CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20697

ADMINISTRATIVE DOCUMENTS

ATTACHMENT

CERTIFICATION REGARDING U.S. PATENT NO. 5,476,875

The undersigned declares that Patent No. 5,476,875 claims a method of use for the product that is the subject of this New Drug Application for which the patent owner seeks approval.

Thomas J. Watson
Manager, Drug Regulatory Affairs

PATENT INFORMATION[1]

1.	Active Ingredient(s):	tolcapone
2.	Strength(s):	100mg, 200 mg
3.	Trade Name:	Tasmar™
4.	Dosage form and	
	Route of Administration:	tablet, oral
5.	Application Firm Name:	Hoffmann-La Roche Inc.
6.	NDA Number:	20-697
7.	First Approval Date:	None[2]
8.	Exclusivity:	Subject to patent rights, first ANDA can be submitted five years from date of pending NDA approval.

[1] While this submission was prepared in good faith, no warranty or guarantee is made regarding the accuracy or completeness of the information contained therein.

[2] Since the New Drug Application has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application has been approved.

9. Patent Information:

A. Patent number and

Expiration date:	5,236,952	08/17/2010[3]
Type of Patent:	Drug	
Patent Owner:	Hoffmann-La Roche Inc.	

B. Patent number and

Expiration date:	5,476,875	12/19/2012[3]
Type of Patent:	Method of use (see attached Certification)	
Patent Owner:	Hoffmann-La Roche Inc.	

[3] Subject to patent term extension provisions of 35 USC 156 et seq.

EXCLUSIVITY SUMMARY for NDA # 20-697 SUPPL # _____

Trade Name Tasmar Generic Name Tolcapone
Applicant Name Hoffman La-Roche HFD- 120

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /_✔_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_✔_/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_✔_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____ .

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /✔___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_✔__/

If yes, NDA #_____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_✔__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_✔_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES /___/ NO /___/ Explain: ____

_____

Investigation #2

IND # ____ YES /___/ NO /___/ Explain: ____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Signature 3/7/97 Date

Title: Project Manager

Signature of Division Director 5/16/97 Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # _20-697 Trade (generic) names : Tasmar (tolcapone) 100 mg & 200 mg tablets

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 and #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✔ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

___ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

Signature of Preparer

3/7/97
Date

cc:
Orig NDA 20-697
HFD-120 Division File
NDA Action Package

DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under 21 U.S.C. 335a (a) and (b), in connection with this application.

REQUEST FOR TRADEMARK REVIEW

JUL 16 1996

(646)

TO: Labeling and Nomenclature Committee
Attention: Daniel Boring, Chair, (HFD-530) MPN II, (827-2333)

Thru: Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products, HFD-120

From: Teresa Wheelous, Regulatory Management Officer (594-5535)
Division of Neuropharmacological Drug Products, HFD-120

RETURNED
AUG 26 1996

Date: July 16, 1996

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: TASMAR **NDA#:** 20-697

Established name, including form: Tolcapone tablets 100 mg & 200 mg

Other trademarks by the same firm for companion products: None

Indications for Use (may be a summary if proposed statement is lengthy): Parkinson's Disease

Initial comments from the submitter: (concerns, observations, etc.)

None.

cc:
NDA 20-697
HFD-120/division file
HFD-120/Leber
HFD-120/Katz/Tresley
HFD-120/SBlum/DScarpetti
HFD-120/Wheelous

m:dos\wpfiles\nda\20697\nomen.con
final: July 16, 1996

Consult #646

TASMAR tolcapone tablets

This name was found acceptable when submitted at the IND stage (consult #429) and remains acceptable at the NDA stage.

D Boring 8/22/96, Chair
CDER Labeling and Nomenclature Committee

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: May 16, 1997

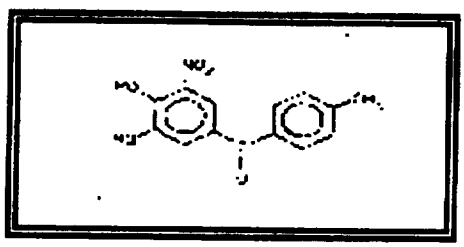
FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Tasmar [tolcapone] NDA 20-697, approvable action

TO: File NDA 20-697
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys my recommendation that Hoffmann-La Roche's NDA 20-697 for Tasmar, which allows for tolcapone's marketing as an adjunct to L-DOPA/L-AADC-[1]) therapy in the management of patients with Parkinson's Disease, be declared approvable.

Chemistry:



(3,4-dihydroxy-5-nitrophenyl)(4-methylphenyl)-1-methanone

Pharmacology

Mechanism and Rationale

Tolcapone is an orally bioavailable, reversible, inhibitor of catechol O methyl transferase [COMT], an enzyme widely distributed throughout the

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[1]AADC: aromatic aminoacid decarboxylase inhibitor

tissues of the body. Highest concentrations are found in the liver and kidney; the enzyme is also present in the brain.

Systemic COMT is said (Goodman and Gilman) to play an important role in the metabolism of circulating epinephrine and nor-epinephrine (i.e, it facilitates the methylation of the 3-hydroxy group of these adrenergic compounds), but not in their inactivation within the synapse cleft. Presumably, this explains why, despite the seeming importance of COMT to the metabolism of adrenergic compounds of both endogenous and exogenous origin, the systemic administration of COMT inhibitors has few, if any, detectable clinical consequences for normal subjects.

In Parkinson's Disease patients using L-DOPA, COMT inhibition reduces the latter's conversion to 3 methoxy-4-hydroxy-L-penylalanine (3-OMD). This, itself, may be advantageous because it increases the bioavailability of orally administered L-DOPA. Another possible benefit may derive from the reduction in the amounts of 3-OMD formed if, as postulated, 3-OMD in some way interferes with the therapeutic efficiency of exogenously administered L-DOPA.

Preclinical Toxicology

Outcomes of standard/routine tests:

1. The Rat 104 week CA study is considered positive; Renal adenomas and carcinomas in mid and high dose males and female, uterine adenocarcinomas in high dose females, and carcinomas and papillomas in forestomach of high dose males.

2. Mouse 95/80 (M/F) week CA study is negative.

3. Mutagenicity tests are equivocally positive.

4. The product is clastogenic.

5. Renal tubular injury occurs after chronic treatment of rats (2 year study).

Both Dr. Steel, the reviewing pharmacologist, Dr. Fitzgerald, the supervisory pharmacologist, agree that the NDA is approvable provided product labeling provides a fair and accurate description of the pathologies/findings observed.

Biopharmaceutics

The primary reviewer, Dr. Mahmood and the Office of Clinical Pharmacology and Biopharmaceutics raise no objection to the application being declared approvable; labeling comments are provided, however.

