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,

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

Enclosure