CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20697

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

TASMAR™

(tolcapone)

Tablets

NDA 20-697

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF NEUROPHARMACOLOGICAL
DRUG PRODUCTS (HFD-120)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-697

Tasmar™(tolcapone) Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Tasmar™ (tolcapone) Tablets, Hoffmann-La Roche Inc.** has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Tasmar™ (tolcapone) tablets will be administered orally as a treatment for Parkinson's disease. The drug substance and drug product will manufactured by the applicant in Switzerland and New Jersey respectively. The finished drug product will be used in hospitals, clinics and patient's homes throughout the United States.

Tolcapone may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The projected environmental introduction concentration from use is less than 1 ppb. CDER has routinely found that concentrations less than 1 ppb have no effect on relevant standard test organism, therefore the applicant has submitted a Tier 0 EA without format items 7, 8, 9, 10 and 11.

Disposal in the United States may result from returned, recalled or expired goods and user disposal of empty or partly used product and packaging. Returned, recalled or expired goods will be sent to a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

4/2/97
DATE

PREPARED BY
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

4/2/97
DATE

CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

c.c. original to NDA 20-697 through TWheelous/HFD-120
HFD-357/EA File NDA #20-697
HFD-357/Docket File
HFD-205/FOI COPY

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ORIGINAL NEW DRUG APPLICATION

ENVIRONMENTAL ASSESSMENT

TASMAR™ (TOLCAPONE)

TABLETS

1. DATE

March 4, 1996

2. NAME OF APPLICANT

Hoffmann-La Roche Inc.

3. ADDRESS

340 Kingsland Street
Nutley, New Jersey 07110

4. DESCRIPTION OF PROPOSED ACTION

a. Requested Approval

Hoffmann-La Roche Inc. is filing a New Drug Application pursuant to section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Tasmar tablets (100 and 200 mg strength). It will be packaged in HDPE bottles fitted with a metal/plastic child-resistant closure with tacseal and cotton. This Environmental Assessment (EA) has been submitted pursuant to 21 CFR 25.31 a(a).

b. Need for Action

Tasmar will be used in humans for the treatment of Parkinson's disease throughout the United States. The drug is expected to be used for a long-term use in the treatment of Parkinson's disease.

c. Production Locations

The manufacturing of Tasmar will be carried out in two to three locations:

- F. Hoffmann-La Roche Ltd., Basle, Switzerland.
- Roche AG, Sisselin, Switzerland.
- Hoffmann-La Roche Inc., Nutley, New Jersey

The manufacturing responsibilities are as follows:

- The synthesis of the drug substance from starting material 1,2 Dimethoxybenzene will be carried out by F. Hoffmann-La Roche Ltd., Basle, Switzerland.

- The milling of drug substance will be carried out by F. Hoffmann-La Roche Ltd., Basle, Switzerland or Roche AG, Sisselin, Switzerland.

- The final dosage form (Tolcapone drug product) will be produced at the Hoffmann-La Roche Inc. site in Nutley, New Jersey. The tablets will be packaged at the Hoffmann-La Roche Inc. facility in Nutley, New Jersey.

The detailed description of the three manufacturing sites are as follows:

F. Hoffmann-La Roche Ltd., Basle, Switzerland: The Roche Basle plant is located on Basle city ground in a mixed industrial and residential zone at the Rhine river. The Basle plant occupies approximately 120,000 square meters area and is mostly covered with buildings. In the close proximity, the Ciba-Geigy and Sandoz plants are located northwest of the Roche plant. The Roche Basle plant is a manufacturing site for pharmaceuticals and chemicals for the Roche group. It is also a research and administrative site (Corporate headquarters) for the Roche group.

Roche AG, Sisselin, Switzerland: Roche AG Sisselin is located on the grounds of the two communities Sisselin and Eiken in Switzerland, approximately 12 to 13 miles east of Basle in an industrial zone adjacent to the Rhine river. The operation is run by the Roche Vitamins division which employs approximately 1,100 employees. The Sisselin plant occupies approximately 910,000 meter square area which was founded in 1958. The Sisselin plant is primarily a manufacturing site for vitamins and pharmaceutical active substances. In addition chemical-technical work is also performed at the site. To be in compliance with various environmental protection regulations, the plant operates an installation for waste air incineration from production units as well as a six stage waste water treatment plant.