The primary pharmacokinetic properties of interest include:

1. An absolute oral bioavailability of 60% that is reduced by food.
2. A volume distribution of about 9 liters in volunteers, but about 16 liters in Parkinson patients.
3. Very high protein binding: > 99.8%, almost all to albumin
4. Very extensive metabolism, primarily via glucuronidation of the parent.

   A substantial fraction of the parent drug is glucuronidated at the 3 hydroxy position; in vivo, concentrations of tolcapone are likely to be well below the Km of UDP-glucuronyl transferases involved in the conjugation.

   Oxidation of the parent (to an alcohol) and its methylation (to 3-O-methyl tolcapone) are CYP 450 mediated.

5. The two major metabolites in the plasma are the 3-O-glucuronide and the 3-O Methyl (aka-Ro 40-7591). The latter is said to be "inactive."

6. Plasma clearance of tolcapone after a single dose is about 7L/hr [$t_{1/2}$ = 1.3 hours]; in a multidose study of 55 - 75 yo volunteers, no accumulation of tolcapone plasma levels was seen until the daily dose exceeded 400 mg t.i.d.

7. Liver disease decreases the clearance of unbound tolcapone by about 50%, this does not alter the $t_{1/2}$, however, because the V_d is also increased; nonetheless, the dosage must be adjusted downward to avoid increased plasma concentrations.

8. Renal impairment of the kind evaluated did not cause an impairment in elimination of tolcapone or even, as might be expected, the elimination of its 3-O-glucuronide metabolite.

9. In subjects without renal or liver disease, the PK of tolcapone is linear over oral doses of 50 mg to 400 mg; the clearance of the 3-O-methyl metabolite is not.

10. CYP 450 Interactions are not likely to present a problem although there is some evidence that tolcapone inhibits CYP 2C9

Linkage between plasma tolcapone and Erythrocyte COMT activity:

Erythrocyte COMT [RBC-COMT] serves as an indicator of tolcapone's capacity to inhibit COMT. Tolcapone inhibits RBC-COMT in a dose dependent manner; recovery of COMT activity after a single dose is dependent on the size of that dose, ranging from 4.5 hours after 5 mg to 24 hours after 800 mg.

CLINICAL

Evidence of Efficacy

The sponsor's development program was designed to evaluate the efficacy of tolcapone as an adjunct to L-DOPA therapy of Parkinson's Disease [PD] in two, more or less, distinguishable stages of response to L-DOPA that are exhibited by patients over the course of their illness. Typically, PD patients initially exhibit a relatively predicable[2], clinically satisfactory, response to L-DOPA; within a few years (3 to 5), however, the response becomes increasingly erratic. The explanation for this change presumably

[2] What the sponsor terms a "non-fluctuating" response

lies, at least in part, in the fact that with the progressive degeneration of the involved neuronal systems, the residual pool of still functioning dopaminergic neurons that project to the striatum eventually looses its capacity to synthesize sufficient dopamine from the exogenous L-DOPA being administered to facilitate muscle movement over the entire dosing interval[3]. Thus, with the progression of Parkinson's Disease, L-DOPA must be given more frequently, and in larger amounts, to be even partially effective.

Giving more L-DOPA, more often, is not an entirely satisfactory solution, however, because after prolonged periods of use, other factors (e.g., presumably attributable to alterations/adaptations occurring at the post-synaptic receptor level and beyond), cause clinically troublesome phenomena (e.g., dyskinesias) that limit the upwards titration of the dose and dosing frequency.

The sponsor's development program includes 8 randomized controlled clinical trials. Seven rely on a placebo controls; one uses bromocriptine. Two of the trials were conducted with PD patients early in the course of their illness; six studies[4] evaluated tolcapone's value as an adjunct in advanced disease (i.e., in fluctuators).

The review team's assessment of tolcapone's effectiveness is based primarily on the findings of the 3 placebo controlled trials of longer duration (4 shorter placebo controlled trials are supportive, but not deemed as important).

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[3] The failure may, in part, be attributable to increasing wastage of exogenous l-DOPA reaching the neuropil; the residual neurons function adequately enough at an individual level, but there are not sufficient numbers of them to "trap" enough of the L-DOPA during the portion of the dosing interval in which L-DOPA is present at sufficient concentration to allow efficient neuronal uptake. This is one reason why a given dose of L-DOPA, administered by duodenal infusion produces a better result than the same dose given orally in a solid dosage formulation. This reasoning also drove the development of the extended release formulation of L-DOPA.

[4] Of the six, 5 were placebo controlled.

Placebo controlled Studies in "fluctuating" patients

Study NZ14654, a 13 week long, multiclinic [US and Canada], fixed dose, 3 arm, parallel comparison of the adjunctive benefits of tolcapone, 100 mg tid, tolcapone 200 mg tid and placebo tid in PD patients [N = 202] exhibiting end of dose failure while being treated with "a maximally tolerated, stabilized, dose" of L-DOPA.

The primary, protocol specified outcome variable was the change from baseline in the time spent "on" or "off." The experiment wide decision rules called for an overall test of an effect which, if significant, was to be followed by a was to be based on a

Study NZ14655, a 13 week long, multiclinic [24 European centers], fixed dose, 3 arm, parallel comparison of the adjunctive benefits of tolcapone, 100 mg tid, tolcapone 200 mg tid and placebo tid in PD patients [N = 177] exhibiting end of dose failure while being treated with "a maximally tolerated, stabilized, dose" of L-DOPA.

The primary protocol specified outcomes were "Percent of Time Awake Spent in ON or OFF" status. Both active doses proved superior to placebo, leading to about a 11% increase in time on, and somewhere between 10 and 13% decrement in time off. The failure of the sum of Time on and Off to reach 100% is presumably an artifact of the measurement system.

Other placebo controlled studies in fluctuators

Three six week long randomized controlled trials providing comparisons of tolcapone and placebo were conducted in fluctuating patients

Study	Number of subjects	Daily mg Doses compared (given tid)	Favorable Statistical Significance
NZ14136	161	0, 150, 600, 1200	off time, all doses
BZ14114	154	0, 150, 300, 600	off time, 200 only
NN14971	215	0,300, 600	off and on time, all doses

Placebo controlled studies in Non-fluctuating patients

Study NZ14653 is a multiclinic [20 centers in US and Canada], 6 month long trial in 298 patients with PD randomized 1:1:1 to placebo, 100 mg and 200 mg of tolcapone (tid dosing regimen).

The primary protocol specified outcome measure was subscale II[5] of the United Parkinson's Disease Rating Scale [UPDRS] evaluated during an "ON" period.

An LOCF analysis up to and including 6 month observations finds a statistically significant advantage among those treated with tolcapone, that is an improvement of about 22% in the high dose and 19% as compared to no change in those randomized to placebo.

