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ASSOCIATES**

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

September 9, 1999

Rusty Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products
Center of Drug Evaluation and Research (HFD-120)
Office of Drug Evaluation I
Woodmont II Building
1451 Rockville Pike, Room 4039, 4th Floor
Rockville, MD 20852

**RE: Orion Corporation
NDA 20-796/COMTAN[®] (Entacapone 200 mg Tablets)
Response to requests made by Dr. Sevka**

Dear Dr. Katz:

On behalf of Orion Corporation we are hereby submitting a response to the requests made by Dr. Sevka on the following dates:

- August 13, 1999
- August 20, 1999
- September 3, 1999

This submission contains an Archival, Review, and Desk copy. To date, there are no more outstanding issues related to Dr. Sevka's questions.

Please let me know if I can be of further assistance.

Sincerely,

A handwritten signature in black ink that reads "Robert J. McCormack" followed by a stylized flourish.

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs
Target Research Associates



**TARGET
RESEARCH
ASSOCIATES**

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

July 28, 1999

ORIGINAL

ORIGINAL AMENDMENT

N-(BS)

Russ Katz, M.D.
Acting Director
Division of Neuropharmacologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

JUL 29 1999

RECEIVED HFD-12

**RE: Orion Corporation
NDA 20-796/Comtan[®] (entacapone 200 mg tablet)
Submission of additional data for the Celomen study**

Dear Dr. Katz:

Reference is made to the July 21, 1999 request of Dr. Khun He for additional information from the Celomen study, specifically the "on time" data for all patients.

On behalf of Orion Corporation we are hereby providing two diskettes (a review and an archival copy) containing SAS data sets with the "on time" data for all patients in the Celomen study and a detailed description of the datasets.

Please let me know if you have any questions or need additional information.

Sincerely,

Jill A. Powers
Manager, Regulatory Affairs



INICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL AMENDMENT

ORIGINAL *NEC 1*

July 15, 1999

Russ Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th Floor
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

JUL 18 1999

RECEIVED HFD-120

**RE: Orion Corporation, Comtan™ (Entacapone) 200mg Tablet, NDA #20-796
Response to request from FDA pharmacology reviewer**

Dear Dr. Katz,

Enclosed, in duplicate, is a response to the request by the pharmacology reviewer for the definition of the term "endometriosis lesions" seen in the report of the histologic evaluation extension from the 104-week carcinogenicity study in mice, which was submitted to the agency on May 17, 1999.

This histologic evaluation extension study was conducted at a contract facility (Inveresk Research, Scotland) therefore the enclosed explanation related to the endometriosis issue has been provided by them. Please be advised that in researching the request by FDA, Inveresk needed to modify Table #4, in the original report, and this document is also being submitted at this time. The modification to Table #4 does not present any new information which would affect the overall conclusions presented in the initial study report.

Please let me know if you have any questions.

Sincerely,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

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ASSOCIATES**

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

May 25, 1999

CENTER FOR DRUG EVALUATION
AND RESEARCH

ORIG AMENDMENT MAY 26 1999

Russ Katz, MD, Acting Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL.
Rockville, MD 20852

RECEIVED HFD-120

~~NEW CORRESP~~

ORIGINAL

Re: Orion Corporation, Comtan™ (Entacapone) 200 mg tablet, NDA #20-796
Notification of changes made to the [redacted] for Entacapone
[redacted]

Dear Dr. Katz,

Reference is made to the NDA #20-796 for Comtan® 200 mg tablet submitted to the Agency on January 2, 1998; and to telephone conversations between Dr. Martha Heimann of FDA and Mr. Ilkka Larma of Orion Pharma.

On behalf of Orion Corporation we are hereby submitting in triplicate (archival copy, review copy, field copy) a notification of changes submitted to the FDA by Orion Corporation [redacted] in a Supplement to a [redacted] for Entacapone active drug substance [redacted]

If you have any questions, please, do not hesitate to contact me.

Sincerely,


Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

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RESEARCH
ASSOCIATES**

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIostatISTICS

May 24, 1999

Russ Katz, M.D.
Acting Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research (HFD-120)
Woodmont II Building
1451 Rockville Pike, Room 4039, 4th Floor
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

MAY 25 1999

RECEIVED HFD-120

ORIG AMENDMENT

N(BP)

ORIGINAL

Dear Dr. Katz,

Reference is made to the approvable letter for entacapone dated Dec. 31, 1998 and to Orion's complete response to the NDA approvable letter submitted to the agency on April 16, 1999.

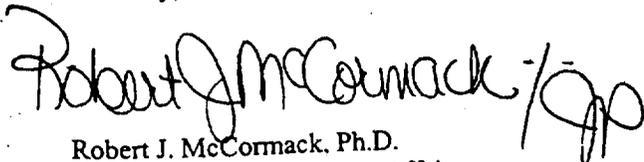
As part of the complete response to the Pharmacology/Toxicology issues, Orion committed, as per the NDA approvable letter, to submitting additional histopathology results in male and female animals from the 20 mg/kg/day dose group and male animals from the 100 mg/kg/day dose group from the 104-week carcinogenicity study conducted in the mouse with entacapone.

Therefore, on behalf of Orion Corporation, we are hereby providing in duplicate a report containing the results of the additional histopathology evaluations conducted on the mice from the 104-week carcinogenicity study with entacapone. Please be advised that in addition to the animals from the 20 and 100 mg/kg/day dose groups all animals from the second control group were also evaluated.

The findings from all animals at low (20 mg/kg/day) and intermediate (100 mg/kg/day) dose level did not alter the previous conclusion that the administration of entacapone at doses up to 600 mg/kg/day was not associated with any neoplastic or non-neoplastic histopathological findings.

If you have any questions or additional comments, please feel free to contact me.

Sincerely,



Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs



**TARGET
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CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

April 16, 1999

Russ Katz, M.D.
Acting Director
Division of Neuropharmacologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

**RE: Orion Corporation
NDA 20-796/Comtan® (entacapone 200 mg tablet)
Submission of complete response to NDA approvable letter**

Dear Dr. Katz:

Reference is made to the approvable letter dated 12/31/98 for the Comtan® NDA, to the meeting which took place with the Agency on February 11, 1999 and to a subsequent phone conversation with Teresa Wheelous where Orion was informed that a complete efficacy report for the Celomen study would need to be submitted as part of the complete response to the NDA approvable letter.

On behalf of Orion Corporation we are hereby providing a review and an archival copy of the complete response to the NDA approvable letter for the Comtan® NDA. Also provided for use by the individual NDA reviewers are three extra copies of Volume 1 which contains the Comtan® labeling. Diskettes containing an electronic version of the labeling have been included inside the front cover of Volume 1 of the archival copy and the review copy. Please be advised of the following, related to the information enclosed in the complete response:

- The labeling has been modified to include the missing sections which were present at the time the approvable letter was issued. Other than providing the missing information, the package insert is essentially the same as the version received from FDA as part of the approvable letter.
- A full efficacy report of the Celomen study has been provided as per FDA's request. Safety information for this study has been provided as part of the safety updates submitted to the agency on May 15, 1998 and Dec. 7, 1998.
- Orion believes that its response to the approvable letter has been timely; therefore, a safety update has not been included. As you are aware, a safety update was provided to the agency on Dec. 7, 1998 covering the period through Oct. 31, 1998. Since that time, there has been relatively little new entacapone safety data that would warrant the submission of a third safety update report to the NDA.
- A copy of the introductory promotional materials have not been submitted at this time but will be sent to the agency once the labeling for the product has been finalized.

- The response has been organized as follows:
 - Volume 1 contains an overall table of contents and a copy of the Comtan[®] labeling. Two copies of the label have been provided. The first copy shows the changes that have been made to the FDA version received as part of the approvable letter. The second copy is a clean copy of the entire label.
 - Volumes 2-14 contain the efficacy report for the Celomen study.
 - Volume 15 contains the response to the clinical safety questions.
 - Volume 16 contains information related to the response for the pharmacology / toxicology questions.
 - Volume 17 contains information related to the response for the biopharmaceutical questions.

Please let me know if you have any questions and we look forward to hearing from the agency within the six month time period for review.

Sincerely,



Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

**TARGET
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ASSOCIATES**

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

December 7, 1998

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
Office of Drug Evaluation
Woodmont II Building
1451 Rockville Pike, Room 4039, 4th Floor
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

DEC 08 1998

RECEIVED HFD-120

RE: **NDA 20-796**
Comtan[®] 200 mg Tablets (entacapone)
Indication: Adjunctive treatment with levodopa/carbidopa in patients
with Parkinson's Disease
Submission of second Safety Update Report

N(SU)

ORIG AMENDMENT

Dear Dr. Leber:

Enclosed, on behalf of Orion Corporation, we are hereby submitting, in duplicate, eleven volumes comprising the second entacapone Safety Update Report, which was requested by Division personnel in a teleconference which took place on November 18, 1998.

The original NDA submission for entacapone contained safety information on patient events that occurred up to October 31, 1996. The 120-Day Safety Update Report contained new safety data for the period of November 1, 1996 - October 31, 1997. The enclosed safety update contains the previously submitted safety data on serious adverse events, deaths, and drop-outs due to adverse events, together with this type of information from the period of November 1, 1997 - October 31, 1998.

As requested by FDA in the conference call on November 18, 1998, the Safety Update Report contains among other things the following specific information:

- Updated exposure table (contained in Volume 1)
- Summary and discussion of hepatic reactions, neuroleptic malignant syndrome, rhabdomyolysis, fever and hematologic events including anemia (contained in Volume 11)
- Post-marketing data (contained as part of the above-referenced summary in Volume 11)
- Complete set of narrative summaries for all patients that experienced a serious adverse event (contained in Volumes 4 through 10)

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- Summary of comparative toxicological studies with entacapone and tolcapone in the rat (contained in Volume 11)

A complete Table of Contents for the Safety Update Report has been provided in Volume 1. Each subsequent volume of the submission contains a Table of Contents detailing the information contained in that specific volume.

Please let me know if you have any questions regarding the enclosed safety information. We are looking forward to working with the agency in order to receive an approval letter for entacapone by January 2, 1999.

Sincerely,



Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

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**TARGET
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DUPLICATE

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

December 1, 1998

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-101)
Office of Drug Evaluation
Woodmont II Building
1451 Rockville Pike, Room 4039, 4th Floor
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

DEC 02 1998

RECEIVED HFD-120

NEW CORRESP

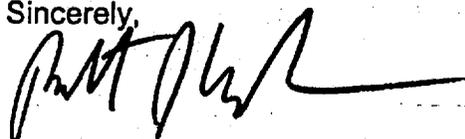
RE: NDA 20-796
Comtan[®] 200 mg Tablets (entacapone)
Indication: Adjunctive treatment with levodopa/carbidopa in patients
with Parkinson's Disease
Letter of authorization allowing Novartis personnel to contact the
agency

Dear Dr. Leber:

Enclosed, in duplicate, is a letter from Orion Corporation allowing Novartis personnel to contact the agency directly on certain matters related to the Comtan[®] (entacapone) NDA.