Hoffmann-La Roche Inc., Nutley, New Jersey: The street address for the Hoffmann-La Roche Inc. plant is 340 Kingsland Street, Nutley, New Jersey 07110. The Hoffmann-La Roche Inc. plant is located approximately 10 miles west of the New York City in Nutley, New Jersey. The Nutley plant is located in an industrial/residential area. The state highway 3 runs along the north boundary of the site. The Passaic river is located approximately one mile east of the plant. The Nutley plant occupies approximately 122 acres of land and mostly occupied by office, research and manufacturing buildings. The entire state of New Jersey is a non-attainment zone for ozone, the Nutley environs are in attainment for all other criteria pollutants. The Roche Nutley plant is a manufacturing site for pharmaceuticals and other chemicals for the Roche group. It is also a research and an administrative site (US headquarters) for the Roche group.

d. Locations of Use

Tasmar drug product primarily will be used in patients homes, hospitals and clinic throughout the United States.

e. Disposal Sites

Returned, expired or rejected drug product will be returned to Hoffmann-La Roche Inc. in Nutley, New Jersey for disposal. The returned, expired or rejected product will be incinerated in an on-site medical waste incinerator and/or will be placed in a sealed polyethylene bag and sealed in a fiber drum for disposal in an off-site commercial incinerator. The permit number for on-site medical waste incinerator is 113190, expiration date 5/26/96. This permit will be automatically renewed for 90 day conditional extension cycle to allow additional time to complete the stack test. The off-site facility currently being used is Rollins Environmental Services (NJ) Inc., Routes 322 and 295, P. O. Box 337, Bridgeport, NJ which is licensed by the State of New Jersey Department of Environmental Protection (NJDEP) to destroy hazardous material under Permit No. 0809D1HP08 (expiration date 03/1994). The application to renew permit has been already filed with the NJDEP. The decision on the permit renewal application has not yet been made by the NJDEP, the permit is automatically extended pending NJDEP action.

The Roche Basle and Sisselin plant has an incinerator on site which can treat hazardous solid waste. A certificate of compliance signed by high ranking company official and from regulatory authorities, indicating that the milling of Tasmar drug substance will be in compliance with all local and national laws for Roche Sisselin and Roche Basle plant, respectively, is included in Appendix B.

There are no special method of disposal of waste by the end user is anticipated. United States hospitals, pharmacies or clinics will disposed of empty or partially empty packages in accordance with applicable local, state and federal regulations. In home, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

5. **IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION**

Proprietary Name: Tasmar

Generic Name: Tolcapone (Ro 40-7592)

Chemical Name: 3,4-dihydroxy-4'-methyl-5-nitrobenzophenone

CAS No: 134308-13-7

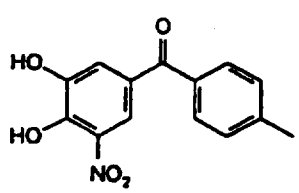
Empirical Formula: $C_{14}H_{11}NO_5$

Molecular Weight: 273.24

Melting Point: 145

Physical Description: Yellow, odorless, nonhydroscopic, crystalline powder

Structural Formula:



(273.2)
Ro 40-7592

Additives:

The list of chemical substances associated with the manufacture of drug product along with CAS No. and copies of available MSDSs are provided in confidential Appendix E.

Impurities:

There are no single impurities detected in the drug substance or the drug product that exceed more than 1 %.

The details of physical chemical property data and chemicals utilized in production of Tasmar are provided as follows:

- Appendix A: It contains the physical chemical property data of Tolcapone (RO 40-7592) and Material Safety Data Sheet for the drug substance.
- Appendix D (confidential): It contains the list of chemical substances associated with the manufacture of drug substance along with CAS Number and copies of available MSDSs for the raw materials utilized.
- Appendix E (confidential): The list of chemical substances associated with the manufacture of drug product along with CAS Number and copies of available MSDSs are provided in confidential Appendix E.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

All manufacturing operations are carried out under carefully controlled conditions and in compliance with applicable environmental regulations of the countries in which the operations occur.