Study BZ14115 compared 97 PD patients randomized to 200 mg and 400 mg of tolcapone (tid) with placebo. The primary outcome measures was decrease in l-DOPA dose. Pairwise comparisons to placebo failed to attain statistical significance when corrected for multiple contrasts, although they did attain nominal 'p' values of ≤ 0.05

Active Controlled Study

Study NZ 14657 is a multiclinic randomized trial comparing 146 patients randomized to either tolcapone 200 mg a day or bromocriptine. L-DOPA dose was reduced to a statistically greater extent among those randomized to tolcapone as those randomized to bromocriptine.

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[5] Subscale II consists of 13 items: Speech, Salivation, Swallowing, Handwriting, Cutting Food, Dressing, Hygiene, Turning in Bed, Falling, Freezing, Walking, Tremor, and Sensory Complaints. Items are rated from 0 (Normal)-4 (Maximum Deficit).

Safety for use

The information provided in the Tasmar NDA supports a tentative conclusion that tolcapone is safe for use. The conclusion is offered as a tentative one primarily because precise counts of adverse events and the exact size of the risk set used by the sponsor to calculate incidence rates are unclear. Also, details needed to draft reliable descriptions of adverse events for product labeling are missing. Importantly, however, the review has not identified any adverse risk of sufficient seriousness to preclude eventual NDA approval. The deficiencies in the NDA are, nonetheless, multifold; they are enumerated in detail in Dr. Katz's 4/6/97 supervisory memorandum.

First, the NDA fails to provide a comprehensive and detailed explication of the extent (time and dose) of clinical experience that has been with tolcapone. Tabled immediately below is a summary of the numbers of patients evaluated (as described in Dr. Katz's supervisory memorandum).

Nature of exposure to tolcapone	Number reported in original NDA	Number reported in Safety update 4 /1/96
at least 1 dose in anyone	> 2300	
at least 1 dose in PD patients	> 1500	
participants in controlled trials	>1400	
exposed to daily dose of ≥ 200 mg		> 1300
exposed to 200 mg/d or more ≥ 6 months		> 1060
exposed to 200 mg/d or more ≥ 1 year		> 600

This mode of presentation is inadequate because it fails to provide information about the level and duration of tolcapone exposure among these patients, and, therefore, precludes the use of patient-time denominators for incidence estimates [6].

Moreover, as noted above, the review team finds that other aspects of the information vital to the evaluation of the NDA is inconsistently and/or incompletely reported. There are what, on face, appear to be contradictory statements concerning the numbers of patients within "at risk" groups (see page 12 of Dr. Katz's memorandum) used by the firm to calculate estimates for "event incidence" tabulations. In addition, Dr. Katz finds that the detail provided in reports is inadequate to allow an independent assessment of whether or not the sponsor has adequate justification for classifying individual cases in the manner that it has. (see, for example, the discussion concerning orthostatic hypotension appearing on page 22 of Dr. Katz"s review).

Nonetheless, these criticisms notwithstanding, it seems highly probable, in light of the information that has been submitted to the NDA to date, that the adverse clinical events reported in association with the use of tolcapone are, with a rare possible exception (e.g. diarrhea), the very events that would be likely to be observed in any sample of similar PD patients being treated with L-DOPA/AADC. This is certainly so of the more important risks of use.

Deaths

The mortality incidence reported for the sample of patients included in the original NDA, about 12 deaths per 1000 PYs (11 / 883 patient-years) does not exceed the incidence seen either in recent antiPD drug applications[7] or the literature. Since the original submission, there have

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[6] To be fair, some patient-time exposure data was provided for patients reported in the original NDA (i.e., 883 PYs of exposure)

[7] In the pramipexole NDA, the incidence among early PD patients was around 7 to 9 per 1000 PYs and 13 to 25 per 1000 PYs in the advanced PD samples. In the ropinerol, NDA the incidence of fatalities was in the 10 to 20 per 1000 PYs

been additional deaths (as of 4/1/96 we were aware of 26 among a presumed 1586 exposed), but none are of a kind that would support a conclusion that tolcapone played a contributory role (see Dr. Katz's memorandum for further details).

Clinical events associated with discontinuations

Similarly reassuring is the fact that the team's review of the events associated with premature discontinuations from tolcapone clinical trials provides no indication of any serious tolcapone associated risk that would preclude NDA approval. This is not to assert that tolcapone use will be without adverse consequences, but that the events reported are, in the review team's judgment, acceptable in a product intended for the management of PD. Among these events **diarrhea** was the one most often cited to explain discontinuations. Also common were **dyskinesia, confusion** and **nausea**. **Hallucinations** were also reported, but these are not at all unexpected in PD patients with more advanced disease being treated with L-DOPA/AADC.

Labeling

Given the deficiencies enumerated, the draft labeling developed by the Division review team is to a great extent as much a "work order" for the firm as it is a source of text we ask them to adopt.

Discussion

Although some details remain to be ironed out, the sponsor has provided reports that provide support for a conclusion that tolcapone, at a dose of 600 mg a day, given on a tid basis, is 1) effective in use and, 2) albeit somewhat more tentatively offered, safe for use within the meaning of the Act if it is marketed under labeling that provides the information and takes the form requested [8] by the Division review team.

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[8] These requests are embedded within the body of the draft product labeling attached to the approvable action letter.

Recommendation

The Tasmar NDA should be declared approvable.

5/16/97

Paul Leber, M.D.
5/16/97

NDA 20-697
cc:
HFD-101
Temple
HFD-120
Katz
Tresley
Fitzgerald
Steele
Hoberman
Blum
Scarpetti
Wheelous
HFD 860
Hossain
Mahmood

MEMORANDUM

DATE: April 6, 1997

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-697

SUBJECT: Supervisory Review of NDA 20-697, Tasmar, an Adjunct to L-Dopa Treatment in Patients with Parkinson's Disease

BACKGROUND

NDA 20-697 for Tasmar, a Catechol O Methyl Transferase (COMT) inhibitor to be used as adjunctive therapy to l-dopa in patients with Parkinson's Disease (PD), was submitted by Hoffman-La Roche, Inc., on 5/30/96. The NDA contains reports of 8 controlled trials designed to demonstrate the effectiveness of Tasmar as adjunctive treatment in patients either with or without fluctuations in their PD due to chronic l-dopa treatment. Six (6) of the trials were in fluctuating patients, and 2 were in non-fluctuating patients. Of the 6 studies in fluctuating patients, 5 were placebo controlled, and 1 was an active control study comparing tolcapone to bromocriptine. Both studies in non-fluctuators were placebo controlled. Of the 7 placebo controlled trials, 2 were 13 weeks in duration (fluctuators) and 1 was 26 weeks in duration (non-fluctuators); the other 4 were only 6 weeks long.

Dr. Richard Tresley, medical reviewer in the Division, and Dr. David Hoberman of Biometrics, have limited their detailed reviews of the effectiveness of tolcapone to these latter 3 studies. In addition, Dr. Tresley has performed a detailed review of the safety data in the NDA in reviews dated 11/15/96 and 11/26/96. In this memo, I will briefly summarize the pertinent safety and effectiveness data, and present my recommendation for action on this NDA.