Please let me know if you should have any questions.

Sincerely,



Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

RJM/llp

Enclosure(s)



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ORION

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DUPLICATE

CAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

December 1, 1998

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-101)
Office of Drug Evaluation
Woodmont II Building
1451 Rockville Pike, Room 4039, 4th Floor
Rockville, MD 20852

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AND RESEARCH

DEC 02 1998

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ORIG AMENDMENT

N (bom)

**RE: NDA 20-796
Comtan® 200 mg Tablets (entacapone)
Indication: Adjunctive treatment with levadopa/carbidopa in patients
with Parkinson's Disease
Summary of FDA teleconference on November 18, 1998 and
submission of information requested during the teleconference**

Dear Dr. Leber:

In a telephone conversation between the Division and Orion personnel on November 18, 1998, we were made aware by the agency of their desire to issue a final approval letter for entacapone by the Prescription Drug User Fee deadline of January 2, 1999. Dr. Katz stated that issuing an approval letter by January 2, 1999, would be possible if (1) a safety update focusing on hepatic reactions, neuroleptic malignant syndrome, rhabdomyolysis, fever, and hematologic events could be submitted to the agency in the near future, (2) labeling could be negotiated and finalized, and, (3) entacapone would be able to be marketed in the US in a reasonable time after approval. Orion plans to do everything possible to ensure that an approval letter for entacapone is issued by January 2, 1999, and, therefore, hereby commits to submitting the requested safety update to include patient events that occurred through October 31, 1998, to FDA no later than December 7, 1998.

As you are aware, Novartis will be responsible for packaging, distribution, and marketing of entacapone tablets in the US. Novartis is also willing to make every effort necessary to receive an approval letter for Comtan® by January 2, 1999. Novartis believes they can begin marketing and distribution of Comtan® during the first quarter of 1999 providing that they, together with Orion personnel, can engage in labeling discussions with the agency early in December 1998. Additionally, in order for Novartis to begin marketing and distribution of Comtan® in the first quarter of 1999, Orion Corporation [redacted] will need to increase production of entacapone bulk drug substance. Since the current Orion

Corporation [redacted]
the expected marketing demands in the US, the [redacted] would
need to be amended to allow for production of entacapone active ingredient

[redacted] FDA review of [redacted]

During the telephone conversation on November 18, 1998, FDA also asked for additional information. This information is detailed below along with Orion's response.

FDA Request #1: Was CPK data collected as part of the entacapone clinical program?

Response: CPK data was not collected as part of the entacapone clinical program.

FDA Request #2: FDA is under the impression that when multiple adverse events occurred in a single patient only selected events were reported in the NDA.

Response: All multiple adverse events for a single patient were reported in the NDA. E.g., if one patient reported 1) dyskinesia, 2) nausea, and 3) pain, these all are presented in the AE tables (e.g., in NDA-ISS Table 8.2 and in the corresponding post-text Table 17). In the case of AE discontinuations (see NDA-ISS in post-text Table 14, located in Volume 76, page 8-393), all events are similarly listed. If confusion still exists regarding this point, then we will need to schedule a conference call to discuss specific examples FDA may have related to this issue.

FDA Request #3: Are there any additional efficacy data from studies 2939052, 2939062, and 2939065?

Response: No additional efficacy data are available for the three studies listed above. As the study reports are finalized, the information will be submitted to the agency. All safety data obtained by October 31, 1998 from these studies will be included in the safety update submission being sent to the agency in December 1998.

December 1, 1998

FDA Request #4: Please submit postmarketing data to include a list of countries where the product is approved and the date the product was launched in each respective country.

Response: This information will be provided as part of the safety update submission which will be sent to the agency in December 1998.

FDA Request #5: Please provide a copy of the entacapone label to be used in the United Kingdom.

Response: A copy of the label for entacapone in the United Kingdom was submitted to the agency on November 23, 1998.

FDA Request #6: Submission of preclinical data which evaluated liver damage in animals administered either tolacapone or entacapone.

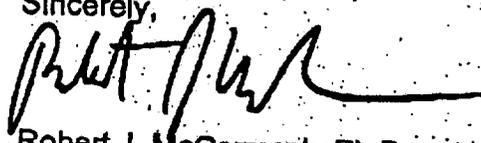
Response: A summary of this preclinical information will be included in the safety update submission to be sent to the agency in December 1998.

FDA Request #7: FDA stated that not all the required narrative summaries are available in the NDA or 120-Day Safety Update. As an example, patient 1802 (study number was not identified), had elevated liver enzymes, and was admitted to hospital. FDA said that they could not locate a narrative summary for this patient.

Response: To the best of Orion's knowledge, all required narrative summaries have been submitted in the NDA and the 120-Day Safety Update. Referring specifically to patient 1802, the narrative for this patient can be located in the ISS, Attachment D1 in Volume 77, page 8-239.

Please let me know if you have any questions regarding the enclosed material. We look forward to working with the agency with the common goal of receiving an approval letter for entacapone by January 2, 1999.

Sincerely,



Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs



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ORIGINAL

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

November 11, 1998

Paul D. Leber, M.D., Director
Division of Neuropharmalogical Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
Office of Drug Evaluation
Woodmont II Building
1451 Rockville Pike, Room 4039, 4th Floor
Rockville, MD 20852

ORIG AMENDMENT

N(BC)

EVALUATION

NOV 11 1998

CENTER FOR DRUG EVALUATION
AND RESEARCH

**RE: NDA 20-796
Comtan[®] 200 mg Tablets (entacapone)
Amendment to Pending NDA**

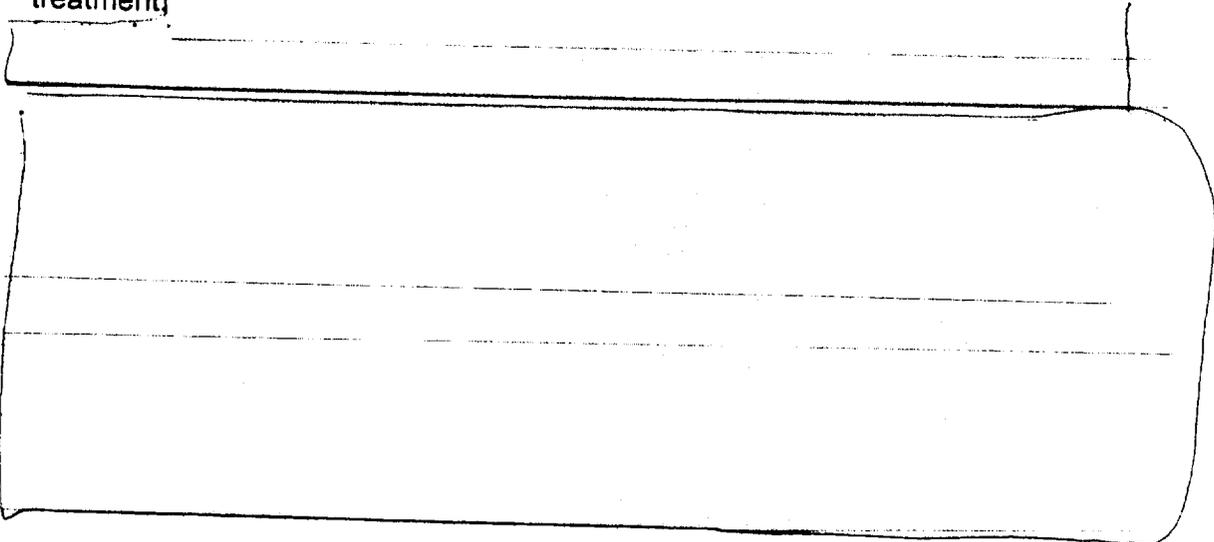
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Dear Dr. Leber:

Reference is made to the Comtan[®] 200 mg Tablets NDA 20-796, resubmitted to the agency on December 23, 1997, for the treatment of signs and symptoms of Parkinson's disease as an addition to levodopa/dopa decarboxylase inhibitor treatment.



Additionally, as discussed with Dr. Martha Heimann on November 10, 1998, we are hereby submitting two revised pages of a stability protocol, which was originally submitted to the Agency as part of our September 30, 1998 submission. The two revised pages are pages 2 of 4 and 3 of 4 of the "Stability Commitment/Additional Batches for Primary Stability Program", and can be located on pages 195 and 196 in Orion's September 30, 1998 submission. The revision made to the protocol is an addition of optional 36- and 48- month testing points.

Should you have any comments or questions regarding this submission, please do not hesitate to contact me directly at 908.322.2402.

Sincerely,



Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

Cc: Ms. Regina Brown
New Jersey District Office, North Brunswick Resident Post/Certified Field Copy



ORIGINAL

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

November 4, 1998

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-101)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

NOV 05 1998

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ORIGINAL AMENDMENT
N(BM)

RE: Orion Corporation
NDA 20-796/Comtan (entacapone 200 mg tablets)

Response to October 23 request from Dr. Michael Sevka for clarifications regarding the Index of Case Report Forms for all studies

Dear Dr. Leber:

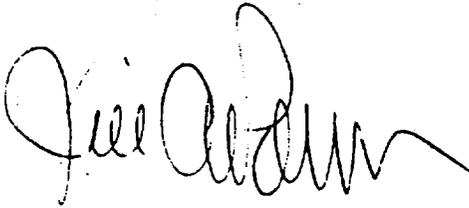
Reference is made to the NDA (#20-796) for Comtan (entacapone 200 mg tablets) resubmitted to the agency on December 23, 1997. On behalf of Orion Corporation, we are hereby submitting, in duplicate, clarifications to questions raised by Dr. Sevka on October 23, 1998 regarding discrepancies between the itemization of Case Report Forms (CRFs) in the CRF Index and the text of the NDA and 120-Day Safety Update. The following clarifications are being submitted:

- A revised Index of Case Report Forms for all studies which, itemizes CRFs submitted in the initial NDA and in the Safety Update. Please be advised that CRFs were submitted only for patients who discontinued due to adverse events or who died.
- The following information clarifies discrepancies occurring between the originally submitted CRF Index and the text of the NDA and 120-Day Safety Update:
 - (1) Two entacapone treated patients in study 293928 were tabulated as having discontinued due to an adverse event in the NDA and Safety Update (NDA-Post-text table 13a., Vol. 76, page 391, and Safety Update-Post-text table 4. Vol. 2, page 008). This tabulation was erroneous, because as reported by the investigator, patient # 24 discontinued due to other reasons and only patient # 1 discontinued due to an adverse event (CRF of patient # 1 submitted in the original application in Vol. 276, page 180).