The annual production volume and general compliance information is provided as follows:

- Appendix F (confidential): It contains the information on the maximum projected annual use of Tolcapone for the five-year period following introduction of Tasmar.
- Appendix B : Compliance statements signed by a high ranking company official from Roche Sisselin and Hoffmann-La Roche Inc., Nutley, New Jersey are included in it. It also include compliance statement signed by regulatory authorities for Roche Basle plant.

Control of environmental emissions for the various manufacturing operations is outlined below:

6.1 Manufacture of the Tolcapone Drug Substance - F. Hoffmann-La Roche Ltd., Basle, Switzerland

Roche Basle plant in Switzerland is producing the drug substance (may include milling operation) under carefully controlled conditions and in compliance with the rules of Good Manufacturing Practices and the Swiss Environmental Protection Laws. A compliance certificate signed by the regulatory authorities is included in Appendix B:

6.2 Milling of the Tolcapone Drug Substance - Roche AG, Sisselin, Switzerland

Roche Sisselin plant in Switzerland is producing the drug substance under carefully controlled conditions and in compliance with the rules of Good Manufacturing Practices and the Swiss Environmental Protection Laws. A compliance certificate signed by high ranking company official certifying that the milling of Tasmar drug substance:

- will be in compliance with all local and national environmental laws
- will be in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and
- that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws

is included in Appendix B.

6.3 Drug Product Manufacture : Hoffmann-La Roche Inc., Nutley, New Jersey

The Tasmar drug product consists of 100 mg and 200 mg tablets produced at the Hoffmann-La Roche Inc. plant in Nutley, New Jersey.

All manufacturing operations are carried out under carefully controlled conditions and in compliance with applicable environmental regulations of the United States Environmental Protection Agency (USEPA) and New Jersey Department of Environmental Protection and Energy (NJDEP).

Emissions of pollutants into the air and water and disposal of solid waste for the Hoffmann-La Roche Nutley facility are regulated to a high degree by the State of New Jersey, specifically in Title 7, Environmental Protection, of the New Jersey Administrative Code.

6.3.a Substances Expected to be Emitted

During the manufacturing process some material may be released in the following phases:

- **Air Phase (Air Emissions)** Air emissions consist of minor amounts of pharmaceutical dust (active ingredients plus excipients, Appendix E) lost during loading of dry ingredients into the blending and tablet manufacturing equipment.

- **Aqueous Phase (Wastewater Emission)** The wastewater from the Tasmar tablet manufacturing process consists mainly of equipment washdowns. The wastewater from the blending and tablet operations contains residual amounts of active ingredients along with excipients and other components used in the manufacture of the drug product (Appendix E).

- **Terrestrial Phase (Solid/Liquid Waste)** Solids for disposal consist mainly of broken tablets, rejected tablets and unused product. Appendix E contains of the list of excipients in the tablets.

The Tasmar drug substance and the excipients listed in Appendix E has potential for release in the air phase, aqueous phase and solid phase. However, very minute quantities are expected to be released during the tablets manufacturing and packaging operation.

6.2.b Controls Exercised

During the manufacture of Tasmar drug product, the following control measures are utilized to minimized emissions in the air phase, aqueous phase and solid phase:

- **Air Phase (Air Emissions)** Emission of particulate matter is controlled by means of fabric filter dust collectors,

which enables the dust emissions to remain within the limits of New Jersey regulations. The various types of equipment used in the blending, granulation, drying, milling and tablet operations for the production of Tasmar are serviced by dust collectors, of the fabric filter type. The operating efficiency of fabric filter dust collectors is probably greater than 85 %. The level of dust in the processing areas during product blending and tablet manufacturing operations will be controlled by local exhaust ventilation and general room ventilation. In addition, employee exposure levels will be minimized by the use of personal protective equipment such as respiratory protectors, if required.

- **Aqueous Phase (Wastewater Emission)** Wastewaters from the Tasmar process are combined with wastewater from other manufacturing processes and discharged through a pretreatment system to the Passaic Valley Sewerage Commission (PVSC) treatment plant (a POTW).