EFFECTIVENESS

Studies in Fluctuating Patients

Study NZ14654

This was a multi-center, randomized double blind, multiple fixed dose, placebo controlled trial comparing tolcapone 100 mg TID, 200 mg TID, and placebo in patients with idiopathic PD.

In this trial, patients who exhibited end of dose wearing off symptoms on a stable, maximally tolerated dose of l-dopa were randomized to receive one of the 3 treatments listed above. Patients were screened within 4 weeks of randomization, during which time their l-dopa dose was stabilized. In addition, during the screening phase, patients filled out a diary recording, in 30 minute increments for an 18 hour period (the waking hours) , whether they were "On" (a period of relatively good functioning), "0ff" (a period of decreased, poor functioning), "Intermediate" (neither On nor Off), .or "Sleeping". This diary was completed for 3 days of each week of screening, and for 3 days of each week prior to a study visit post-randomization. The average of the 3 day ratings was used to calculate the percentage of time spent in each condition for each assessment on treatment. In the event of dopamine related adverse events, the protocol stated that it would be preferable to increase the dose interval of Sinemet, rather than decrease individual doses. Increases in Sinemet dose were not to be permitted before Month 3.

Patients were evaluated at baseline, and at 6 weeks, and 3, 6, 9, and 12 months after randomization. Patients were to continue treatment until all patients had completed 3 months and at least 30% of patients completed 12 months, and the primary analysis was to be of this 3 month data. The primary outcome was to be a comparison of the change from baseline in the amount of time spent "On" or "Off". The protocol stated that each dose would be tested against placebo at 0.05 if the overall test (analysis of variance) was significant. If it was not, a closed testing procedure would be utilized using 0.025 and 0.05 as the nominal alphas.

Secondary measures to be assessed were the change in daily l-dopa dose,

various subscales of the Unified parkinson's Disease Rating Scale (UPDRS), a frequently used rating scale designed to measure both neurologic function (e.g., bradykinesia, tremor, etc.) as well as functional capacity (e.g., dressing, eating, etc.), the Symptom Impact Profile (SIP), a scale of 136 items grouped into 12 domains (e.g., ambulation, social interaction, alertness,etc.) which the sponsor described as a quality of life measure, and an Investigator's Global Assessment of Change, which assessed function in 5 areas: severity of PD symptoms, wearing-off phenomena, overall efficacy, overall tolerance, and dyskinesia. The first 4 items were measured with a 9 point scale, and dyskinesia was measured on a 7 point scale. Additional measures were the Beck Depression Inventory, a 21 item self rating instrument designed to evaluate depression, and the Medical Resource Assessment, designed to obtain information about extra-protocol medical care.

A total of 180 patients were to be enrolled to give 138 evaluable patients. Patients who withdrew were not to be replaced. The enrollment could have been increased based on the results of other studies being evaluated at the time of the conduct of this study, or based on an analysis of the proportion of non-evaluable cases observed in this study itself.

RESULTS

A total of 202 patients were randomized at 11 centers in the United States and Canada. The following table, taken from the sponsor and reproduced in Dr. Hoberman's review as Figure 1, displays the patient flow in this trial:

	Placebo	**100 mg**	**200 mg**
Randomized	66	69	67
Completed 3 months	59	59	58
Completed 6 months	54	54	47
Completed 12 months	23	21	21

All patients at one center (6 in each group) were excluded from the intent-to-treat population included in the primary analysis because of multiple protocol violations and incomplete data. In addition to these 18,

14 more patients did not have post-randomization data to carry forward. As a result, a total of 170 patients (55 Pla, 59 100 mg, and 56 200 mg) were included in the intent-to-treat population. Note that the number of patients with data included in the intent to treat analysis is **fewer** than the number reported in the table above by the sponsor as having completed 3 months in study. We cannot reconcile this discrepancy; however, the number included in the analysis was derived from Dr. Hoberman's painstaking efforts in identifying each individual with post-randomization data. The following chart displays the results of the primary outcomes:

Percent Of Time Awake Spent in On or Off

Percent OFF

	Baseline	Month 3	Diff	P-value
Pbo	38.9	31.1	-7.8	
100 mg	39.8	27.1	-12.2	0.17
200 mg	36.8	19.0	-18.8	<0.001

Percent ON

Pbo	54.5	62.8	8.6	
100 mg	50.4	63.9	12.6	0.27
200 mg	56.6	73.8	18.2	0.008

Although these results are presented as percent of wake time spent ON or OFF, the protocol was somewhat ambiguous as to the primary analysis. Dr. Hoberman performed an additional analysis of the simple change from baseline not taking into account sleep time and found similar results.

Secondary Outcomes

No statistically significant between treatment differences were seen for any of the domains of the SIP, subscales of the UPDRS, or the Beck Depression Inventory. However, statistically significant differences were seen for the following secondary measures, which were analyzed as per the protocol ($P<0.01$ for all drug-pbo comparisons):

	Pbo	100 mg	200 mg
Investigator's Global (% improved)			
Wearing Off	37	68	95
Severity	32	60	79
Efficacy	42	71	91
L-Dopa Dose (Change in mg)	15.5	-166.3	-207.1

STUDY NZ14655

This was a study of essentially similar design to NZ14654, performed in Europe with Madopar as concomitant treatment.

RESULTS

A total of 177 patients were randomized in 24 centers in Europe. The following chart, taken from the sponsor and reproduced as Figure 2 in Dr. Hoberman's review, outlines the patient flow in this trial:

	Placebo	**100 mg**	**200 mg**
Randomized	58	60	59
Completed 3 months	48	52	52
Completed 6 months	37	42	43
Completed 12 months	10	11	11

The following chart displays the results of the primary outcomes:

Percent Of Time Awake Spent in On or Off

Percent OFF

	Baseline	Month 3	Diff	P-value
Pbo (N=51)	37.8	33.5	-4.2	
100 mg (N=56)	40.3	27.0	-12.7	0.008
200 mg (N=55)	37.4	27.7	-9.8	0.08

Percent ON

Pbo	53.4	52.6	-0.7	
100 mg	50.8	62.0	10.8	0.003
200 mg	52.4	63.3	10.8	0.003

Secondary Measures

Statistically significant differences were seen between tolcapone 200 mg and placebo on UPDRS Motor and Total scores, as well as on rare domains of the SIP. The following statistically significant findings were also seen:

	Pbo	100 mg	200 mg
Investigator's Global (% improved)			
Wearing Off	37	74	75
Severity	29	75	73
Efficacy	37	70	78
L-Dopa Dose (Change in mg)	-29	-109	-122

NON-FLUCTUATING PATIENTS

Study NZ14653

This was a multi-center, randomized, double blind parallel group trial comparing placebo, tolcapone 100 mg TID, and tolcapone 200 mg TID in patients with idiopathic PD without end of dose wearing off phenomena. In this trial the primary outcome was subscale II (Activities of Daily Living) of the UPDRS, evaluated during an ON period, and the study was considered to have ended when all patients completed 6 months and 30% of patients completed 12 months. The primary analysis was of the 6 month data, and was essentially the same as that for the previously described 2 studies. Subscale II of the UPDRS is a 13 item scale, assessing Speech, Salivation, Swallowing, Handwriting, Cutting Food, Dressing, Hygiene, Turning in Bed, Falling, Freezing, Walking, Tremor, and Sensory Complaints. Each item is rated from 0 (Normal)-4 (Maximum Deficit).