- (2) One placebo treated patient in study 293928 was erroneously tabulated as having discontinued due to an adverse event in the NDA and Safety Update (NDA-Post-text table 13b., Vol. 76, page 392, and Safety Update-Post-text table 5., Vol. 2, page 010). However, as reported by the investigator, the patient # 2 discontinued due to intercurrent illness.
- (3) One entacapone treated subject (#17) in study 293904 was erroneously tabulated as having discontinued due to an adverse event in the NDA and Safety Update (NDA-Post-text table 13a., vol. 76, page 391 and Safety Update-Post-text table 4., vol. 2, page). However, the reason for discontinuation should have been intercurrent illness as explained in the study report (NDA vol. 82, pages 013-014).

Please let me know if you have any questions or require any additional information.

Sincerely:



Jill A Powers
Manager, Regulatory Affairs

APPEARS THIS WAY
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CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

November 3, 1998

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

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NOV 04 1998

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ORIGINAL AMENDMENT
N(BB)

RE: Orion Corporation
NDA 20-796/Comtan (entacapone 200 mg tablets)
Submission of Individual Creatinine Clearance Values
for Healthy Patients Who Participated in Study 2939057

Dear Dr. Leber:

Reference is made to the NDA (#20-796) for Comtan (entacapone 200 mg tablets) resubmitted to the agency on December 23, 1997, and to a telephone conversation with Dr. Sayad Al-Habet on October 13, 1998, in which he requested the individual creatinine clearance values for healthy patients who participated in study 2939057 (entacapone pharmacokinetics in renally impaired patients) be submitted to the agency.

Please be advised that individual creatinine clearance values for healthy patients were not determined in this particular study although the creatinine clearance value of $>1.33\text{ml/sec}/1.73\text{m}^2$ was stated as an inclusion criterion for the patients enrolled in the control group of this study (those with normal renal function). Instead, creatinine clearance values were derived using a formula referenced in the literature.

On behalf of Orion Corporation, we are hereby submitting, in duplicate, the justification of using derived renal creatinine clearance values for healthy patients in Study 2939057. The following documentation is being submitted to support this justification:

- Statement by the principle investigator of Study 2939057 which explains how derived creatinine clearance values were determined
- A table listing the derived creatinine clearance values of healthy subjects used in Study 2939057

Please let me know if you have any questions or require any additional information.

Sincerely:

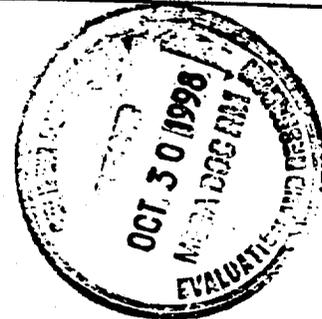
Jill A. Powers
Manager, Regulatory Affairs



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ORIGINAL

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS



October 28, 1998

Paul D. Leber, MD, Director
Division of Neuropharmalogical Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

NOV 03 1998

RECEIVED HFD-120

NEW CORRESP

**RE: Orion Corporation
NDA 20-796/Comtan (entacapone 200 mg tablets)
Submission of teleconference meeting minutes**

Dear Dr. Leber:

Attached is a copy of the minutes of a telephone conference held between Dr. Choudhury and Orion personnel on October 23, 1998.

Please let me know if you have any questions.

Sincerely:

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

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ON ORIGINAL

RJM/llp

Attachment



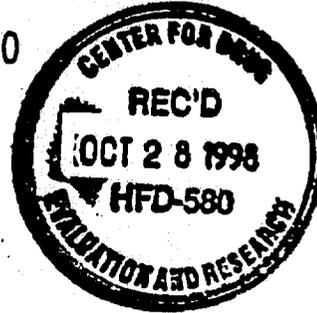
**TARGET
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CLINICAL RESEARCH, REGULATORY AFFAIRS & BIostatistics
CENTER FOR DRUG EVALUATION AND RESEARCH

OCT 30 1998

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October 27, 1998

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

NEW CORREL

**RE: Orion Corporation
NDA 20-796/Comtan (entacapone 200 mg tablets)
Submission of information requested by Dr. Japobrata Choudhury**

Dear Dr. Leber:

Reference is made to the NDA (#20-796) for Comtan (entacapone 200 mg tablets) resubmitted to the agency on December 23, 1997, and to a telephone conversation with Dr. Japobrata Choudhury in which he requested unblinding dates of entacapone studies 2939033 and 2939044.

Therefore, on behalf of Orion Corporation, we are hereby submitting, in duplicate, the following information, which was faxed to Dr. Choudhury on October 15, 1998, at his request.

Study 2939033 was unblinded on December 8, 1995

Study 2939044 was unblinded on October 6, 1995

Please let me know if you have any questions.

Sincerely,

Jim Powers
Manager, Regulatory Affairs

JP:llp



**TARGET
RESEARCH
ASSOCIATES**

ORIGINAL

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

October 7, 1998

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

OCT 08 1998

RECEIVED HFD-120

RE: **Orion Corporation**
NDA 20-796/Comtan (entacapone) 200 mg tablets

ORIG AMENDMENT
N(87)

**Response to September 29 request from Dr. Michael Sevka for a combined
NDA and 120-day Safety Update glossary of adverse events.**

Dear Dr. Leber:

Reference is made to the NDA (#20-796) for Comtan (entacapone 200 mg tablets) resubmitted to the agency on December 23, 1997. On behalf of Orion Corporation, we are hereby submitting, in duplicate, a glossary of adverse events requested by Dr. Sevka on September 29, 1998. The glossary combines the reporting of adverse events in both the NDA and the 120-day Safety Update. Please be advised that adverse events which, were previously submitted in the 120-day safety update are designated in the current glossary with "NEW" listed in both the *New Term* and *New Symptom* columns. Those adverse events designated by "NEW" in only the *New Symptom* column are either a corrected or new symptom of a previously reported adverse event.

Please let me know if you have any questions or require any additional information.

Sincerely,

Jill A Powers
Manager, Regulatory Affairs



ORIGINAL

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

October 1, 1998

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

OCT 02 1998

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ORIG AMENDMENT

N(CS)

**RE: Orion Corporation
NDA 20-796/Comtan (entacapone 200 mg tablets)
Response to Dr. Japobrata Choudhury's questions from
Teleconference held on September 28, 1998**

Dear Dr. Leber:

Reference is made to the NDA (#20-796) for Comtan (entacapone 200 mg tablets) resubmitted to the agency on December 23, 1997; to submissions dated August 27 and September 10, 1998, which provided additional information requested by Dr. Choudhury; and to a conference call on September 28, 1998, where Dr. Choudhury requested clarifications be provided for some of the information contained in the August 27 and September 10, 1998, submissions.

Therefore, on behalf of Orion Corporation, we are hereby submitting, in duplicate, a complete response to the questions raised by Dr. Choudhury in the September 29, 1998, teleconference. Also enclosed is a copy of the minutes of the teleconference prepared by Target Research Associates and the statistical analysis plan for study 2939044.

Please let me know if you have any questions or require any additional information.

Sincerely:

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs - -

RJM:llp
Enclosure(s)



**TARGET
RESEARCH
ASSOCIATES**

ORIGINAL

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

October 1, 1998

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

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AND RESEARCH

OCT 02 1998

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ORIG AMENDMENT

N(311)

**RE: Orion Corporation
NDA 20-796/Comtan (entacapone 200 mg tablets)**

Response to September 29 request from Dr. Michael Sevka for clarifications regarding coding of laboratory values, glossary of adverse events and discontinuation of OR-462 development

Dear Dr. Leber:

Reference is made to the NDA (#20-796) for Comtan (entacapone 200 mg tablets) resubmitted to the agency on December 23, 1997. On behalf of Orion Corporation, we are hereby submitting, in duplicate, clarifications to questions raised by Dr. Sevka on September 29, 1998. For ease of review, the questions raised and the responses are outlined below.

Please clarify the following coding of laboratory values for Study # 033.

1) NC_ variables (Normal/abnormal)- Does this coding refer to each study center's individual laboratory?

This coding refers to each individual laboratory's reference ranges which are used in the determination of normality/abnormality.

2) ST_ variables (Standardized value)- What is standardized value?

Standardized values are used to calculate mean descriptive statistics. Standardization is needed because the laboratory results come from different laboratories and thus have different reference ranges and different units. The standardization procedure is described in ISS in section 3.6.3.2. (Ref. Sect. 8, Vol.76/p.234 and Ref. Sect. 10, Vol.169/p.234).

3) AL_ variables (Alert value)- What does Alert value mean and what is its relationship to High, Low and Normal?

This coding is done by the sponsor. Original non-standardized values (CO_ variables) are compared with reference ranges provided by individual laboratories. If the observed value is greater than the upper reference limit, coding High (H) is used. If the observed value is less than the lower reference limit, coding Low (L) is used. Coding Normal (N) is used for non-missing values within the reference range.

4) Please clarify whether the glossary of adverse events submitted to the agency on September 10 covered the adverse events submitted in the 120-Day Safety Update or adverse events submitted only in the NDA.

The glossary of adverse events submitted on September 10, 1998 included information for AEs in the NDA only. The requested combined NDA and 120-Day glossary will be available in a few days and will be submitted to the agency at that time.

5) Please explain why Orion discontinued the development of OR-462.

OR-462 is still in Orion's clinical development program and is currently undergoing phase II clinical studies in Europe for the treatment of diabetes induced nephropathy.

The reason for discontinuing OR-462 in the parkinsonian project was not at all related to safety issues. There have been no safety or specific toxicological issues related to the development of OR-462. It was entirely a strategic choice made by the company after it had been shown in preclinical studies that OR-462 possesses other pharmacological properties in addition to COMT-inhibition, ie, OR-462 is a very effective antioxidant and in experimental diabetic models it normalizes glomerular filtration and albumin excretion. Since orally administered entacapone is a more effective COMT-inhibitor than OR-462 in peripheral tissues of experimental animals, the decision to develop entacapone for the treatment of parkinsonian patients was made.

Please let me know if you have any questions or require any additional information.