- **Terrestrial Phase (Solid/Liquid Waste)** As mentioned under item 4e, the solid/liquid waste will be placed in a sealed polyethylene bag and sealed in a fiber drum for disposal in an off-site commercial incinerator.

6.3.c Citation of and Statement of Compliance with Applicable Emission Requirements

The manufacturing of Tasmar will be in accordance with all applicable Federal, State and local emission requirements, including occupational health. The following are the regulatory requirements in New Jersey:

- **Air Emission Regulations and Permits** Air emissions in New Jersey are regulated under N.J.A.C. 7:26-1 et seq., the Bureau of Air Pollution Control portion of the New Jersey Administrative Code. These regulations include subchapters governing allowable emissions of particulate matter and volatile organic substances from manufacturing processes, as well as setting forth the requirements for obtaining permits to construct or alter process equipment. The granulation dryer and its dust collector are covered by NJDEP certificate to operate

number 102287 (expiration date October 10, 1998). The remaining particulate collection equipment predates the current permit system and is thus "grandfathered." All equipment operates in compliance with current requirements for particulate emissions. The air ventilation in Tasmar process is further covered by permit numbers 112942 (expiration date 4/23/96), 112943 (expiration date 4/23/96) and 111960 (expiration date 3/13/96). The application to renew these permits have been already filed with the NJDEP. The decision on the permit renewal application has not yet been made by the NJDEP, the permit is automatically extended pending NJDEP action.

- **Wastewater Emission Regulations and Permits** Wastewaters from the Tasmar process are combined with wastewater from other manufacturing processes and discharged through a pretreatment system to the Passaic Valley Sewerage Commission (PVSC) treatment plant (a POTW) under PVSC Permit Number 24402882 (expiration date April 14, 1996). The application to renew permit has been already filed with the PVSC. The decision on the permit renewal application has not yet been made by the PVSC, the permit is automatically extended pending PVSC action. The State of New Jersey regulates the Roche/Nutley pretreatment facility as a significant industrial user and has issued non-contact cooling water and storm water discharge permit number NJ 0034185 (expiration date January 31, 2000) under the New Jersey Pollutant Discharge Elimination System (NJPDES) regulations.

- **Solid Emission Regulations and Permits** Disposal of solid waste and hazardous waste is controlled under the New Jersey Department of Environmental Protection and Energy (NJDEP) regulations, N.J.A.C. 7:25-1 et seq. Disposal and processing of solid/liquid waste from the Tasmar process will be in compliance with the NJDEP waste regulations referenced above. The permit information is provided under item 4e.

- **OSHA Regulated Compounds** The chemical substances used as ingredients in the manufacture of Tasmar tablets

are listed in Appendix E. Copies of available MSDS's are included in Appendix E [Confidential]. Manufacturing of Tasmar is in accordance with applicable OSHA regulations.

- **Statement of Compliance** A compliance certificate signed by high ranking company official certifying that the manufacture of Tasmar drug product:

  1. will be in compliance with all local and national environmental laws
  2. will be in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and
  3. that approval and the subsequent increase in production at the facility is not expected to affect compliance with current emission requirements or compliance with environmental laws

is included in Appendix B.

6.3.d Discussion of the Effect of Approval on Compliance with Current Emission Requirements

Manufacture of the drug product at Nutley site is not likely to have a significant impact on compliance with current emission requirements, since the majority of waste will be in solid form, which will be incinerated by a licensed incineration facility regulated by the NJDEP and/or EPA. A small quantity of the drug substance and other excipients is likely to be released in the wastewater due to equipment washdowns. However, the quantity of released into wastewater is going to be in small amount to cause any significant impact on the wastewater discharge limits. Therefore, approval and subsequent increase in production of the drug product at the Nutley site is not expected to significantly affect compliance with current emission requirements.

6.3.e Expected Introduction Concentrations

The projected annual production volume based on five-year production estimates is provided in the confidential Appendix F. The expected introduction concentrations

from use and disposal are calculated based on the 5th year projected estimates.

