

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20697

CHEMISTRY REVIEW(S)

JAN - 6 1997

Division of Neuropharmacological Drug Products

NDA: 20-697

Review of Chemistry, Manufacturing, and Controls

	<u>Letter Date</u>	<u>Stamp Date</u>	<u>Rec'd by Chemist</u>	<u>Completed</u>
Initial Submission	03-Jun-96	05-Jun-96	12-Jun-96	27-Aug-96

Chemistry Review #1 Sponsor Roche Pharmaceuticals

Review Chemist D. Scarpetti, Ph.D. Address 340 Kingsland Street
Nutley, NJ 07110-1199

Product Name

Proprietary:	Tasmar
Nonproprietary/USAN:	Tolcapone
Code Name/#:	Ro 40-7592/000, Ro 40-7592/001

Chemical Name, Structural and Molecular Formula

3,4-Dihydroxy-4'-methyl-5-nitrobenzophenone, C₁₄H₁₁NO₅, MW 273.24

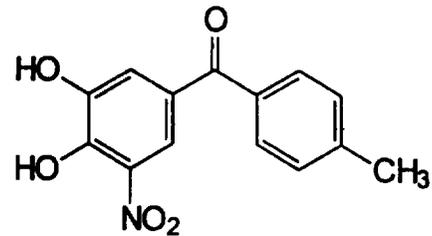
Dosage Form/Route of Administration

100/200 mg tablets/Oral

Pharmacological Category/Indication

Catechol O-Methyltransferase inhibitor/Treatment of Parkinson's Disease

Supporting Documents



Ro 40-7592

Remarks

Conclusions and Recommendations

Regarding chemistry, manufacturing and controls the submission is approvable.

cc:

Original NDA 20-697
HFD-120/Division File
HFD-120/DScarpetti
HFD-120/
HFD-120/SWBlum
Init by: SWB/

MR
1/3/97

David Scarpetti 2/27/96
David Scarpetti, Ph.D., Chem Reviewer

Division of Neuropharmacological Drug Products

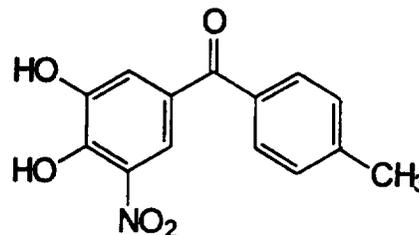
Review of Chemistry, Manufacturing, and Controls

NDA: 20-697

<u>Initial Submission</u>	<u>Letter Date</u>	<u>Stamp Date</u>	<u>Rec'd by Chemist</u>	<u>Completed</u>
Amendment BC	03-Jun-96	05-Jun-96	12-Jun-96	27-Aug-96
BC	20-Nov-96	22-Nov-96	26-Nov-96	15-Jan-97
BC	17-Dec-96	19-Dec-96	21-Dec-96	15-Jan-97
BC	07-Jan-97	09-Jan-97	11-Jan-97	15-Jan-97

Chemistry Review #2 **Sponsor** Roche Pharmaceuticals**Review Chemist** D. Scarpetti, Ph.D. **Address** 340 Kingsland Street
Nutley, NJ 07110-1199**Product Name**

Proprietary:	Tasmar
Nonproprietary/USAN:	Tolcapone
Code Name/#:	Ro 40-7592/000, Ro 40-7592/001

Chemical Name, Structural and Molecular Formula3,4-Dihydroxy-4'-methyl-5-nitrobenzophenone, C₁₄H₁₁NO₅, MW 273.24

Ro 40-7592

Dosage Form/Route of Administration

100/200 mg tablets/Oral

Pharmacological Category/Indication

Catechol O-Methyltransferase inhibitor/Treatment of Parkinson's Disease

Supporting Documents**Remarks****Conclusions and Recommendations**

Regarding chemistry, manufacturing and controls the submission is approvable.

cc:

Original NDA 20-697

HFD-120/Division File

HFD-120/DScarpetti

HFD-120/

HFD-120/SWBlum

Init by: SWB/

AMB
5/27/97

resubmitted
David Scarpetti 5/27/97
David Scarpetti, Ph.D., Chem Reviewer

Division of Neuropharmacological Drug Products

Review of Chemistry, Manufacturing, and Controls

NDA: 20-697

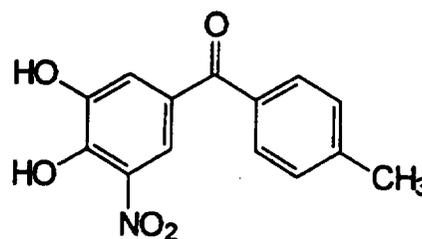
	<u>Letter Date</u>	<u>Stamp Date</u>	<u>Rec'd by Chemist</u>	<u>Completed</u>
Initial Submission	03-Jun-96	05-Jun-96	12-Jun-96	27-Aug-96
Amendment BC	30-Apr-97	02-May-97	04-May-97	27-May-97

Chemistry Review #3 **Sponsor** Roche Pharmaceuticals**Review Chemist** D. Scarpetti **Address** 340 Kingsland Street
Nutley, NJ 07110-1199**Product Name**

Proprietary:	Tasmar
Nonproprietary/USAN:	Tolcapone
Code Name/#:	Ro 40-7592/000, Ro 40-7592/001

Chemical Name, Structural and Molecular Formula3,4-Dihydroxy-4'-methyl-5-nitrobenzophenone, C₁₄H₁₁NO₅, MW 273.24**Dosage Form/Route of Administration**
100/200 mg tablets/Oral**Pharmacological Category/Indication**

Catechol O-Methyltransferase inhibitor/Treatment of Parkinson's Disease

**Supporting Documents****Remarks**

This amendment provides for an additional drug substance purification step and an update on drug product stability in the "to be marketed" packaging configuration (18 month data).