Secondary outcomes were the daily Sinemet dose, the other scales of the UPDRS, and the SIP.

A total of 300 patients (for 250 evaluable) were to be enrolled. Dropouts were not to be replaced.

In this trial, as in the previous 2 studies, an attempt to first increase the dosing interval for Sinemet was to be made to ameliorate dopamine related adverse events. In this trial, however, dosage increases of Sinemet were permitted, at the discretion of the investigator.

RESULTS

A total of 298 patients were randomized at 20 centers in the United States and Canada. The following chart, taken from the sponsor and reproduced in Dr. Hoberman's review as Figure 5, outlines the patient flow in this study:

	Placebo	100 mg	200 mg
Randomized	102	98	98
Completed 3 months	90	84	87
Completed 6 months	88	73	77
Completed 12 months	38	33	35

The following results were seen on the primary outcome for the intent to treat population:

Mean Change From Baseline in Subscale II of the UPDRS

	Baseline	Month 6	Diff	P-value
Pbo (N=102)	8.5	8.5	0.1	
100 mg (N=97)	7.5	6.2	-1.4	<0.001
200 mg (N=98)	7.9	6.3	-1.7	<0.001

As can be seen, it appears that there were considerable numbers of patients who did not complete 6 months, but for whom sufficient data were available to be included in the intent to treat analysis (e.g., 97 patients included in the ITT LOCF for the 100 mg group, but, ostensibly, only 73 competed 6 months). To examine the effect, if any, of the dropouts on the results, the sponsor performed an Observed Cases analysis. The results of these analyses yield results that are substantially better for tolcapone than the one described above. Dr. Hoberman has examined these results and finds them acceptable.

Secondary Outcomes

Statistically significant differences between each dose of tolcapone and placebo were seen for the total UPDRS and the Motor subscale of the UPDRS, as well as for change from baseline in the daily l-dopa dose (a decrease of 21 and 32 mg/day, respectively for the 100 and 200 mg doses compared to an increase of 47 mg/day for the placebo group. There were scattered nominally significant differences on at least 1 domain (Physical) of the SIP.

Other studies

As noted earlier, the sponsor submitted the results of several additional studies designed to examine the effectiveness of tolcapone. These studies were of 6 weeks duration and are listed below:

Fluctuating patients

Study NZ14136

A multi-center study (N=161) comparing tolcapone 50, 200, and 400 mg TID and placebo. Statistically significant differences on decrease in OFF time were seen for all doses compared to placebo.

Study BZ14114

A multi-center study (N=154) comparing tolcapone 50, 100, and 200 mg TID and placebo. Statistically significant differences on decrease in OFF time were seen only for the 200 mg TID dose.

Study NN14971

A multi-center study (N=215) comparing tolcapone 100 and 200 mg TID and placebo. Statistically significant differences on OFF and ON times, as well as on decrease in l-dopa dose and investigator globals were seen for each dose compared to placebo.

Non-fluctuating patients

Study BZ14115

A multi-center study (N=97) comparing tolcapone 200 and 400 mg TID and placebo. Nominally significant results were obtained for each dose compared to placebo for decrease in l-dopa dose (the primary outcome), but these comparisons were not significant when adjusted for multiple comparisons.

Active Controlled Trial

Study NZ 14657

A multi-center, randomized, open label study (N=146) comparing tolcapone 200 mg TID to bromocriptine (maximum daily dose 30 mg). Patients on tolcapone had a statistically significant decrease in daily l-dopa dose compared to bromocriptine treated patients, but there were no other consistent significant differences between treatments.

SAFETY

As of the cut-off date for the NDA (which is still unknown), a total of 2333 individuals had received at least 1 dose of tolcapone. Of these 2333, 1586 were patients with PD. Of these 1586, a total of 1445 patients were enrolled in controlled (placebo, active) or long term uncontrolled studies at any dose of tolcapone. As of April 1, 1996, the cut-off date for the 4 month safety update, a total of at least 1339 patients had been exposed to tolcapone at a daily dose of 200 mg TID. Of these 1339, duration of exposure information is apparently available for at least 1325. Of these 1325, at least 1060 had been exposed for at least 6 months, with at least 647 exposed for at least 1 year.

It is critical to note at this point that, after detailed discussions with Dr. Tresley as well as a re-reading of the sponsor's introduction to the safety update and their description of the patients included in it, an unambiguous accounting of the exact number of patients included in the safety update is not possible at this time. Specifically, in the introduction to the

update, the sponsor states:

> ...this Four-month Safety Update focuses on the safety data for the 1241 parkinsonian patients who participated in ongoing uncontrolled/extension therapeutic studies up to the Safety Update closing date of April 1, 1996....The uncontrolled extension of study NZ14653 was not included since patients entered the extension between November 1995 and March 1996 and very little data was available as of April 1, 1996.

This statement, and other related statements, implies that the only data included in the update was data derived from uncontrolled exposure.

On page 1 of Dr. Tresley's 11/30/96 review of the safety update, Table 1 (taken from the sponsor) includes exposure data for the 1241 patients to which the sponsor referred in the statements described above. However, a footnote to Table 1 states that:

> For those patients who participated in uncontrolled extension studies, exposure during the initial double-blind phase is also included.

As noted above, this chart specifically excludes patients from Study NZ14653 because it did not represent uncontrolled experience.

These 2 statements appear contradictory. If the footnote is correct, the safety update data for the 1241 patients includes controlled and uncontrolled data. However, we know that it does not include **all** data, because patients in Study NZ14653 (who had only controlled data as of 11/95) were not included. Further, we cannot tell, from the data as submitted, whether the 1241 includes patients who entered an uncontrolled extension or uncontrolled trial, but who withdrew prior to the **NDA** cut-off date (presumably, patients who were in an uncontrolled setting **after** the NDA cut-off date, but withdrew prior to the safety update cut-off date, are included in the 1241, but even this is somewhat unclear). Nor, for example, can we tell whether a patient who withdrew during the controlled portion of a trial (and hence did not have uncontrolled exposure) is included in this cohort of 1241.