I. Expected Introduction Concentrations from Use

The expected introduction concentration (EIC) entering into the aquatic environment from patient use was calculated as follows:

EIC - Aquatic (ppm) = A x B x C x D

where A = kg/year production
B = 1/liter per day entering POTW's*
C = year/365 days
D = 10^6 mg/kg (conversion factor)

* 1.115×10^{11} liters per day entering publicly owned treatment works (POTW's), as cited in "Guidance for Industry: for the Submission of an Environmental Assessment in Human Drug Applications and Supplements" published by Center for Drug Evaluation and Research (CDER), November 1995.

The actual calculation is shown in confidential Appendix G. The EIC was calculated, assuming that all the drug substance produced is used, even distribution through the U. S. per day, and no metabolism or depletion mechanisms exists. Based on this calculation, the criteria for Tier 0 are met.

The drug is not likely to enter the terrestrial environment in significant amount through usage except where reclaimed sludge is applied to the land. In U.S., the reclaimed sludge is usually incinerated, therefore the drug substance is not likely to present in significant quantity to cause detrimental effects in the terrestrial environment.

ii. Expected Introduction Concentrations from Disposal

During the manufacture of the drug product, the majority of pharmaceutical waste will be disposed of as solid/liquid waste. As mentioned under item 4e, the pharmaceutical waste will be disposed of by incineration, therefore the EIC

arising from disposal is not likely to be in significant quantity to have any impact.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

This environmental assessment is filled pursuant to 21 CFR 25.31 a(a) which meets the circumstances (criteria) described in Tier O approach mentioned in the 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. Therefore, item 7 is omitted from the environmental assessment.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTRATES

This environmental assessment is filled pursuant to 21 CFR 25.31 a(a) which meets the circumstances (criteria) described in Tier O approach mentioned in the 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. Therefore, item 8 is omitted from the environmental assessment.

9. USE OF RESOURCES AND ENERGY

This environmental assessment is filled pursuant to 21 CFR 25.31 a(a) which meets the circumstances (criteria) described in Tier O approach mentioned in the 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. Therefore, certain information normally presented under item 9 is omitted from the environmental assessment.

A **Natural Resources and Energy** The maximum annual production of the drug substance for the U.S. market over the five year period following introduction and natural resources and energy information is provided in confidential Appendix F.

B **Effect on Endangered or Threatened Species** There are no effects expected upon endangered or threatened species due to the proposed action.

C **Effect on Property Listed in or Eligible for Listing in the National Register of Historic Places** There are no effects expected upon

property listed in or eligible for listing in the National Register of Historic Places due to the proposed action.

10. MITIGATION MEASURES

This environmental assessment is filled pursuant to 21 CFR 25.31 a(a) which meets the circumstances (criteria) described in Tier O approach mentioned in the 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. Therefore, item 10 is omitted from the environmental assessment.

11. ALTERNATIVES TO THE PROPOSED ACTION

The FDA has two alternatives by which to respond to this proposed action:

- Approval of the proposed action through the issuance of Finding of No Significant Impact (FONSI)
- Non-approval and notification of intent to prepare an Environmental Impact Statement (EIS)

We believe that the first action, issuance of a FONSI, is fully justified by this Environmental Assessment. Manufacturing operations will be in compliance with the regulations of the applicable governmental agencies. This environmental assessment meets the circumstances (criteria) described in Tier O approach mentioned in the 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, which clearly indicates that the no observed adverse effects on standard environmental organisms at drug concentrations below 1 ppb. The estimated EIC value for Tasmar drug substance is less than 1.0 ppb (The actual calculation is shown in Appendix G).

Approval of the proposed action will make available to the physician a significantly valuable, potentially improving the quality of life of patients, and environmentally safe drug in the treatment of Parkinson's disease.

12. LIST OF PREPARERS

P.V. Shah, Ph.D
Senior Industrial Toxicologist
Corporate Environmental and Safety Affairs.

(See Curriculum Vitae - Appendix C)

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 C 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

4/17/96
Date

14. REFERENCES

There are no references cited in the environmental assessment for Tasmar 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.