Sincerely:



Jill A Powers
Manager, Regulatory Affairs



ORIGINAL

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS
October 1, 1998

CENTER FOR DRUG EVALUATION
AND RESEARCH

OCT 02 1998

RECEIVED HFD-130

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

RE: Orion Corporation
NDA 20-796/Comtan (entacapone 200 mg tablets)
Submission of Individual Creatinine Clearance Values
for Patients Who Participated in Study 29393057

ORIG AMENDMENT

N(3B)

Dear Dr. Leber:

Reference is made to the NDA (#20-796) for Comtan (entacapone 200 mg tablets) resubmitted to the agency on December 23, 1997, and to a telephone conversation with Dr. Sayad Al-Habet on September 16, 1998, in which he requested the individual creatinine clearance values for patients who participated in study 29393057 (entacapone pharmacokinetics in renally impaired patients) be submitted to the agency.

Therefore, on behalf of Orion Corporation, we are hereby submitting, in duplicate, the individual creatinine clearance values for the patients who participated in study 29393057. Additionally, please be advised that when reviewing the 29393057 study report, in preparing the table of creatinine clearance values, there was a discrepancy noted in Tables 3.1 and 4.1 on pages 6-082 and 6-084. The column headings for the severely impaired and renal replacement patients had been inadvertently switched when preparing the report. New revised pages have been provided showing the correct headings. The grouping of all patients, in calculating the pharmacokinetic parameters for entacapone, was verified and found to be accurate.

Please let me know if you have any questions or require any additional information.

Sincerely:

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

RJM:llp

Enclosure(s)

ORIGINAL



CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

APPENDIX 1

September 22, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

SEP 23 1998

RECEIVED HFD-120

ORIGINAL AMENDMENT

N(BP)

RE: Orion Corporation
NDA 20-796/Comtan (entacapone 200 mg tablets)
Submission of additional information requested by Theresa Wheelous on
September 18, 1998.

Dear Dr. Leber:

Reference is made to the NDA (#20-796) for Comtan (entacapone 200 mg tablets) resubmitted to the agency on December 23, 1997 and to a telephone conversation with Ms. Theresa Wheelous on September 18, 1998 in which she requested that individual animal data be submitted for study #F95101210605 entitled "A Special Stain for Protein in the Kidneys of Rats Treated for 52 Weeks with Entacapone". Based on this request, we are hereby providing, in duplicate, on behalf of Orion Corporation, a table which shows the kidney pathology results for those animals with chronic nephropathy.

Please let me know if you have any questions or require any additional information.

Sincerely:

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

RJM:llp
Enclosure(s)

MEMO

**TARGET
RESEARCH
ASSOCIATES**

ORIGINAL

CAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

September 10, 1998

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

SEP 11 1998

RECEIVED HFD-120

GENC ALMENDRA

N (BM)

RE: Orion Corporation
NDA 20-796/Comtan (entacapone 200 mg tablets)
Response to additional information requested by Dr. Michael Sevka

Dear Dr. Leber:

Reference is made to the NDA (#20-796) for Comtan (entacapone 200 mg tablets) resubmitted to the agency on December 23, 1997; to the 120-Day Safety Update submitted to the agency on May 15, 1998; and to a telephone conversation with Dr. Michael Sevka on August 18, 1998 in which he requested that clarifications be provided on the safety information which was submitted in the NDA and the 120-Day Safety Update.

Therefore, on behalf of Orion Corporation, we are hereby submitting in duplicate a complete response to the information requested by Dr. Sevka.

Please let me know if you have any questions.

Sincerely:



Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

RJM:llp
Enclosure(s)

**TARGET
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ORIGINAL

CAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

September 10, 1998

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

SEP 11 1998

RECEIVED HFD-120

RE: Orion Corporation
NDA 20-796/Comtan (entacapone 200 mg tablets)
Response to the outstanding items requested by Dr. Japobrata Choudhury
on August 12, 1998

Dear Dr. Leber:

Reference is made to the NDA (#20-796) for Comtan (entacapone 200 mg tablets) resubmitted to the agency on December 23, 1997; to the submission dated December 30, 1997 which provided information related to pivotal studies 2939033 and 2939044; to a telephone conversation with Dr. Choudhury on August 12, 1998 in which he requested clarifications be provided for information which was submitted in the NDA and December 30, 1997 submission; and to the submission dated August 27, 1998 which provided a partial response to Dr. Choudhury's questions from August 12, 1998.

Enclosed in this submission, on behalf of Orion Corporation, we are hereby submitting in duplicate a response to the two outstanding items requested by Dr. Choudhury on August 12, 1998. We trust that the information provided previously on August 27, 1998 and in the enclosed submission adequately address Dr. Choudhury's requests.

Please let me know if you have any questions.

Sincerely:



Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

RJM:llp
Enclosure(s)

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REGULATORY RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

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AND RESEARCH

August 27, 1998

AUG 31 1998

RECEIVED HFD-120

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

~~AMENDMENT~~
N(BS)

RE: Orion Corporation
NDA 20-796/Comtan (entacapone 200 mg tablets)
Partial response of additional information requested by Dr. Japobrata
Choudhury

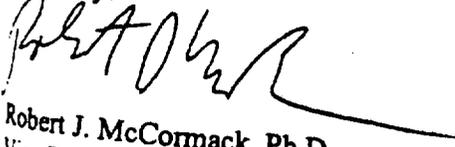
Dear Dr. Leber:

Reference is made to the NDA (#20-796) for Comtan (entacapone 200 mg tablets) resubmitted to the agency on December 23, 1997; to the submission dated December 30, 1997 which provided information requested by Dr. Choudhury related to pivotal studies 2939033 and 2939044; and to a telephone conversation with Dr. Choudhury on August 12, 1998 in which he requested that clarifications be provided for information which was submitted in the NDA and December 30, 1997 submission.

Therefore, on behalf of Orion Corporation, we are hereby submitting in duplicate a partial response to the information requested by Dr. Choudhury. All other requested information will be submitted to the agency no later than September 11, 1998.

Please let me know if you have any questions.

Sincerely:



Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

RJM:llp
losure(s)



**TARGET
RESEARCH
ASSOCIATES**

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

August 5, 1998

Division of Neuropharmacologic Drug Products
Center for Drug Evaluation and Research (HFD-110)
Office of Drug Evaluation I
Woodmont II Building
1451 Rockville Pike
Rockville, Maryland 20852

Attn: Teresa Wheelous
Consumer Safety Officer
Division of Neuropharmacologic Drug Products

**Re: Request by reviewing statistician for additional material for NDA #20-796
Comtan® Tablet, 200 mg (entacapone)**

Dear Ms. Wheelous:

As per your telephone request of July 30, 1998, on behalf of Orion Corporation, we are providing to the reviewing statistician the following:

- An additional copy of entacapone study report 2939052 (5 volumes).
- A copy of the statistical report for study 2939052.
- Two diskettes that contain the SAS data sets for entacapone studies 2939033 and 2939044 along with a description of the codes and variables used in formatting the data sets.
- One copy of the entacapone 120-day safety update (23 volumes).

Please let me know if I can be of further assistance.

Sincerely,

Jill A. Powers
Manager, Regulatory Affairs



CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

*NAI
JW
6/24/98*

ORIGINAL

June 18, 1998

NEW CORRECT

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL.
Rockville, MD 20852

**Re: Orion Corporation, Comtan™ (Entacapone) 200 mg tablet, NDA #20-796
Additional copy of Vol. #3 of the 120 Day Safety Update Report**

Dear Dr. Leber,

Reference is made to the NDA #20-796 for Comtan™ 200 mg tablet submitted to the Agency on January 2, 1998.

At the Agency's request we are hereby submitting, on behalf of Orion Corporation, an additional copy of Vol. #3 (of 23) of the 120 Day Safety Update Report initially submitted to the Agency on May 15, 1998.

If you have any questions, please, do not hesitate to contact me.

Sincerely,

R McCormack (for)

Dr. Robert McCormack
Vice President, Regulatory Affairs
Target Research Associates

CENTER FOR DRUG EVALUATION
AND RESEARCH

JUN 19 1998

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ORIGINAL

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

May 15, 1998

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

MAY 18 1998

RECEIVED HFD-120

RE: NDA 20-796 Comtan™(entacapone 200 mg Tablets)
Submission of the 120 Day Safety Update Report

ORIG AMENDMENT

NCSU

Dear Dr. Leber,

Reference is made to NDA #20-796 for Comtan™ (entacapone) 200 mg tablet received at the Agency on January 2, 1998. As required by 21 CFR 314.50 (d)(5)(vi)(b), we are submitting, on behalf of Orion Corporation, the 120-Day Safety Update Report.

The cut-off date for safety information in the initial NDA submission was October 31, 1996. This safety update includes data collected from phase III extension studies initially submitted in the NDA and new studies during the period from November 1, 1996 to October 31, 1997.

This 120-Day Safety Update Report contains the following:

- Volume 1: Safety Report
- Volume 2: Post Text Tables
- Volumes 3-5: Attachments (inclusion/exclusion criteria, patient narratives and lab value data listings)
- Volumes 6-23: Case Report Forms for patients that died or discontinued studies due to adverse events (submitted in the archive copy only)

For your information, tables found in the NDA Integrated Summary of Safety have been modified to include updated information and are contained in Volume 2. In addition, case report forms which were incomplete when they were submitted in the NDA have been amended are included in this safety update.

Dr. Leber
Page 2

No new significant nonclinical safety information became available during the period covered by this safety update report (November 1, 1996 to October 31, 1997).

If you have any questions or need additional information, please contact the undersigned.

Sincerely,

A handwritten signature in black ink, appearing to read 'R. McCormack', with a long horizontal flourish extending to the right.

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL



**TARGET
RESEARCH
ASSOCIATES**

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CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

May 8, 1998

CENTER FOR DRUG EVALUATION
AND RESEARCH

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL.
Rockville, MD 20852

MAY 11 1998

RECEIVED HFD-120

Re: Orion Corporation, Comtan™ (Entacapone) 200 mg tablet, NDA #20-796
Stability Update Amendment on the Dosage Form

~~CLASSIFIED~~
N(BC)

Dear Dr. Leber,

Reference is made to the NDA #20-796 for Comtan™ 200 mg tablet submitted to the Agency on January 2, 1998.

Stability results on the primary stability studies covering 6 months storage period were submitted in the original New Drug Application.

Please, find enclosed, in duplicate, the updated Stability Report covering a storage period of 18 months for the primary stability studies, and 48 months for the supportive stability studies, respectively. Statistical analysis of the stability data utilizing the SAS-method recommended by FDA has been performed, and the results are summarized in the Stability Report.

In accordance with the 21CFR 314.60(c), a field copy of the stability update amendment has been prepared. Since the pre-approval inspection of the drug product manufacturing site is scheduled to begin on May 18, 1998, the field copy will be made available for the FDA Investigators at the Espoo plant. The field copy is a true and accurate reproduction of this amendment.

