . . .: Empty containers must be triple rinsed prior to disposal, recycling, or reuse.

SECTION 14. TRANSPORTATION INFORMATION

Enforcement Agency .: US Dept. of Transportation

Country/Community .: USA

Proper Ship. Name .: Non-regulated

Enforcement Agency .: International Air Transport Association

Country/Community .: International

Proper Ship. Name .: Non-regulated

SECTION 15. REGULATORY INFORMATION

No regulatory information available on this material.

SECTION 16. OTHER INFORMATION

APPROVAL INFORMATION

Preparer: Hesham M. Soliman

Approver: Corporate Environmental & Safety Affairs

Approval Date: 05/26/94

Reason For Issue . . .: General revision. Enter onto Roche CE&SA MSDS Database.

Material Name: Orlistat
MSDS Number :: m-003673.asc

Page: 6
Approved: 05/26/94

The information presented on this MSDS is, to the best of our knowledge, accurate and reliable. It is provided in good faith without warranty or acceptance of any liability on the part of Hoffmann-LaRoche, Inc. It is the responsibility of the user to evaluate the relevance and completeness of this information for their application and to determine the safety, suitability and status under applicable regulations relating to this product or byproducts arising out of their process.

PHYSICAL PROPERTY DATA SUMMARYORLISTAT1. Solubility

Water <0.01 mg/ml
n-Octanol 280 mg/ml
Ethanol 350 mg/ml
Dimethyl sulfoxide 540 mg/ml
Dichloromethane 520 mg/ml

2. Partition CoefficientsAqueous medium

n-octanol/aqueous buffers 7.5 > 1,000
n-octanol/water 4.4 (Kow, calculated)

3. Melting Range 42-44°C as per USP Method I

APPENDIX B

COMPLIANCE STATEMENTS SIGNED

BY A

HIGH RANKING OFFICIAL

FROM

VARIOUS COMPANIES

GENERAL COMPLIANCE STATEMENT

██████████ states that it is in compliance with, or on a schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Hydroxy- β -Lactone at its facilities in ██████████, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of Hydroxy- β -Lactone at its facilities in ██████████. The approval and the subsequent increase in production of Hydroxy- β -Lactone is not expected to affect compliance with current emission requirements or compliance with environmental laws.

██████████
././SI

Head of department Safety and
Environmental Protection

██████████

██████████
././SI

Head of department
Manufacturing

██████████



GENERAL COMPLIANCE STATEMENT



states

that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Orlistat Intermediate Ro 19-3052 at its facilities in  as well as emission requirements set forth in applicable national and local statutes and regulations applicable to the production of Orlistat Intermediate Ro 19-3052 at its facilities in 

The approval and the subsequent increase in production of Orlistat Intermediate Ro 19-3052 is not expected to affect compliance with current emission requirements or compliance with environmental laws.


Technical Director
/s/ April 3rd 1996

-GENERAL COMPLIANCE STATEMENT

Hoffmann-La Roche Ltd. states that it is in compliance with, or on a schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Orlistat at its facilities in Basle, Switzerland, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of Orlistat at its facilities in Basle, Switzerland. The approval and the subsequent increase in production of Orlistat is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Head of department Safety and
Environmental Protection

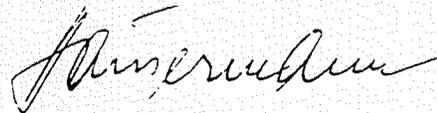
Pharma Headquarters Basel



Dr. M. Brüstlein

Head of Pharma Operations
Manufacturing

Chemical Production



Dr. W. Häusermann

-GENERAL COMPLIANCE STATEMENT

Roche Ltd., Sisseln states that it is in compliance with, or on a schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of Orlistat at its facilities in Sisseln, Switzerland, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of Orlistat at its facilities in Sisseln, Switzerland. The approval and the subsequent increase in production of Orlistat is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Date: May 3, 1996



Dr. H.-R. Hunziker

Head of Department Production

Date: May 3, 1996



A. Hofstetter

Head of Department Safety and
Environmental Protection

[REDACTED]

F. HOFFMANN-LA ROCHE Ltd
Pharmaceuticals Division
4070 Basel

Switzerland

Balerna, April 26, 1996

GENERAL COMPLIANCE STATEMENT FOR ORLISTAT

[REDACTED] states that it is in compliance with all emission requirements established for the conduct of its operations in Balerna, [REDACTED]. Jetpharma SA has established controls for air, water and solid emissions and waste. The approval and subsequent increase in processing volume of ORLISTAT, [REDACTED] at the [REDACTED] facility is within the expected plant capacity. The addition of the ORLISTAT process volume is not expected to affect compliance with current requirements for emissions or with compliance with environmental laws.

Responsible for Safety and
Environmental Protection

[REDACTED]
/s/ [REDACTED]
[REDACTED]

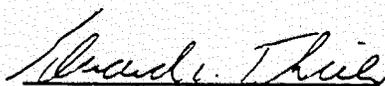
Head of Department
Manufacturing

[REDACTED]
/s/ [REDACTED]
[REDACTED]

[REDACTED]

GENERAL COMPLIANCE STATEMENT

Hoffmann-La Roche Inc. states that it is in compliance with, or on a schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the capsules manufacturing and packaging of the Xenical drug product at its facilities in Nutley, New Jersey as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the capsules manufacturing and packaging of the Xenical drug product at its facilities in Nutley, New Jersey. The approval and the subsequent increase in production of Xenical capsules is not expected to affect compliance with current emission requirements or compliance with environmental laws.



Edward C. Thiele
Vice President
Pharmaceutical Operations