15. APPENDICES

A. Physical - Chemical Property Data and Material Safety Data Sheet (MSDS) for Tasmar drug substance

B. Compliance Statements signed by a High Ranking Official from various Companies and regulatory authorities.

C. Curriculum Vitae.

D. List of Chemical Substances along with CAS No. associated with manufacture of Drug Substance and copies available MSDSs (confidential).

E. List of Chemical Substances along with CAS No associated with manufacture of Drug Product and copies of available MSDSs (confidential).

F. The maximum Projected Annual Production and Energy Utilization Data (confidential).

G. Calculation of Expected Introduction Concentration (EIC), Maximum Expected Environmental Concentrations (MEEC) and Expected Environmental Concentrations (EEC) [confidential].

APPENDIX A

PHYSICAL - CHEMICAL PROPERTY DATA

AND

MATERIAL SAFETY DATA SHEET

(MSDS)

FOR

TASMAR DRUG SUBSTANCE

PHYSICAL-CHEMICAL PROPERTY DATA SUMMARY

TOLCAPONE (RO 40-7592

1. Solubility

Water <0.01 g/100 ml
1 - Octanol 0.4 g/100 ml
Acetone >10 g/100 ml
Ethanol 3 g/100 ml
Dimethyl sulfoxide >10 g/100 ml
Dichloromethane 2.50 g/100 ml
Ethyl acetate 5 g/100 ml

2. pKa Value

pKa = 4.3

3. Partition Coefficients

Aqueous medium	log P
n-octanol/water	about 0.2
n-octanol/water 4.6	3.21
n-octanol/aqueous buffers 6.9	1.07
n-octanol/aqueous buffers 7.4	0.18
n-octanol/aqueous buffers 8.1	0.13

4. Melting Point 145°C

5. pH = 4.6 in 1% suspension in water

6. Stability Ro 40-7592 is fairly stable at pH 3 to 13 but a tautomer sodium salt of Ro 40-7592 was isolated from an alkaline methanolic solution indicating that it can exist in different tautomeric forms.

ROCHE **Hoffmann-La Roche**

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199
Information No. (201) 235-3729
Emergency No. (201) 235-6660

Material Safety Data Sheet

FILE NO	PAGE
D-01683	1 of 4

EFFECTIVE: 6/29/92

SUPERSEDES: New

I. PRODUCT IDENTIFICATION

PRODUCT NAME: (3,4-Dihydroxy-5-nitrophenyl)(4-methylphenyl)methanone
CAS No. 134308-13-7
Ro. No. 40-7592/000 (unmilled), /001 (milled)
CODE No. Not assigned
SYNONYMS:
3,4-dihydroxy-4'-methyl-5-nitrobenzophenone
CHEMICAL FAMILY: Nitrobenzophenone
FORMULA: $C_{14}H_{11}NO_5$
MOLECULAR WEIGHT: 273.24
FORMULATION(S): Not applicable

II. HAZARDOUS INGREDIENTS

INGREDIENT NAME [CAS No.]	CONCENTRATION	EXPOSURE LIMITS OSHA PEL	EXPOSURE LIMITS ACGIH TLV	SARA Title III Section 313
Ro 40-7592 [134308-13-7]	98.0 - 102.0%	Not established		Not listed

III. HAZARD STATEMENT

WARNING! DECOMPOSES VIOLENTLY WHEN HEATED.
FORMS EXPLOSIVE DUST-AIR MIXTURES.
SCIENTIFIC DATA ON THE HEALTH HAZARDS OF THIS SUBSTANCE ARE LIMITED.

IV. PHYSICAL/CHEMICAL CHARACTERISTICS

Appearance and Odor: Yellow crystalline powder, odorless
Boiling Point, 760 mm Hg: Not applicable
Vapor Pressure (mm Hg): Unknown
Vapor Density (air=1): Not applicable
Specific Gravity (H_2O=1): Not applicable
Melting Point: 145°C
Evaporation Rate (Butyl Acetate=1): Not applicable
Solubility in Water: Insoluble
Soluble in: Acetone, dimethyl sulfoxide, tetrahydrofuran

ROCHE Hoffmann-La Roche

V. FIRE AND EXPLOSION HAZARD DATA

Flash Point: Not applicable
Flammable Limits: Not applicable
Extinguishing Media: Apply water spray with caution.
Fire Fighting Procedures: Wear positive pressure self-contained breathing apparatus and full protective clothing. Use water to keep fire-exposed containers cool. Use caution in approaching fire.
Unusual Fire and Explosion Hazards: Severe dust explosion hazard based on testing with the modified Hartmann tube at concentrations greater than or equal to 100 g/m^3; decomposes violently when heated above 150°C.