If you have any questions, please, do not hesitate to contact me by telephone at (908) 322-2404 or by telefax at (908) 322-5277.

Sincerely,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

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ASSOCIATES**

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIostatISTICS

CENTER FOR DRUG EVALUATION
AND RESEARCH

May 1, 1998

MAY 04 1998

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL.
Rockville, MD 20852

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~~ORIG AMENDMENT~~
N/CBC

Re: Orion Corporation, Comtan™ (Entacapone) 200 mg tablet, NDA #20-796
Amendment [redacted]

Dear Dr. Leber,

Reference is made to the NDA #20-796 for Comtan™ 200 mg tablet submitted to the Agency on January 2, 1998.

[redacted]

The packaging procedure and packaging materials [redacted]

As an enclosure the applicable amended pages for the NDA including the name, address and contact person for the [redacted]

If you have any questions, please, do not hesitate to contact me.

Sincerely,



Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs



**TARGET
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ASSOCIATES**

ORIGINAL

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

April 24, 1998

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

APR 27 1998

RECEIVED HFD-120

*ORIG AMENDMENT
N(BC)*

**RE: NDA 20-796 Comtan™(entacapone 200 mg Tablets)
Submission of a Categorical Exclusion for Environmental Assessment**

Dear Dr. Leber,

Reference is made to the NDA #20-796 for Comtan™ (entacapone) 200 mg tablet submitted to the Agency on January 2, 1998.

In the NDA Orion Corporation filed a full Environmental Assessment (EA). At the Agency's request Orion reviewed the EA and determined that entacapone would qualify for categorical exclusion under 21 CFR §25.31(b) (presented in the Federal Register, Vol. 62, No. 145 of July 29, 1997), Expected Introduction Concentration being less than 1 ppb.

On behalf of Orion Corporation, with this letter we are formally withdrawing the full EA that was submitted in the initial NDA and are replacing it with the enclosed documentation supporting the claim for categorical exclusion.

If you have any questions, please, do not hesitate to contact me.

Sincerely,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs



**TARGET
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ASSOCIATES**

ORIGINAL

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

December 30, 1997

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

DEC 31 1997

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CRIG AMENDMENT
N(BS)

RE: NDA 20-796 (entacapone 200 mg Tablets)
Submission of Additional Information Requested by Dr. Japobrata
Choudhury

Dear Dr. Leber:

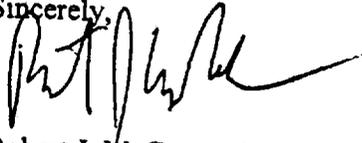
Reference is made to the entacapone NDA (#20-796) resubmitted to the Agency on December 23, 1997 and to a telephone conversation with Dr. Japobrata Choudhury on December 11, 1997 in which he requested additional information for study numbers 2939033 (NOMECOMT) and 2939044 (SEESAW). In response to Dr. Choudhury's request we are hereby submitting in duplicate on behalf of Orion Corporation the following information for the studies cited above.

- Results of the primary efficacy variable for individual study centers
- Number and proportion of patients in the study over time
- Comparison of the results for the primary efficacy variable between dropouts and observed cases at different points in the study
- Results from intent to treat analysis using LOCF and OC for the primary and important secondary efficacy variables
- Cumulative distribution of the primary efficacy variable

December 30, 1997
Page 2

Please let me know if you have any questions. I will be sending you the electronic version of the data for both studies in SAS format in the near future.

Sincerely,



Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

RJM:jt
Enclosure(s)

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CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

December 14, 1997

Paul D. Leber, MD, Director
Division of Neuropharmacological Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
1451 Rockville Pike, Rm. 4039 4th FL
Rockville, MD 20852

CENTRE FOR DRUG EVALUATION
AND RESEARCH

DEC 18 1997

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GENIC AMENDMENT
N(BM)

**RE: NDA 20-796 (entacapone 200 mg Tablets)
Submission of Narrative Summaries For Patients Whose Serious Adverse
Events Were Considered Unrelated to Entacapone Treatment**

Dear Dr. Leber:

Reference is made to the New Drug Application for Comtan (entacapone) received at the Agency on October 24, 1997 and to FDAs preliminary review of the NDA where it was determined that the application did not contain narrative summaries for those patients who experienced serious adverse events not attributable to entacapone administration. Therefore enclosed we are hereby submitting, in duplicate, on behalf of Orion Corporation, one volume (80 pages) containing narrative summaries for those patients who experienced non-causal related adverse events related to entacapone treatment including patients receiving entacapone placebo medication. Also provided is a personal desk copy for Ms. Teresa Wheelous, CSO.

The narrative summaries enclosed in this submission are for those patients who had a serious adverse event up through October 31, 1996, the cut off date used for the ISS for these types of events in the initial NDA filing. Orion will provide additional narrative summaries for patients who experienced serious adverse events after October 31, 1996 in the 120-Day NDA Safety Update Report.

Orion acknowledges the initial NDA for entacapone did not contain all the appropriate narrative summaries for patients who experienced serious adverse events. We respectfully request however, that the Neuropharmacologic Division consider whether the lack of patient narratives for unrelated entacapone events renders the application insufficient to begin a substantive review and ultimately resulting in the single refusal to file issue.

Page 2
December 14, 1997

Please feel free to contact me should you have any questions.

Sincerely,

A handwritten signature in black ink, appearing to read "Robert J. McCormack", with a long horizontal flourish extending to the right.

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

RJM:jt

Enclosure(s)

APPEARS THIS WAY
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NOV - 7 1997

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Division of Neuropharmacologic Drug Products
 Center for Drug Evaluation and Research (HFD-120)
 Office of Drug Evaluation I
 Woodmont II Building
 1451 Rockville Pike
 Rockville, Maryland 20852

ORIGINAL

Attn: Ms Theresa Whelous CSO

Re: Electronic format of Package Insert / New Drug Application (#20,796)
 Comtan® Tablet 200 mg (entacapone)

CRIC AMENDMENT

N(BL)

Dear Ms Theresa Whelous,

Please find here enclosed the electronic copy of entacapone Annotated Package Insert. It has been converted from MAC to PC, format World Perfect 6.0a.

Please note that after the conversion when reviewing the annotation we find some typing errors in the original leaflet. All these corrections are now made to this PC-version and also to the paper copy of the Annotated Package Insert which is enclosed. This paper copy is a MAC-document.

For technical reasons the figures on pages 1, 4 and 5 are missing from the PC-version of the Annotated Leaflet.

Please let us know if you have any problems with the diskette.

APPEARS THIS WAY
 ON ORIGINAL

Eva Saukko
 Eva Saukko
 Regulatory Affairs

Date

CC: Bob McCormack, Target Research Associates

Non Corporation ORION PHARMA

Monnintie 1
 00000 ESPOO
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CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

October 24, 1997

Division of Neuropharmacologic Drug Products
Center for Drug Evaluation and Research (HFD-110)
Office of Drug Evaluation I
Woodmont II Building
1451 Rockville Pike
Rockville, Maryland 20852

Attn: Paul D. Leber, M.D., Director
Division of Neuropharmacologic Drug Products

**Re: Initial Filing of New Drug Application (#20,796)
Comtan® Tablet, 200 mg (entacapone)**

Dear Dr. Leber:

Pursuant to paragraph 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR314.50, we are hereby submitting in duplicate on behalf of Orion Corporation a New Drug Application (#20,796) for Comtan® Tablets (entacapone, 200 mg).

Entacapone is a peripherally acting catechol-O-methyltransferase (COMT) inhibitor. Comtan® is indicated in the treatment of signs and symptoms of parkinsons disease as an addition to levodopa/dopa decarboxylase inhibitor treatment. The efficacy of entacapone has been proven in two multicenter, double blind clinical studies in patients with mild to severe parkinsons disease. Entacapone can be used with both standard and controlled release preparations of levodopa.

The NDA consists of controlled, uncontrolled and biopharmaceutical studies which were identified in the pre-NDA meeting on March 20, 1997. The non-clinical technical data section consists of pharmacology, ADME and a full battery of safety assessment studies conducted with entacapone. Also included in the non-clinical section of the NDA are 13-week studies in the rat and monkey as well as two genotoxicity studies (Ames Test and Micronucleus Test, *In Vivo*) with the combination of entacapone and levodopa/dopa decarboxylase inhibitors. As agreed with the agency (S-146 dated 5/29/97), it was not necessary to conduct a segment II teratology program with the combination of entacapone/levodopa/dopa decarboxylase inhibitors.

Paul D. Leber, M.D.
October 24, 1997
Page 2

A complete Application to Market a New Drug for Human Use (Form FDA 356h) is enclosed. Since the currently approved Form FDA 356h was not available when preparation of the entacapone NDA was initiated, the NDA was arranged according to the item numbers listed on the previously approved form FDA 356h dated 5/96. This application consists of 304 volumes, which are numbered consecutively, individually paginated and organized in accordance with 21 CFR314.50. We have provided both a complete archival copy (blue binders) and a review copy of the volumes. Also, we have provided five additional review copies of the Application Summary so that it can be supplied to each reviewer of the five technical sections. The binders are color coded to represent each technical data section and the copy for the CSO is in a black binder. The organization and locations of the various sections of the NDA are listed in Volume 1.1 of the Application Summary. Be advised that the 120-day Safety Update will be submitted subsequent to this submission as well as an update of the primary stability program.

After following the advice of the Neuropharmacologic Drug Products Division, we believe that this Application is complete for review by your staff. We would look forward to discussing informally, the status of your review in approximately 45 days.

Should any questions arise during the review of this NDA, please do not hesitate to contact the undersigned at 908-322-2402.

Sincerely,



Robert J. McCormack
Vice President - Regulatory Affairs

MEMORANDUM OF TELEPHONE CONVERSATION
NDA 20-796

Drug: Comtan
Sponsor: Orion
Date: August 13, 1999
Conversation Between:

Agency:
Dr. M. Sevka – Safety Reviewer
Ms. T. Wheelous – Project Manager

Sponsor:
Dr. McCormack – Regulatory Affairs

Purpose: Information Request Telecon

Discussion:

Dr. Sevka explained to Dr. McCormack that he has some concerns regarding the responses to the Agency's Approvable letter and additional information is needed.

The specific information requested is as follows:

Question 4 of Approvable Letter:

In coding the adverse events in your development program, falls have been coded as falling, fractures, dislocations, etc. We ask that you examine all adverse reactions in the RCT database identifying all falls. Please focus first on all falls, falls resulting in hospitalization and then falls resulting in fractures, and then re-analyze separately for each study and then across all RCTs.