Conclusions and Recommendations**Status:** NDA 20-697 is approvable with respect to chemistry, manufacturing and controls.**Site Inspections:** Hoffman La-Roche, NJ/Dosage Form, Acceptable (AC) as of 15-Apr-97.

Hoffman La-Roche, Basle/DS mfg, AC as of 23-Jul-96.

Roche Ag, Sisseln, Switzerland/DS mfg, AC as of 07-Apr-97.

Environmental Assessment: Deficient as of 15-Nov-96.**Methods Validation:** Methods have had minor changes made, ready to be sent to validating labs, not sent out yet. No problems anticipated.

cc:

Original NDA 20-697
HFD-120/Division File
HFD-120/DScarpetti
HFD-120/TWheelous
HFD-120/SWBlum
Init by: SWB/

David Scarpetti, Chem Reviewer

Division of Neuropharmacological Drug Products

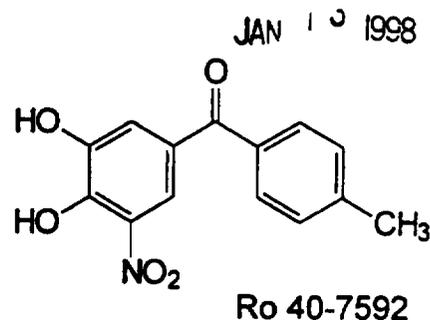
NDA: 20-697

Review of Chemistry, Manufacturing, and Controls

	<u>Letter Date</u>	<u>Stamp Date</u>	<u>Rec'd by Chemist</u>	<u>Completed</u>
Initial Submission	03-Jun-96	05-Jun-96	12-Jun-96	27-Aug-96
Amendment BC	14-Feb-97	18-Feb-97	20-Feb-97	20-Aug-97
BC	10-Mar-97	11-Mar-97	13-Mar-97	20-Aug-97
BC	21-Mar-97	25-Mar-97	27-Mar-97	20-Aug-97
AZ	28-Jul-97	30-Jul-97	01-Aug-97	20-Aug-97

Chemistry Review #4 **Sponsor** Roche Pharmaceuticals**Review Chemist** D. Scarpetti **Address** 340 Kingsland Street
Nutley, NJ 07110-1199**Product Name**

Proprietary: Tasmar
Nonproprietary/USAN: Tolcapone
Code Name/#: Ro 40-7592/000, Ro 40-7592/001

Chemical Name, Structural and Molecular Formula3,4-Dihydroxy-4'-methyl-5-nitrobenzophenone, C₁₄H₁₁NO₅, MW 273.24**Dosage Form/Route of Administration**

100, 200 mg tablets/Oral

Pharmacological Category/Indication

Catechol O-Methyltransferase inhibitor/Treatment of Parkinson's Disease

Supporting Documents**Remarks****Conclusions and Recommendations**

NAI

cc:

Original NDA 20-697
HFD-120/Division File
HFD-120/DScarpetti
HFD-120/TWheelous
HFD-120/MGuzewska
Init by: MG/

M. Guzewski
(.13)38

David Scarpetti
David Scarpetti, Chem Reviewer

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

SUMMARY REVIEW

JAN 10 1998

NDA 20-697

REVIEW DATE 13-JAN-98

SUBMISSION TYPE
ORIGINAL

DOCUMENT DATE
03-JUN-96

CDER DATE
05-JUN-96

ASSIGNED DATE
N/A

NAME AND ADDRESS OF APPLICANT

ROCHE Pharmaceuticals
340 Kingsland Street
Nutley, NJ 07110-1199

DRUG PRODUCT NAME

Proprietary:
USAN [1993]:
Code Name/Number:
Chem. Type/Ther. Class:

TASMAR
tolcapone
RO 40-7592/000 and Ro 40-7592/001
1 S

PHARMACOLOGICAL CATEGORY/INDICATION

Catechol O-Methyltransferase Inhibitor/
Treatment of Parkinson's Disease

DOSAGE FORM

Tablets

STRENGTHS

100 and 200 mg

ROUTE OF ADMINISTRATION

Oral

DISPENSED

RX OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

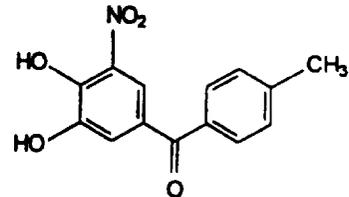
3,4-Dihydroxy-4'-methyl-5-nitrobenzophenone

C₁₄H₁₁NO₅

Mol. Wt. 273.25

CAS Registry #:

134308-13-7



SUPPORTING DOCUMENTS:

RELATED DOCUMENTS:

CONSULTS: The proposed trademark "TASMAR" is acceptable by the CDER Labeling and Nomenclature Committee. The CGMP compliance status of the manufacturing facilities is acceptable as of 15-APR-97 (copy attached). The MV package is in preparation.

REMARKS/COMMENTS: In the response to the AE letter (N (AZ) dated 28-JUL-97), the sponsor accepted the following "interim" dissolution specification:

The recommended expiration dating period is 24 months at controlled room temperature, 20-25°C (68-77°F) [see USP]. Stability data provided in the NDA do not support the requested by Roche extension to 36 months since significant physical changes (darkening of the tablet) occur at 24 months at 25°C/60%RH (see Review #5 for details).

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-697, as amended, be APPROVED with a 24 months expiration dating period. We expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

cc: Orig. NDA 20-697
HFD-120/Division File
HFD-120/MGuzewska
HFD-120/TWeelous
HFD-810/CHOiberg
HFD-810/JSimmons

1. 13.98

M. Guzewska, Ph.D., Chemist

Filename: n20697.sum