VI. REACTIVITY DATA

Stability: ( ) Unstable (X) Stable under standard conditions
Conditions to avoid: Dust accumulation, airborne dust, sources of ignition (dust explosion potential); process temperatures greater than 90°C (may cause exothermic decomposition).
Incompatibility (Materials to Avoid): Unknown
Hazardous Decomposition Products: Carbon monoxide, carbon dioxide, oxides of nitrogen
Hazardous Polymerization: ( ) May Occur (X) Will Not Occur
Conditions to avoid: Not applicable

VII. HEALTH HAZARD DATA

ROUTE(S) OF EXPOSURE: Ingestion, inhalation

SHORT-TERM/LONG-TERM EFFECTS OF EXPOSURE (signs and symptoms/organs affected): Exposure may cause headache and mild drowsiness based on one clinical study. Gastrointestinal effects such as diarrhea and vomiting may occur at high exposure levels based on animal studies.

MEDICAL CONDITIONS GENERALLY AGGRAVATED BY EXPOSURE: Unknown

NOTE: Increased incidence of spontaneous abortions in animal studies were observed; therefore, females planning to have a child and pregnant women should exercise caution regarding potential exposure.

LISTED AS CARCINOGEN OR POTENTIAL CARCINOGEN:
NTP? (No) IARC Monographs? (No) OSHA? (No)

EXPERIMENTAL TOXICOLOGY:

Oral Toxicity:

Acute oral LD_{50}(rat) is greater than 2,000 mg/kg body weight (limit test) at 14 days under the study conditions utilized. No deaths occurred during the study period; however, symptoms such as muscular incoordination, slow breathing rate and reduced motor activity were observed.

Mutagenicity:

No evidence of mutagenicity was observed in the mouse micronucleus assay, in the unscheduled DNA synthesis assay and in the following studies with and without metabolic activation: the Ames standard plate incorporation and preincubation assays, the HGPRT assay and in the chromosomal aberration assay under the study conditions utilized.

Teratogenicity:

No evidence of embryotoxicity or teratogenicity was observed in rabbits at doses of 25, 100 and 400 mg/kg/day when administered orally on days 6 to 18 of pregnancy and in rats at doses of 50 and 150 mg/kg/day when administered orally from day 6 to 15 of pregnancy under the study conditions utilized. Pregnant rabbits aborted fetal tissue on days 20 to 29 of pregnancy in the 100 and 400 mg/kg/day dosed groups.

FIRST AID: For EYE contact, flush with plenty of water. If eyes are irritated, get medical attention. For SKIN contact, flush with plenty of water and wash contact area with soap and water. If skin is irritated, get medical attention. Remove contaminated clothing and shoes and wash before reuse. If INHALED, remove to fresh air. If discomfort occurs or persists, get medical attention.

VIII. CONTROL MEASURES

Respiratory Protection: NIOSH/MSHA approved air-purifying dust respirator if use results in high or excessive dust conditions.
Ventilation: Local exhaust: For dusty operations
Mechanical (General): Recommended
Other: Not applicable
Protective Gloves: Rubber
Eye Protection: Safety glasses
Other Protective Clothing or Equipment: Not applicable

Precautions:

Do not heat above 90 degrees C.
Do not generate dust or expose to ignition sources.
Ground and bond all transfer equipment.
Avoid contact with eyes and skin.
Avoid breathing dust.
Use with adequate ventilation.
When handling, use proper personal protective equipment as needed.
Wash thoroughly after handling.
Keep container closed when not in use.