1. Regarding question #4 of the approvable letter - please verify that the information regarding the number of falls in the RCTs is accurate. Do the numbers in the Tables for the response to question #4 include other verbatim terms such as orthostasis, syncope, fractures, ataxia, purpura, etc? The number of falls (58) reported in the Tables appears to be smaller than the number of verbatim terms for falls (preliminary estimate > 63), without counting other verbatim terms which may represent other injuries or events related to a fall.

Question 5 of Approvable Letter:

Similarly, the coding of events that could represent orthostatic hypotension needs re-examination. Therefore, we ask that a similar review (as described above for falls) of events that could represent orthostatic hypotension or syncope be undertaken for the RCT database. For this analysis, we ask that you include a separate category that consists of only patients who had objective findings of confirmed blood pressure changes consistent with orthostasis. For syncope, include a separate category for patients with reported loss of consciousness.

2. Similar to the question above regarding Question 4 of the approvable letter, please verify if the number of orthostasis events is accurate. The response appears to imply that only adverse events (AEs) reported as a preferred term for postural hypotension, syncope, and dizziness were counted. Were other orthostatic terms counted even if they were subsumed to other preferred terms? Further, the approvable response indicates that no patient was reported as

"loss of consciousness" yet loss of consciousness and blackouts are listed as verbatim terms in the glossary of AEs.

Question 8 of Approvable Letter

Vital sign and ECG data provided in the NDA do not include information as to when these measurements were obtained relative to entacapone administration. It is possible that many measurements may have been obtained before entacapone administration when serum concentrations were at their nadir.

3. In Table I, Vital Signs of Phase I and II Trials, there is no description of EKG or vital sign data collected for several studies (e. g, #28, 29, #39). For example, on p. 8, 43 of the amended final protocol for study #28 it is stated that vitals and ECGs were to be obtained yet ECG collection strategy is not mentioned in the Table. Further for each study only an interpretation of the data was provided. Please modify Table 1 to include all protocol-specified plans for collection of ECG and vital sign data. If none were obtained please so indicated. If obtained but data not collected or not available please explain. For each study listed in Table 1 please submit the analyses conducted to arrive at the summary of results presented. Analyses should include change from baseline in vital signs and ECGs for each post-drug time point for days when serial observations were conducted. Also for ECGs, analyses of change from baseline for interval length (PR, QRS, QT, and QTc) should be included. The data for studies 13,14,28,29,35, and 48 are imperative, since supine and standing vital signs were obtained. In the Phase III trial, statistical analysis for vital signs and ECG intervals are needed (studies 33,44,52, and 63). The timing of the ECGs is stated as 1½ to 3 hours. How was this time interval obtained?

Dr. McCormack stated that he would request the information from Orion in Finland and notify the project manager prior to submitting the information.

Cc: NDA 20-796

HFD-120

Burkhart/ Sevka/ Kapcala/ Wheelous

Draft 8/19/99 & 9/22/1999

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APPEARS THIS WAY
ON ORIGINAL

TELECON

MEMORANDUM OF TELEPHONE CONVERSATION
NDA 20-796

Drug: Comtan
Sponsor: Orion
Date: August 20, 1999
Conversation Between:

Agency:
Dr. M. Sevka – Safety Reviewer
Ms. T. Wheelous – Project Manager

Sponsor:
Dr. McCormack–Regulatory Affairs

Purpose: Information Request Telecon

Discussion:

1. In glossary of subsumed verbatim terms, how many patients are reflected for each verbatim term?
2. Q4 & Q5 (@ falls and orthostasis) – In re-examination of verbatim terms what strategy was used for ensuring complete capture of other verbatim terms representing trauma or injury resulting from falls or orthostasis but reported by terms other than falls and orthostasis.
3. In glossary, there are verbatim terms subsumed to other preferred terms (e.g., headache may have a verbatim of laceration of head requiring stitches). Is this a result of a fall? Look at all trauma and injury verbatims for verification of relatedness to falls or orthostasis:

Examples of preferred terms with trauma verbatim terms that may have been due to fall/orthostasis/syncope:

Preferred Terms	Preferred term disorder number
Pain	0730
Fall – fracture lateral malleolus	1444
Joint Dislocation – fingers (secondary terms)	1646
Arthropathy	0065
Bone Disorder	0067
Pathologic Fracture	0069
Myopathy	0074
Tendon Disorder	1074
Headache	0109
Purpura	0459
Joint. Dislocation (musculo-skeletal system)	1646
Skin Disorder	0037

Some falls are secondary to some other event (orthostasis, fall, etc.) How are they accounted for? Are they listed separately as one term or in both terms?

NDA 20-796
PAGE 2

Q5 – asked for identification of patients with syncope or loss of consciousness. Response states that there are no patients with syncope (loss of consciousness). However, listed in verbatim is blackout or loss of consciousness? Please clarify.

Q6 – In the response tables do they consist of original adverse events only or both original adverse event report plus the new verbatim criteria combined terms. Especially for trauma terms please update to reflect the new counts.

Q8 – Table of studies containing serial EKGs and vitals. Were the studies parallel or crossover design trials? Was it from in patients or subjects? Please reformulate table to include this info. How were analysis used to arrive at summary of results? If no EKGs are available then provide reason for omission.

Q11 – Regarding reduction in adverse events in the 9b Table of second safety update, initially the # was 17 and was reduced in the second update. What is the reason for the reduction in count for adverse events except chest pain? (May be a result of reclassification)

APPEARS THIS WAY
ON ORIGINAL

cc: Orig NDA 20-796
HFD-120/
/G. Burkhart/M. Sevka /L. Kapcala/T. Wheelous

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TELECON

APPEARS THIS WAY
ON ORIGINAL

**MEMORANDUM OF TELEPHONE CONVERSATION
NDA 20-796**

Drug: Comtan
Sponsor: Orion Pharmaceuticals
Date: May 26, 1999
Conversation Between:

Agency:
R. Katz – Acting Div. Director
R. Tresley – Medical Reviewer
G. Fitzgerald – Pharmacology Team Ldr.
P. Roney – Pharmacology Reviewer
M. Sevka – Safety Reviewer
L. Fossom – Pharmacology Trainee
T. Wheelous – Project Manager

Sponsor:
Dr. Robert McCormack – Reg. Affairs, Target
Dr. Ilka Larma

Purpose: To continue discussion of the completeness of the April 16, 1999 Resubmission compared to the requests in the December 31, 1998, approvable letter.

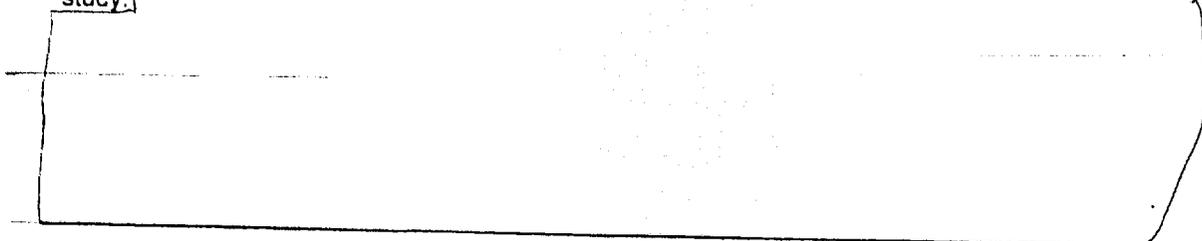
Discussion:

It was agreed upon in a May 24, 1999 telecon that the sponsor would provide the Division with the requested information. Subsequent to the telecon the sponsor notified the Division of the requested information was within the NDA and a follow-up telecon was agreed upon. This is the follow-up telecon.

The Pharmacology/Toxicology section of the December 31, 1998, approvable letter under discussion requests the following:

1. The Center's Executive Carcinogenicity Assessment Committee (ExecCAC) has recommended that demonstration of an adequate study in the mouse is essential to appropriately assess the human carcinogenic risk of Comtan. The ExecCAC report states that:
The validity of the mouse carcinogenicity study was questionable because of inadequate survival at the high dose, the large spread in dose (based on nominal dose) between the high dose and middle dose, the absence of data to support the middle dose as the appropriate 'back-up' dose, and the absence of a full histopathological analysis, particularly in middle dose males."

Therefore, we request that you initiate studies as soon as possible in an attempt to validate the mouse study.



[Redacted]

2. Please provide specific findings that are summarized as "chronic progressive nephropathy" in the one-year rat study and describe these findings in labeling.

PHARMACOLOGY/TOXICOLOGY POINTS

I. Mouse Carcinogenicity

[Redacted]

◆ In the resubmission Orion has committed to providing histopathology data and reports. This information was received on May 25, 1999.

[Redacted]

II. Summarization of Specific Findings (Item #2 above)

◆ The specific findings summarizing "chronic progressive nephropathy" in the one-year rat study were located in the response to the approvable letter and in an October 1998 submission to the NDA.

◆ The resubmission is considered adequate for review event though not necessarily adequate to validate the study, and the review clock continues without change.

FORMULATION USED IN THE CELOMEN STUDY

Formulation #54 was used in the Celomen study. The sponsor refers the Division to Table 3 in volume 17, p.7, of the response to the approvable letter, which reflects the formulations, used in the various studies.

POST MARKETING REPORTS OF RHABDOMYOLISIS

Since, Orion was not aware of potential cases of rhabdomyolysis being reported to the Agency; Orion was informed that the Division might not be able to disclose the source.

INFORMATION REQUEST

While there is a letter on file from Orion authorizing the Division to communicate with Novartis regarding some review issues the working relationship between Novartis and Orion is not clear to the Division. Specifically, the Division is not clear about the amount of information exchange that is legally permissible between the Division and [redacted] Orion and Novartis.