If the intention of the sponsor was to present safety data from controlled and uncontrolled settings separately, they could have done so, but the current presentation is inadequate, because it contains **some** controlled trial data combined with (perhaps not all) uncontrolled data. The absence of a simple table which includes, for example, **all** patients who received treatment (or a given dose), with their appropriate durations of exposure, regardless of the conditions of exposure (controlled vs uncontrolled), makes an adequate interpretation of the exposure data impossible at this time. Given the uncertainty about how many patients are included in the safety update, all incidences of adverse events described below should be taken as approximate until further explicit exposure information is obtained. The incidences of adverse events derived from the controlled trial data base, should, on the other hand, be reliable, given that these trials were completed prior to the safety update.

Also, although the sponsor explicitly states that data from the extension trial of NZ14653 were not included in the safety update, they do state that information of serious ADRs and deaths "received from any ongoing studies are included..." in the safety update (this presumably means any of these events that occurred up to the safety update cut-off date).
Finally, the minimum numbers of patients exposed that I quoted in the first paragraph of this section were obtained by adding the appropriate numbers of patients from Study NZ14653 as taken from Dr. Hoberman's review, Figure 5, which describes patient flow in this trial. (Besides the serious deficiencies in reporting exposure described above, we have additional reason to believe that the numbers in the sponsor's flow charts may be slightly inaccurate.)

DEATHS

A total of 26/1586 (1.6%) patients with PD died during, or shortly after discontinuing, treatment with tolcapone as of 4/1/96 (an additional 7 deaths occurred after this date; we do not have detailed information about these deaths, nor do we have more recent exposure data than that included in the safety update). In the controlled trials, the mortality was 1.3%, 1%, and 0.7% for the placebo, 100 mg TID, and 200 mg TID groups, respectively.

Overall, there were 22/1339 (1.6%) deaths in patients receiving 200 mg TID.

Person-years of exposure are available for the data in the original NDA submission. At that time, the sponsor had accrued 883 person years and there were 11 deaths on treatment. This rate of 1.2 deaths per 100 patient years compares favorably to that of a relatively similar PD population recently described in the literature (see Dr. Tresley's review of 11/15/96, page 29).

Dr. Tresley has reviewed case report forms and narrative summaries of all the deaths. Duration of treatment at the time of the event that led to death ranged from 33-725 days, with a mean time of 256 days. In general, the causes of death can be categorized as follows:

Pneumonia: 7 cases

Cardiac: Heart failure: 4 cases
MI: 2 cases

Carcinoma: 5 cases

Sudden death/Cardiac arrest: 4 cases

Stroke: 2 cases

Other: Aortic stenosis: 1 case; Jaundice: 1 case

Review of most of these cases suggests that they can reasonably be related to causes other than treatment with tolcapone. The 4 cases characterized as sudden death/cardiac arrest are not completely clear; brief summaries are provided below:

1) 84 year old man treated for 444 days with 200 mg TID at the time of hospitalization for aspiration pneumonia. Ten days later developed A. Fib, found 8 days later unresponsive.

2) 77 year old man treated with 200 mg TID for 271 days at the time he

was found down in front of his house, at which time he was hypothermic, hypotensive, and had a fractured femur. He died 2 hours later. He had been treated for confusion and neuralgia for several months at the time of his death.

3) 58 year old female on 200 mg TID for 360 days when found collapsed in chair. History of orthostasis, hypokalemia, hemoptysis.

4) 78 year old female on 200 mg TID for 725 days when found dead. History of seizures for 1 year, hypertension.

The one death that appears to be reasonably related to treatment occurred in a 53 year old woman who had received treatment with 200 mg TID for 53 days at the time of onset of diarrhea, followed 4 days later by a yellowing of her skin and eyes. On day 60 of treatment, while a passenger in a car, she experienced prominent dyskinesias, and then died sometime later, still in the car. She had no known history of medical illness, and had been receiving treatment with Sinemet, pergolide, and selegeline at the time of her death. The sponsor attributed the death to cardiac causes (apparently an EKG at some point showed incomplete RBBB), but no autopsy was obtained, and no LFTs were drawn subsequent to the onset of her symptoms. This death is categorized as Jaundice in the list above.

DROPOUTS

The sponsor has submitted information on the cause of dropouts for 1241 patients who received 200 mg TID (these are the patients in Phase 2 and 3 studies, excluding those in Study 53). Over the course of 750 days (the longest duration of follow-up), 37% of patients discontinued treatment with tolcapone. As can be seen from the table of hazard rates for dropouts, reproduced from the sponsor on page 18 of Dr. Tresley's 11/26/96 Safety Update review, approximately 20% of the dropouts occurred within 6 months. The following represent those events which were reported as having been responsible for withdrawal in more than 1% of patients: diarrhea (4.8%), dyskinesia (3.5%), confusion (1.7%), and nausea (1.5%). Information about the timing of dropouts for specific adverse events is unavailable to me. Other events leading to withdrawal appeared not to be unexpected for an anti-PD treatment, some of the more

common non-motor or non-GI events being depression, agitation (6 cases), anxiety (5 cases), and syncope (5 cases).

The following chart displays a comparison of those adverse events that resulted in discontinuation from controlled trials in the 200 mg TID and placebo groups. The chart contains only those events which 1) are responsible for at least 1% of dropouts in drug treated patients and 2) occurred at a rate greater than that in the placebo group:

Adverse Event	**Placebo (N=415)**	**Tolcapone (N=408)**
Diarrhea	7.0%	11.5%
Increased LFTs	0.2%	1.7%
Hallucinations	0.2%	1.2%
Abdominal Pain	0.5%	1.0%

SERIOUS ADVERSE EVENTS

The following serious events were reported in 1% or greater of the 1241 patients who received 200 mg TID of tolcapone: fractures (1.9%), dyskinesia (1.7%), and falling, confusion, hallucination, and pneumonia (1% each). Inspection of the other reported serious adverse events revealed little of concern save for possible neuroleptic malignant syndrome associated with tolcapone withdrawal or dosage decrease. Although this was reported only once in the database of 1241 patients, Dr. Tresley has determined that there were 4 potential cases altogether, with 3 having been reported from studies in Japan.

These 4 potential cases occurred in patients, aged 54-65, on tolcapone (as well as other medications) from periods ranging from 16 days to 1 year at the time of its withdrawal or decrease in dosage. All 4 patients experienced elevated temperature and rigidity, while 3 developed elevated CPK and perhaps alterations in mental status. One patient died, 2 presumably improved, and the outcome of the other patient was unknown at the time of the Safety Update submission.