ROCHE Hoffmann-La Roche

Storage and Handling Conditions: Operate in an oxygen deficient atmosphere, e.g., inert with nitrogen. Eliminate potential ignition sources. Do not allow dust to accumulate on equipment and structure; remove dust by HEPA vacuuming. Provide explosion relief venting on all dust handling equipment and material transport systems. Place dust collectors on the roof of the building or outside in a remote location. Avoid localized heating. Closely monitor process temperatures. Milling/drying must be done at the lowest possible temperature (less than or equal to 50°C) and under vacuum or inert conditions. Store in closed containers at room temperature.

IX. SPILL/RELEASE REPORTING, SPILL CONTROL, WASTE TREATMENT AND DISPOSAL

Spill/Release Reporting: Spills or releases of this material need not be reported to the EPA National Response Center. State or local regulations may require reporting.

Spill Control: Use personal protective equipment and clothing as specified previously. Shut off source of spill or leak if safe to do so. Scoop or shovel spilled material into a suitable labeled open-head drum. Secure drum cover and move the container to a safe holding area. Mop or flush area with water.

Waste Treatment & Disposal: Landfill in compliance with Federal, State, and local regulations.

X. SHIPPING INFORMATION

DOT/IATA: Non-regulated
RCRA: Non-regulated

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The information contained herein is based upon sources believed to be reliable, however, no representation as to the accuracy or completeness thereof is made by Hoffmann-La Roche Inc. (Roche). It is the user's responsibility to determine the product's safe use, the suitability of the product for its intended use, either alone or in combination with other products, and the proper disposal of the product. No warranties, either express or implied, of merchantability or fitness or of any nature with respect to the product or to the data herein are made hereunder.

APPENDIX B

COMPLIANCE STATEMENTS SIGNED

BY A

HIGH RANKING OFFICIAL

FROM

VARIOUS COMPANIES

AND

FROM

REGULATORY AUTHORITIES

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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 tablets manufacturing and packaging of the Tasmar 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 tablets manufacturing and packaging of the Tasmar drug product at its facilities in Nutley, New Jersey. The approval and the subsequent increase in production of Tasmar tablets is not expected to affect compliance with current emission requirements or compliance with environmental laws.

Edward C. Thiele
Vice President
Pharmaceutical Operations

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Roche

ROCHE AG

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 Tolcapone at its facilities in Sissein, Switzerland, as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of Tolcapone at its facilities in Sissein, Switzerland. The approval and the subsequent increase in production of Tolcapone is not expected to affect compliance with current emission requirements or compliance with environmental laws.

date: 16. February 1996
ROCHE AG

H-R. Hunziker

Dr. H.-R. Hunziker

Head of Department Production

date: 16. February 1996
ROCHE AG

A. Hofstetter

A. Hofstetter

Head of Departement Safety and Environmental Protection

CH-4334 Sissein, Schweiz Telephon 062/866 21 11 Telefax 062/866 25 10

BAUDEPARTEMENT
KANTON BASEL-STADT

ENVIRONMENTAL PROTECTION CERTIFICATE

1. The company F. HOFFMANN-LA ROCHE LTD operates facilities for chemical and pharmaceutical manufacturing at the following address:

F. HOFMANN-LA ROCHE Ltd.
Grenzacherstrasse 124
CH-4002 Basel
Switzerland

2. These production facilities may only operate in accordance with permits issued by the responsible Authorities. In the permits are laid down the purpose for witch buildings and plants may be used and the legal conditions with which the Company must comply.

3. The above-described permits also cover the preparation of the Active Substance

Tolcapone

and the Pharmaceutical Preparation

TASMAR Tablets

4. All buildings and plants of the company F. Hoffmann-La Roche Ltd. must comply with the federal and cantonal laws and regulations concerning safety, protection of the environment and working conditions.

5. The relevant departments of the Cantonal Authorities perform periodic inspections.

6. It can here be stated that the undersigned Governmental Office has proved the correct building and producing permits are given.

BAUDEPARTEMENT BASEL-STADT
Der Departementssekretär

Basel, 11. Dezember 1995

Dr. G. Vischer

MÜNSTERPLATZ 11 · CH-4001 BASEL TELEFON 061 267 81 81 · TELEFAX 061 267 91 50