Consequently, separate letters were requested from both Orion and Novartis clearly defining the allowable extent of communication between all parties. These letters are to state (1) whether or not the Agency can share all information with both Orion and Novartis [redacted] and (2) authorize the Agency to discuss all issues with both parties. [redacted]

cc: NDA 20-796
HFD-120
//Katz
/Tresley
/Burkhart
/Sevka
/Fitzgerald
/Roney
/Guzewska
/Heimann
/AI-Habet
/Wheelous
HFD-860/Baweja/AI-Habets

APPEARS THIS WAY
ON ORIGINAL

Draft: May 27, 1999

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TELECON

**MEMORANDUM OF TELEPHONE CONVERSATION
NDA 20-796**

Drug: Comtan
Sponsor: Orion Pharmaceuticals
Date: May 24, 1999
Conversation Between: (908) 322-2402

Agency:

R. Katz – Acting Div. Director
R. Tresley – Medical Reviewer
G. Fitzgerald – Pharmacology Team Ldr.
P. Roney – Pharmacology Reviewer
T. Wheelous – Project Manager

Sponsor:

Dr. Robert McCormack – Reg. Affairs, Target
Dr. Ilka Larma
Roy Dodsworth – Novartis

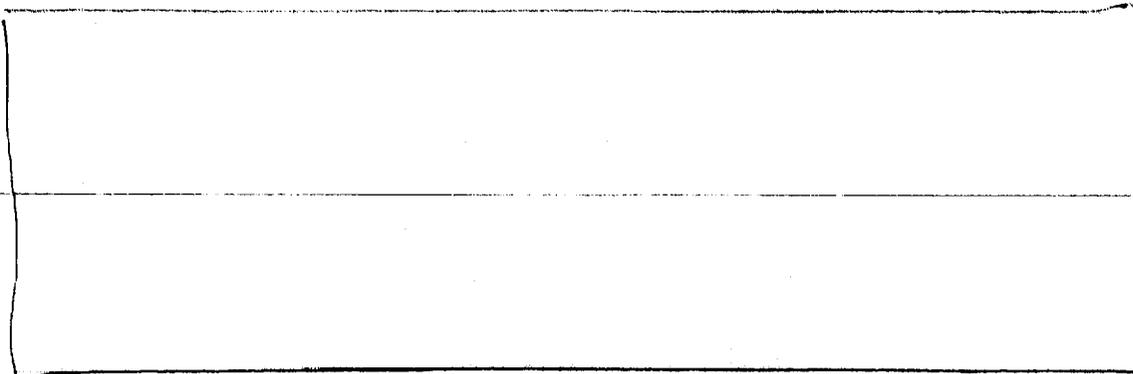
Purpose: To discuss the completeness of the April 16, 1999 Resubmission as compared to the requests in the December 31, 1998, approvable letter.

Discussion:

The Pharmacology/Toxicology section of the December 31, 1998, approvable letter requests the following:

1. The Center's Executive Carcinogenicity Assessment Committee (ExecCAC) has recommended that demonstration of an adequate study in the mouse is essential to appropriately assess the human carcinogenic risk of Comtan. The ExecCAC report states that:

The validity of the mouse carcinogenicity study was questionable because of inadequate survival at the high dose, the large spread in dose (based on nominal dose) between the high dose and middle dose, the absence of data to support the middle dose as the appropriate 'back-up' dose, and the absence of a full histopathological analysis, particularly in middle dose males."



2. Please provide specific findings that are summarized as "chronic progressive nephropathy" in the one-year rat study and describe these findings in labeling.

PHARMACOLOGY/TOXICOLOGY POINTS

I. Mouse Carcinogenicity Study (Item #1 above)

[Redacted]

◆The studies to be conducted should be either a study providing evidence of saturation of absorption of Comtan at middle dose of 100mg/kg and a complete histopathological analysis of all animals in the mouse carcinogenicity study. Alternatively, the sponsor could conduct a 3-month study that 100mg/kg is at least one half of the maximum tolerated dose and histopathological analysis.

[Redacted]

◆Dr. McCormack stated that he had just received the mouse carcinogenicity histopathology reports for the low and intermediate dose about an hour ago and would submit them to the Agency.

II. Summarization of Specific Findings (Item #2 above)

◆The specific findings summarizing (full data report) "chronic progressive nephropathy" in the one-year rat study was not provided in the resubmission. The specific findings should contain the individual data and the pathologist report on chronic progressive nephropathy.

◆The sponsor will check on the availability of this data.

When the requested data (mouse carcinogenicity histopathological analysis, and specific findings data reports) are received by the Agency then the review clock will start.

[Redacted]

FORMULATION USED IN THE CELOMEN STUDY

The sponsor believes that possibly both formulation #54 and formulation #55 were used in the Celomen study. The amounts of each formulation used in the Celomen study will be obtained, if available, and submitted to the Division.

STUDY #44, PIVOTAL TRIAL

Dr McCormack inquired whether or not study #44 would be considered a pivotal trial. Since the details of earlier discussions were not remembered or available during the telecon this inquiry could not be addressed.

SAFETY UPDATE

Only the new serious adverse events should be reported and submitted in the safety update.

POST MARKETING REPORTS OF RHABDOMYOLISIS

The sponsor was asked if there was additional information available about the cases of rhabdomyolysis that have been reported to the Agency. Since, the sponsor was not aware of these reports the Division offered to get back with the sponsor on this matter

cc: NDA 20-796
HFD-120
//Katz
/Tresley
/Fitzgerald
/Roney
/Wheelous
HFD-860/Baweja/Al-Habets
Draft: May 25, 1999

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TELECON

**APPEARS THIS WAY
ON ORIGINAL**

DRAFT

NDA 20-796
PAGE 1

**MEMORANDUM OF TELEPHONE CONVERSATION
NDA**

Drug: Comtan
Sponsor: Orion
Date: November 18, 1998
Conversation Between:

Agency:
Dr. R. Katz – Group Leader
Dr. G. Burkhart – Safety TL
Dr. R. Tresley – Medical Reviewer
Ms. T. Wheelous – Project Manager

Sponsor:
Dr. McCormack – Regulatory Affairs, Target Research
Dr. Ilka Larma

Purpose: Information Request Telecon

Discussion:

Dr. Katz informed Dr. McCormack that the Division would like to go directly to approval, if that is the appropriate decision, as the action of first choice for the Comtan application. However, in order to accomplish this goal cooperation from the sponsor to provide information and to have frequent impromptu telecons is necessary. Dr. McCormack agreed to be assessable at any time and to provide the requested data as rapidly as possible.

Additional Data Requests:

1. Please submit to the NDA or direct us to the location in the NDA for CPK data.
2. Please provide additional safety update available from the previous cut-off date of Oct. 31, 1997.
 - Additional data is available up to Oct. 31, 1998, and will be provided to include all serious adverse events (looking especially for NMS, liver injury, Rhabdomyolysis, and fever) and deaths.
 - In addition to an exposure table, If possible include the timing of the adverse event and/or death relative to the last dose of drug.
 - There is a question about the coding of serious adverse events. It appears that not all of the complications are reported in patients with multiple adverse events. Dr. McCormack agreed to check into this and get back to the Division.
3. This product is a chelater, based on pre-clinical information and based on the hemoglobin level in 6 patients that showed a 2% drop in HCT. Please provide a single report of these patients and any other cases of hematological abnormalities. Be sure to include case report forms and follow-up information.
4. There appears to be some missing narratives. For example, patient #1802 in study #52 had an increase in LFTs, was hospitalized, and continued in study. No narrative was provided.

NDA 20-796
PAGE 2

5. Please provide the safety and efficacy data for trial #52, #62, and #65.
6. This product was approved in Europe @ one month ago and not post-marketing data is available. Please report to the Division all major serious events due to Comtan including events occurring in the European community, and when and where the product has been introduced.
7. Provide us with a copy of the UK product labeling.
8. The sponsor has conducted some pre-clinical studies comparing tolcapone and entacapone. The data will be submitted to the Division when it is available.

Dr. McCormack offered to call the project manager with requested European launch dates and to notify the Division about the timing of the submission containing responses to the above stated requests.

Teresa Wheelous, RPh

cc: Orig NDA 20-796
HFD-120/
/R. Katz
/G. Burkhart
R. Tresley
/T. Wheelous

Draft: 11/23/98
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APPEARS THIS WAY
ON ORIGINAL

TELECON

Wheelous

MAY 27 1999

NDA 20-796

Orion Corporation
Attention: Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs
Target Research Associates
1801 East Second Street
Scotch Plains, N.J. 07076

Dear Dr. McCormack:

We acknowledge receipt on April 19, 1999 of your April 16, 1999 resubmission to your new drug application (NDA) for Comtan (entacapone 200mg) tablets.

This resubmission contains labeling, an efficacy report for the Celomen study, responses to the clinical safety questions, responses to the pharmacology / toxicology questions, and responses to the biopharmaceutical questions submitted in response to our December 31, 1998 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is October 19, 1999.

If you have any questions, contact Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

TS/  5/26/99

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Wheeler

Food and Drug Administration
Rockville MD 20857

NDA 20-796

Orion Corporation
Attention: Robert J. McCormack, Ph.D.
Target Research Associates
1801 East Second Street
Scotch Plains, N.J. 07076

JAN 8 1998

Dear Dr. McCormack:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Comtan (Entacapone) tablet 200 mg.

You were notified in our letter dated January 7, 1998 that your application for Comtan (Entacapone) tablet 200 mg was not accepted for filing due to non-payment of fees required under the Prescription Drug User Fee Act of 1992.

This is to notify you that the Agency has received all fees owed and your application has been accepted as of January 2, 1998.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 3, 1998, in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/s/
Paul Leber, M.D.

1/8/98

Director
Division of Neuropharmacological Drug
Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-796

Food and Drug Administration
Rockville MD 20857

Target Research Associates
Attention: Robert J. McCormack, Ph.D.
1801 East Second Street
Scotch Plains, N.J. 07076

OCT 30 1997

Dear Dr. McCormack:

We have received your new drug application (NDA) resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Comtan (Entacapone) 200 mg Tablets

Therapeutic Classification: Standard

Date of Application: October 24, 1997

Date of Receipt: October 24, 1997

Our Reference Number: 20-796

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 23, 1997 in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Paul Leber, M.D.

Director

Division of Neuropharmacological Drug
Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Wheelous

NDA 20-796 MEETING MINUTES

MEETING DATE: February 11, 1999
NDA & DRUG NAME: 20-796 Comtan (entacapone)
SPONSOR: Orion Pharmaceuticals
TYPE OF MEETING: Approvable Letter Discussion

FDA Attendees & Titles:

Dr. R. Temple – Office Director	Dr. R. Katz – Acting, Division Director
Dr. R. Tresley – Medical Officer	Dr. K. Jin – Biometric Team Leader
Dr. J. Choudhury – Biometric Reviewer	Dr. M. Heimann – Chemistry Reviewer
Dr. M. Guzewska – Chemistry Team Leader	Dr. G. Burkhart – Safety Team Leader
Dr. S. Alhabet – Biopharm Reviewer	Ms. T. Wheelous – Project Manager
Dr. R. Baweja – Biopharmaceutics Team Leader	
Dr. G. Fitzgerald – Pharmacology Team Leader	

External Participant Attendees & Titles:

Orion Corporation

Dr. K. Varkila – V. P., Clinical & Reg. Affairs	I. Linden – Director, Reg. Affairs
H. Heikkinen – Clinical Project Manager	M. Leinonen – Statistician
Dr. K. Reinikainen – Project Director	I. Larma – VP, Orion Reg. Affairs
Dr. R. McCormack – Regulatory, Target Research	

Novartis

Dr. T. Koestler – VP Worldwide Reg. Affairs	Dr. L. Kramer – V. P. Clinical Research
Dr. L. Hauptman – Director DRA	Dr. M. Struck – Regulatory TA Manager
Dr. V. Jamieson – Clinical Research	

MEETING OBJECTIVES: Discuss specific sponsor concerns regarding deficiencies stated in the approvable letter.

