NDA 20-796

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

Dear Dr. McCormack:

Please refer to your new drug application (NDA) dated October 24, 1997, received January 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Comtan (entacapone) Tablets 200 mg.

We acknowledge receipt of your submissions dated:

April 16, 1999	May 24, 1999	May 25, 1999
July 15, 1999	July 28, 1999	July 30, 1999
September 9, 1999	October 5, 1999	

Your submission of April 16, 1999 constituted a complete response to our December 31, 1998 action letter.

This new drug application provides for the use of Comtan (entacapone) 200 mg tablets as an adjunct to levodopa / carbidopa to treat patients with idiopathic Parkinson's Disease who experience the signs and symptoms of end-of-dose "wearing-off" (so-called "fluctuating" patients).

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter. In particular, this approval applies to formulation [--].

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-796." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated April 16, 1999 as requested in our December 31, 1998 action letter. This commitment is described below.

Pharmacology / Toxicology
We do not agree that you have provided evidence for saturation of absorption at doses of 100 mg/kg or higher in the mouse carcinogenicity study, and you have not demonstrated in a 3-month study that 100 mg/kg is approximately one half the maximum tolerated dose. As you have therefore failed to validate the existing study, it will be necessary for you to conduct a mouse carcinogenicity study during Phase 4. This study may be a repeat of the mouse bioassay or an alternative study such as the mouse p53 assay. If you choose an alternative mouse model, your justification for the choice and a protocol should be submitted for evaluation by the Executive Carcinogenicity Assessment Committee (ECAC). We also recommend that, if you choose to repeat the bioassay, you seek concurrence for dose selection from the ECAC. The dose selection studies should be initiated immediately, and the completed studies should be submitted as soon as possible.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. As an IND will not be required to meet your Phase 4 commitment, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632).

We note that in your October 5, 1999 submission, received October 6, 1999, you request a waiver of the pediatric study requirement in accordance with the provisions of 21 CFR 314. We will notify you within 120 days of receipt of your submission, February 3, 2000, whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. In the event that we deny your request for a waiver of the pediatric study requirements and, therefore, conclude that you must perform studies in (a subset of) the pediatric population, you may wish to qualify for pediatric exclusivity. In that case you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. If we do deny your waiver request, we recommend that you submit a Proposed Pediatric Study Request within 120 days from the date that we inform you of this denial. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit, and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Teresa Wheelous, R.Ph., Regulatory Management

Officer, at (301) 594-2850.

Sincerely,

/S/

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

Wheelans

DEC 31 [illegible]

NDA 20-796

Orion Pharmaceutical
c/o Target Research Associates
Attention: Robert J. McCormack, Ph.D.
1801 East Second Street
Scotch Plains, NJ 07076

Dear Dr. McCormack:

Please refer to your new drug application (NDA) dated October 24, 1997, received January 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Comtan® (entacapone) Tablets 200 mg.

We also acknowledge receipt of your submissions dated:

November 4, 1997
December 5, 1997
December 14, 1997
December 19, 1997
December 23, 1997
January 2, 1998
January 8, 1998
April 24, 1998
May 1, 1998
May 6, 1998
May 8, 1998
May 15, 1998
May 20, 1998
June 18, 1998
August 4, 1998
September 10, 1998 (2)
September 22, 1998
September 30, 1998
October 1, 1998 (3)
October 7, 1998
October 27, 1998
October 28, 1998
November 3, 1998
November 4, 1998
November 11, 1998
December 1, 1998 (2)
December 2, 1998
December 7, 1998

We have completed the review of this application; although we are considering it approvable because there is clearly some evidence that entacapone is effective, the overall data now available leave doubts about effectiveness and the results of studies are highly inconsistent. Of the larger studies, only study 33, carried out at various Scandinavian sites, is strongly supportive and shows a clear clinically meaningful effect. Study 44, carried out primarily in the United States, is supportive in that it met its prospectively identified endpoint, but in that study half of the clinics showed numerical superiority for the placebo group and the favorable outcome is importantly driven by a single clinic with 12 patients. The mean percent ON effect, moreover, translates to well less than one added hour of ON time per day compared to placebo, less than a value prospectively considered clinically meaningful at the start of the study and less than what was considered meaningful in study 33. Although we would consider study 44 supportive, despite this small effect, if results were clear, the small mean effect, together with this high degree of dependence on results in a single site, weakens this support. In addition, study 52 shows no kind of a benefit

despite adequate size. The possibility that this result arose because of inclusion of non-fluctuating patients needs to be considered, but this is not yet a convincing explanation. First, you have not yet analyzed the study by fluctuating vs. non-fluctuating subgroups. Second, tolcapone, also a COMT inhibitor, showed clear effects in non-fluctuating patients on the UPDRS motor subscale, the same endpoint used in your study. It seems at least possible that dose-finding has been deficient in this case. The studies identifying 200 mg as the optimal dose were small, with little capacity to distinguish regimens. The method of administering entacapone assures widely different doses, depending on the levodopa dose, a familiar approach in Parkinson's Disease, but not necessary the best way to show effectiveness. We note, however, that your pooled analyses of results by levodopa total dose (and therefore by entacapone total dose) shows no difference over the range of <500 mg to >1000 mg.