In controlled trials, the following serious adverse events were reported 1) in at least 1% of tolcapone treated patients and 2) more frequently in drug compared to placebo treated patients:

Adverse Event	Placebo (N=415)	Tolcapone (N=408)
Diarrhea	0.2%	1.2%
Dyskinesia	0.2%	1.0%
Falling	0.2%	1.0%

Syncope, which occurred in 3 tolcapone treated patients (0.7%) and in 2 placebo patients (0.5%), was the only other serious ADR which was reported to have occurred in more than 2 drug treated patients and at a greater frequency than in the placebo group.

Other Adverse Events

Dr. Tresley has appended a table listing the more common adverse events seen in Phase 3 controlled trials. Many ADRs were seen more frequently in tolcapone 200 mg TID treated patients compared to placebo. The most important were: Dyskinesia (51% vs 20%), Nausea (35% vs 18%), Anorexia (23% vs 13%), Diarrhea (18% vs 8%), Hallucination (10% vs 5%), Vomiting (10% vs 4%), Syncope (5% vs 3%), Dystonia (22% vs 17%), and Hypokinesia (3% vs 1%).

ADVERSE EVENTS OF INTEREST

Diarrhea

Diarrhea was the most common adverse event responsible for withdrawal of tolcapone treatment in controlled trials as well as in the open, uncontrolled experience. Approximately 12% of tolcapone treated patients experienced at least 1 episode. The onset of diarrhea was most common during the period 6-12 weeks after the initiation of treatment, and typically persisted for 4-6 weeks, according to the sponsor, although

little descriptive data is provided by the sponsor. The incidence and severity of diarrhea appears dose related, at least in Phase 3 studies (see Dr. Tresley's 11/15/96 review, page 97).

Increased Liver Function Tests

A total of 30 patients had at least 1 elevated LFT during treatment, 26 of whom had at least 1 elevation greater than 3 times the Upper Limit of Normal. Of the 1205 patients who received 200 mg TID for whom data is available, 29-30 (2.4%) had at least 1 elevation (ALT &/or AST) that was greater than 3 X ULN. Of these, follow-up data are available for 29. Of these 29, 19 continued treatment with return of LFTs to normal, and 10 withdrew treatment. Of these latter 10, 7 had their values return to normal, or their values were returning to normal. However, for the remaining 3, levels continued to rise up to 42 days after discontinuation (ALT 10 X ULN and AST 25 X ULN). I have no further follow-up on these latter 3 patients. According to the sponsor, no cases of liver failure have been reported (as noted above, liver injury is at least implicated in one death).

The greatest incidence of initial LFT elevation occurred between 6-12 weeks after initiation of treatment.

EKG abnormalities

EKGs were generally conducted prior to treatment, as well as at 6 months, and/or at 3 and 12 weeks, depending upon the study. In placebo controlled trials, rare abnormal findings were noted; the most frequent abnormality was ventricular premature contractions (PVCs), which were seen in 5/397 (1.7%) of tolcapone treated patients compared to 1/394 (0.3%) placebo patients. In uncontrolled trials, 15/1241 (1.0%) patients had at least 1 recorded episode of PVC. Although detailed data about sequelae of these episodes is not available to me at this time, only 1/1241 patients discontinued treatment because of an arrhythmia.

Urinalysis

In Study NZ14655, a multi-center European study, there was a dose related increase in "marked" hematuria (1/58 Placebo, 4/60 at 100 mg TID, and 8/59 at 200 mg TID). This marked hematuria was identified by dipstick. The incidence of "marked" hematuria in the combined Phase 3 domestic controlled trials was 2.1%, 2.6%, and 2.6% for the placebo, 100 mg TID, and 200 mg TID groups, respectively. There was also no dose related increases in proteinuria. According to the sponsor, the dipsticks used in Europe and the United States were essentially identical.

The findings are of some concern because studies in the rate carcinogenicity study revealed the occurrence of renal tumors at doses resulting in AUCs approximately 6 times that of humans at the 200 mg TID dose. The sponsor suggests that the increase seen in the European study is related to delays in the delivery of some samples. As Dr. Tresley notes in his 11/15/96 review, it is difficult to understand how, specifically, such a delay results in spuriously high readings for hematuria and why, in a blinded study, this would have an effect in a dose related fashion.

Orthostatic Hypotension/Syncope

Syncope was reported as the reason for discontinuation of 1/408 (0.2%) 200 mg TID patients in controlled trials, compared with 2/415 (0.5%) of placebo patients. In the overall database, as reported by the sponsor, 5/1241 (0.4%) of 200 mg TID patients withdrew due to syncope, with 9/1241 (0.7%) having had syncope that was considered serious.

In controlled trials, the sponsor classified 3/408 (0.7%) of patients receiving 200 mg TID as having syncope that was serious, compared to 3/296 (1%) of 100 mg TID patients, and 2/415 (0.5%) of placebo patients, although they also report at least 15/298 (5%) of 200 mg patients as having syncope compared to 8/298 (2.7%) of placebo patients in phase 3 placebo controlled trials (see Dr. Tresley's 11/15/96 review, page 83).

In controlled trials, 1/408 (0.2%) of 200 mg TID patients withdrew because of hypotension, compared to 0/415 placebo patients (see Dr. Tresley's review, page 82, for definitions). In the overall database, as

reported, 1/1241 (0.1%) withdrew due to syncope, with 4/1241 (0.3%) having hypotension that was considered serious. Hypotension was reported as being serious in 0/408 of th e 200 mg TID patients compared to 1/415 (0.2%) of placebo patients in controlled trials, and in 4/1241 (0.3%) of the tolcapone 200 mg TID patients in the overall database as reported.

The sponsor attempted to address the question of whether or not orthostatic hypotension was symptomatic by aggregating common symptoms that might be related to orthostatic changes (dizziness, syncope, balance loss, falling, and hypotension), and looking at the number of patients who experienced one or more of these symptoms who did or did not have orthostatic hypotension. As can be seen from the chart on page 83 of Dr. Tresley's r eview, 39/298 (13%) of the 200 mg TID patients patients were considered to have had orthostatic hypotension in phase 3 trials compared to 24/298 (8%) of placebo patients. There was a slightly greater incidence of all the 5 "orthostatic" symptoms in the 13% of patients in the treated group compared to those in the 87% of tolcapone treated patients without orthostatic hypotension. This relationship held true, generally, for the placebo patients as well, and, in general, the rates of these symptoms was higher in drug compared to placebo treated patients. However, as Dr. Tresley points out, the numbers are small, and it appears that it is impossible to tell, given the information in hand, whether the symptoms were reported at the time of documented orthostasis. Further, as Dr. Tresley notes, the sponsor did not consider changes in pulse in its identification of cases, although that may be the earliest sign of orthostasis.

Further, the sponsor suggests that patients who were treated with dopamine agonists were more likely to develop orthostatic hypotension at least once during controlled trials compared to those not receiving such therapy; 17/101 (17%) patients receiving 200 mg TID and dopamine agonists compared to 22/197 (11%) of patients receiving 200 mg TID but no dopamine agonists (there was no difference between the 2 subgroups of the 100 mg TID treated group).