DISCUSSION POINTS:

1. Does the Agency agree that, in light of the additional information submitted in the meeting package that Study # 44 should be regarded as a pivotal study, not a supportive study, and that the results would allow FDA to approve the NDA on the basis of currently available data?
 - There's one center in study #44 that appears to be a positive treatment outlier and carries the results. However, the sponsor contends that if the most negative and positive outliers are removed from analysis, then the efficacy results are still statistically significant.
 - Efficacy from study #44 is marginal and may require additional efficacy data, as in study #63.
 - Study #52 seems to be a failure.
 - The study design differs from the tolcapone studies in that (1) there is no restriction in the levodopa dose for Comtan studies, and (2) motor deficit was not an inclusion criterion for Comtan.

➤ The sponsor believes that randomized withdrawal offers indirect positive results because when the drug is removed, the Comtan patient condition worsens relative to placebo patient

➤ Study #63 consists of patients in the on state who may have no room for improvement because there are no motor deficits. Therefore, the UPDRS scores are not significant. A full efficacy report may be needed to further support efficacy, but the decision to request the full report will be decided subsequently.

2. Regarding the response to question # 4 in FDA's approvable letter, does FDA agree with the approach Orion has taken in addressing falls, fractures and dislocations across all RCTs?

Question #4. In coding the adverse events in your development program, falls have been coded as falling, fractures, dislocations, etc. We ask that you examine all adverse reactions in the RCT database identifying all falls. Please focus first on all falls, falls resulting in hospitalization and then falls resulting in fractures, and then re-analyze separately for each study and then across all RCTs.

➤ The proposed approach in addressing falls, fractures, and dislocations in all RCTs appears to be acceptable.

3. Regarding the response to question # 5 in FDA's approvable letter, does the FDA agree with the approach Orion has taken in the re-examination of orthostatic hypotension?

Question #5. Similarly, the coding of events that could represent orthostatic hypotension needs re-examination. Therefore, we ask that a similar review (as described above for falls) of events that could represent orthostatic hypotension or syncope be undertaken for the RCT database. For this analysis, we ask that you include a separate category that consists of only patients who had objective findings of confirmed blood pressure changes consistent with orthostasis. For syncope, include a separate category for patients with reported loss of consciousness

➤ Yes, this approach taken to re-examine orthostatic hypotension is acceptable.

4. Regarding the response to question # 6 in FDA's approvable letter, does the FDA agree with Orion's approach regarding the effect of body weight on various adverse events?

Question #6. Please evaluate the effect of body weight on patient risk for diarrhea, falls, hallucinations, dyskinesia, syncope, orthostasis, etc. by stratifying patients in groups according to baseline body weight. Your analysis should include an evaluation of the effects of age, gender and concomitant medication and should compare event occurrence to placebo patients in the same weight groups.

➤ Patients weighing less than 65 kg appeared to experience more falls and fractures, but it was found that this varies within studies and will be addressed in the response.

5. Does FDA agree that Orion's plan to address the issue outlined in the approvable letter constitutes a "complete response"?

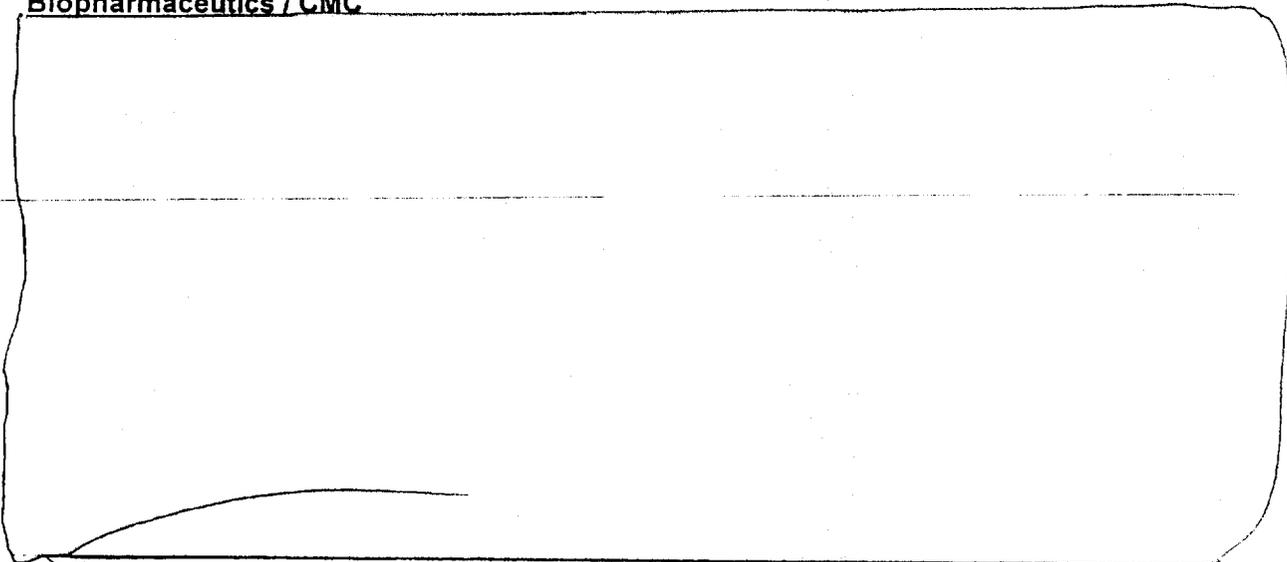
↳ There are still some outstanding issues regarding the need for additional efficacy data and bioequivalence of the to be marketed formulation 54.

↳ The Agency will inform the sponsor about the need for additional efficacy data from study #63, and the bioequivalence issue will be discussed separately with Orion and the Agency's biopharmaceutics representatives.

6. Does FDA agree that since the re-examination of study # 44 is comprised of re-analyses of previously submitted data, and that all other responses deal primarily with labeling issues, that the complete responses will be assigned a 2-month review time as a Type 1 re-submission?

↳ The response may require review of new information not previously reported, i.e., a full study report of study # 63 as well as additional CMC data for substantiation of formulation #54. If either is the case then the resubmission would probably be classified as a Class 2 resubmission allowing for up to 6-months of review time.

Biopharmaceutics / CMC



ACTION ITEMS:

1. Agency will decide whether or not a full efficacy report for study #63 is needed for resubmission.
2. A separate discussion will take place between Orion and the Agency Biopharmaceutics representatives to discuss formulations 54 and 55.

Signature, minutes preparer: /S/

Concurrence Chair: /S/ 4/5 5/10/99

cc:

NDA 20-796

HFD-101/Dr. R. Temple

HFD-120/Dr. R. Katz

/Dr. R. Tresley

/Dr. / Guzewska

/Dr. Burkhart

/Dr. Fitzgerald

/Ms. Wheelous

HFD-710/Dr. K. Jin /Dr. J. Choudhury

HFD-860/ Dr. R. B.

/S/ 4/11/99 - serial draft

/S/ 12345 Heimann MRA 3/22/99 /S/ 22.95

/S/ Alhabe /S/ March 11, 99

NEEDS THIS WAY ORIGINAL

Draft: February 17, 1999 / February 24, 1999

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REQUEST FOR TRADEMARK REVIEW
REGULATION REVIEW

TO: Labeling and Nomenclature Committee
Attention: Daniel Boring, Chair (HFD-120/MPN II (827-2333))

Thru: Paul Leber, M.D., Director [redacted] 10/30/97
Division of Neuropharmacological Drug Products, HFD-120

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

Date: October 30, 1997

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

Proposed Trademark: COMTAN NDA#: 20-796

Established name, including form: Entacapone tablets (IND [redacted])

Other trademarks by the same firm for companion products: None

Indications for Use (may be a summary if proposed statement is lengthy):
Treatment of signs and symptoms of Parkinson's Disease as an adjunct to levodopa/DDC inhibitor treatment.

Initial comments from the submitter: (concerns, observations, etc.)
None.

APPEARS THIS WAY
ON ORIGINAL

cc:
NDA 20-796
HFD-120/division file
HFD-120/Leber
HFD-120/Katz/Rappaport
HFD-120/MGuzewska/DScarpetti
HFD-120/Wheelous

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final: 10\29\97

Consult #901 (HFD-120)

COMTAN

entacapone tablets

The Committee noted sound-alike/look-alike conflicts with the following marketed products: COMTREM and CONTAC. The committee felt there was a low potential for mix-up with these products since they are different marketing classes (Rx vs OTC). There were no misleading aspects found.

The Committee has no reason to find the proposed proprietary name unacceptable.

 /S/ 2/23/98, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

MEMO

To: Division File, NDA 20796
From: Thomas D. Steele /S/
Subject: Phone conversation regarding male rat renal tumors
Date: December 4, 1998

Dr. Rick Hailey of NTP was contacted to get his opinion as an individual knowledgeable in animal pathology on the sponsor's proposed male rat-specific mechanism (α_2 -microglobulin [α_2 - μ G] deposition) of renal tumor formation.

Dr. Hailey was generally briefed on the data, issues of concern, and my general impressions that are detailed my review. Specific details were omitted for confidentiality reasons. Dr. Hailey expressed the following opinions:

1. Data submitted to date suggest that this compound is a subtle α_2 - μ G inducer at most; the incidence of renal tumors in drug-treated male rats of the HD group is higher than that typically seen or expected with subtle α_2 - μ G inducers.
2. The occurrence of tumors in 1 LD and 1 MD female is probably inconsequential as an argument against α_2 - μ G involvement.
3. The absence of findings in the initial evaluation of the one-year rat study, which were subsequently identified in an unblinded re-evaluation of the same tissues, was not unusual, since some of the changes are subtle and require additional scrutiny for identification, and different grading systems may be used by different pathologists or in studies of different durations.
4. The absence of some of the associated pathological features such as linear mineralization of the renal papilla is not of great concern; however, Dr. Hailey noted that it was unusual to not have seen changes such as granular casts in some of the shorter-term (eg. 13-week) studies for a true α_2 - μ G inducer.
5. There is an IARC monograph on α_2 - μ G in renal tumorigenesis that should be consulted to assist in determining if the drug fulfils all the criteria of an α_2 - μ G inducer.