Given these results, as well as other concerns (such as widely differing rates of adverse events across the three studies and others detailed below), we believe additional data are needed to support effectiveness before entacapone can be approved. The ongoing studies 63 and 65 may be able to provide this support, together with responses to the questions and requested analyses given below. We have provided a marked up draft labeling (attachment 2). It includes notes requesting additional displays and analyses. It is likely that the additional data and analyses requested in this letter and the labeling will require further revision of the labeling and it should be considered a very preliminary draft at this time.

In addition to full reports of studies 63 anti 65, we have the following requests:

Safety Information

This section of the letter includes a number of requests for additional information and analysis of your safety database. However, before initiating these analyses, we strongly urge you to contact the Division to discuss how best to proceed.

1. We note that your proposed labeling includes daily doses of Comtan of up to 2000 mg. However, it is not clear from your safety database (including data from your most recent submission of December 7, 1998) that there is sufficient safety information to support a 2000 mg/day maximum dose at this time. We ask that you compute person-years of exposure to Comtan by daily-dose and duration to allow for a more exact characterization of this experience. Specifically, we ask that you examine doses of 1600, 1800, and 2000 mg per day.

2. With regard to the mortality rates from the randomized controlled trials (RCTs) we ask that you compute these rates using deaths within 30 days, and then again for deaths within 7 days of the patient s last exposure to Comtan.

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3. Adverse event rates are strikingly different from one controlled study to another, suggesting either different observational methods or perhaps different treatment practices. These differences need to be considered and if possible explained. Meanwhile the analyses suggested in the following paragraphs should be considered study by study as well as on pooled data.

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.

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.

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.

7. Additionally, using the same body weight grouping as in point # 6 above, and in addition, considering total daily dose please re-analyze the efficacy data with particular attention to the primary outcome measures in studies 33 and 44.

8. 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.

   Please identify trials where vital signs and ECGs were measured at baseline and serially after entacapone administration and describe entacapone effects on these parameters over a dosing interval by comparing baseline to each post-administration time point. We are particularly interested in the collection of blood

pressure measurements and how they relate to timing of dose to allow for an evaluation of any possible relationship of orthostasis to time of dose.

9. Please provide patient narratives for patients who experienced leukopenia. The narratives should be separated for patients in the RCTs and from your uncontrolled experience and should provide as much longitudinal follow-up as possible. For example, did the patient s continue on drug after the laboratory finding, and did they have subsequent WBC counts performed?

10. For patients who had greater than a 2-gram drop in hemoglobin in the RCTs, provide patient narratives that include other lab data (serum iron, TIBC, ferritin, RBC indices, etc) and longitudinal follow-up.

11. We note that your December 7, 1998 safety update includes an update of serious events (see table 9b in volume 1); however, it is unclear why the totals for some events decline with the update. For example, there are 14 chest pains in data through October 31, 1998, but there were a total of 17 through the 120-day update.

12. Please develop a list of catecholamine drugs whose metabolism is likely to be affected by co-administration of inhibitors of COMT and MAO. For the patients taking selegiline and entacapone in the NDA, identify those patients who had any of these drugs co-administered. Finally, please describe any adverse event associated with the concomitant use of a catecholamine with these drugs.

13. With regard to the urinalysis data reported in your safety database, did the urinalysis include a check for blood? If so, please describe the results.

14. We note that you did not submit the narratives for discontinuations due to adverse events in your phase I and 2 studies, although they were listed in the table of contents of Attachment C of the Integrated Safety Summary (vol. 77 p.8-2-2). We ask that they be submitted.

15. We understand that there may have been cases of rhabdomyolysis reported in Europe please summarize these cases and describe regulatory actions to date.

16. Please refer to Attachment 1 to this letter, which is a listing of patients who experienced adverse events during the clinical development of Comtan. If available and as noted in the attachment, please provide additional follow-up.

Safety Update

Under 21 CFR 314.50(d)(5)(vi)(*b*), the Agency usually requires that you update your NDA by submitting all safety information you have regarding your new drug at the time of your

response to an approvable letter. However, we recognize that on December 7, 1998, a safety update providing safety information through October 31, 1998 was submitted to the NDA. Therefore, if your response to this letter is timely, another complete safety update would not be necessary. We would, however, ask that a safety update be provided if your response is delayed. In the event that a safety update is needed, the update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Pharmacology/Toxicology

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. We would prefer that the results of these studies be submitted as a component of your response to this action letter

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

Biopharmaceutics

We acknowledge your request. We note that this formulation has been used in the extension to Study 33, although we cannot tell how many patients received it. We further note. You have requested that we consider only AUC in the determination of bioequivalence, because you assert that the intrinsic intra- and inter-patient variability of entacapone absorption makes Cmax an unreliable marker.

Although we acknowledge that there is considerable variation in the absorption of entacapone, and that the difference in the composition of the tablet is quite unlikely to account for the difference in Cmax's between the two formulations, we cannot be certain that some other factor (e.g., some change in manufacturing procedure) does not account for the difference seen. For this reason, we ask that you provide additional justification for the acceptance of formulation 55.

Finally, we ask that you adopt the following dissolution methodology:

Apparatus II:	USP (Paddles)
Speed:	rpm
Medium:	mL phosphate buffer, pH
Sampling time:	minutes
Specifications:	Not less than (Q), minutes

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

/S/ 12/31/98

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research