Finally, the sponsor suggests that the presence of orthostasis at baseline was correlated with dose related increases in the number of episodes of

orthostasis on treatment. For example, according to the sponsor, the incidence of orthostatic hypotension on treatment for patients with no orthostatic symptoms at baseline was 6%, 10%, and 18% for placebo, 100 mg TID, and 200 mg TID, respectively. The corresponding incidence of orthostatic hypotension on treatment for patients with moderate or severe orthostatic symptoms at baseline was, according to the sponsor, 27%, 36%, and 50%. Individual data for these individuals was not presented by the sponsor.

CONCLUSIONS

The sponsor has presented the results of numerous randomized controlled trials of the effects of tolcapone on the symptoms of idiopathic PD. These studies evaluate the effects of tolcapone in patients with and without end of dose wearing off phenomena. We have chosen to focus on the results of the 3 trials that evaluated the effects of the treatment for more than 6 weeks. These trials demonstrate that tolcapone is effective in treating (some of) the symptoms of PD and that the treatment appears clinically useful, although of moderate degree, on average. Although the most consistently positive findings are in the group treated with 200 mg TID, a dose of 100 mg TID was also found to be generally effective.

Tolcapone, at a daily dose of 600 mg, given as 200 mg three times a day, appears generally well tolerated, and there appear to be no safety concerns that would preclude approval. However, a number of issues need to be addressed.

In general, use of tolcapone is accompanied by a necessary decrease in the daily dose of levodopa/carbidopa, presumably to control dopaminergic adverse effects (e.g., dyskinesia). Even with this decrease, how ever, there persist dose related increases in the incidence of these dopaminergic adverse effects in the treated groups compared to placebo (treated with levodopa/carbidopa alone) patients. While this decrease in l-dopa dose is accompanied by an improvement in control of PD symptoms, it should be borne in mind that, in general, the increase in control of the patients' PD occurs at a price of increased dopaminergic adverse effects.

As I have noted earlier, the sponsor has presented the extent of exposure -

to tolcapone in a manner that makes it difficult to assess the true extent/duration of experience with the drug. As mentioned, they have not presented the total extent and duration of exposure for all patients treated in one cumulative presentation, and they should be asked to do so. Further, as a result, the incidence of adverse events, discontinuations due to specific adverse events, etc., in the total population treated will need to be re-calculated on the basis of this re-presentation of the exposure data.

In addition, the sponsor's description of certain of the more commonly occurring adverse events is less than detailed, and they should be asked to supply additional details. For example, the presentation of the data for orthostatic hypotension/syncope is confusing, and should be clarified. Specifically, the incidences, especially in various sub-groups based on symptoms at baseline, concomitant baseline medications, the temporal relationships between symptoms and documented changes in vital signs, th e time course relative to treatment initiation, and other relative factors should be presented in sufficient detail to permit an independent review of the data. Similarly, detailed information about diarrhea has not been submitted, and similar re-presentation of this data, as well as data for hepatic enzyme abnormalities should be submitted. In particular, detailed patient narratives for patients with significant abnormalities should be presented.

The nature of the chang es made in concomitant l-dopa dose should be discussed in detail. Specifically, when changes were made, whether or not they were made prospectively or in response to increases in dyskinesias or other dopaminergic adverse events, as well as the time course of these dopaminergic effects, and their amelioration in response to l-dopa dosage adjustments should be described.

A more detailed description and discussion of the apparent hematuria seen is necessary. The sponsor's current explanation of the hematuria seen in the European study is unsatisfying, and a coherent and complete assessment of this potential problem should be made, including a description of how often urinalyses were performed, and with what methodology.

An additional problem arises out of the sponsor's desire to market 100 mg and 200 mg formulations that were not ext ensively evaluated clinically. Single dose bioequivalence studies have demonstrated that, while these formulations result in AUCs that are equivalent to those resulting from the clinically studied tablets, they yield C_{max}'s that are greater than those from the clinically studied tablets, and, in fact, fail the criteria for bioequivalence. The failures are relatively small (e.g., the C_{max} of the to be marketed 200 mg tablet was 37% greater than that of the clinical formulation, and the 90% CI of the ratio of the geometric means was 1.24-1.52). Ordinarily, I would not be concerned about the effect of a failure in this direction on the effectiveness of the drug, but it does raise the question of whether or not the difference in C_{max}'s will result in a difference in the profile of ADRs. As pointed out by the Biopharmaceutics reviewers, however, certain facts might be considered to mitigate this failure.

First, there is evidence that the dissolution profile for the 200 mg clinical formulation was considerably slower than that for the 200 mg to be marketed formulation (the latter of which is quite reproducible across batches and similar to that of both the 100 clinical and to be marketed tablets). Second, bioequivalence studies of these formulations performed in Japanese subjects have demonstrated bioequivalence between the various formulations. Further, the NDA contains safety experience in approximately 135 patients who received 400 mg TID. Exposures of this magnitude would certainly be considered to be capable of assuring the safety of a 200 mg tablet that resulted in slightly higher C_{max}'s than the 200 mg tablet studied clinically.

However, the slow dissolution, although a reasonable explanation for the decreased C_{max} of the clinical tablet, may in reality have nothing to do with the in vivo performance of the tablet (I.e., no relationship between in vitro dissolution an in vivo performance. While the finding in the Japanese study is encouraging, it cannot be considered to be cause to dismiss the findings of inequivalence. Finally, the experience at 400 mg TID, while encouraging, is relatively limited in number and, critically, provides no information on treatment for greater than 6 weeks.

For these reasons, it might be important to further evaluate the adverse event profile of the to be marketed 200 mg tablet. Toward this end, it might be useful to ask the sponsor to compare adverse events seen with each formulation (based on telephone conversations with the sponsor, we know that they have some data with the to be marketed dosage forms; some is easily presented separat ely from the data in which the clinical formulation was used, and some will take considerable effort to re-analyze). Any re-analysis of this data will be complicated by the fact that most of the experience with the to be marketed formulation will be in patients who had already been treated with the clinical formulation.

RECOMMENDATIONS

The sponsor has submitted sufficient information to permit a conclusion that tolcapone is effective as an adjunctive treatment to levodopa/carbidopa for PD in patients with or without end of dose wearing off phenomena. In addition, the sponsor has submitted sufficient safety information to permit a preliminary conclusion that tolcapone is acceptably safe. However, before a final decision about the safety of the treatment can be reached, and before adequate labelling can be written, they must submit additional data and re-analyses of information, as described in the preceding section.

For these reasons, I recommend that the sponsor be sent the attached Approvable letter with the appended draft labelling.

Russell Katz, M.D.

cc:
NDA 20-697
HFD-120
HFD-120/Katz/Leber/Tresley/Wheelous
HFD-710/Hoberman