

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-091

APPROVAL LETTER

SEP 30 1999

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated March 13, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Carbidopa and Levodopa Extended-release Tablets, 50 mg/200 mg.

Reference is also made to our tentative approval letter dated February 26, 1999, and to your amendments dated December 31, 1998; and September 8, September 13 (2 submissions), September 15, and September 23, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Carbidopa and Levodopa Extended-release Tablets, 50 mg/200 mg, to be bioequivalent, and therefore, therapeutically equivalent to the listed drug (Sinemet CR Tablets, 50 mg/200 mg, of DuPont Pharmaceuticals Co.).

Your dissolution testing should be incorporated into the stability and quality control program using the same method as proposed in your application. The "interim" dissolution test(s) should be conducted in 900 mL of 0.1N HCl at 37 degrees C using USP 23 apparatus II (paddle) at 50 rpm. The following "interim" specifications are recommended for both whole and half-tablets:

- 0.5 hour
- 1.0 hour
- 2.5 hours
- 4 hours

The "interim" dissolution tests and tolerances should be finalized by submitting dissolution data for the first three production size batches in a supplemental application. The supplemental application should be submitted under 21 CFR 314.70(c)(1) when there are no revisions to the interim specifications or when the final specifications are tighter than

the interim specifications. In all other instances, the supplemental application should be submitted under 21 CFR 314.70(b)(2)(ii).

The listed drug product (RLD) referenced in your application, Sinemet CR Tablets, 50 mg/250 mg, is subject to periods of patent protection which expire on June 16, 2006, (patent 4,900,755 [the '755 patent] and patent 4,832,957 [the '957 patent]). Your application contains patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, sale, or offer for sale of this drug product will not infringe on either of these patents, or that the patents are invalid or unenforceable. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately unless an action is brought before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received. You have notified the Agency that Mylan was granted Summary Judgement in a patent litigation suit heard in the United States District Court for the Eastern District of Pennsylvania (Merck & Co., Inc. v. Mylan Pharmaceuticals Inc., Civil Action No. 97-CV-4241). You have also informed us that the United States Court of Appeals for the Federal Circuit affirmed the district court's decision on September 3, 1999 (Merck & Co., Inc. v. Mylan Pharmaceuticals, Inc., 99-1044).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

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We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Douglas L. Sporn", followed by a large, stylized flourish or initial.

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

9/30/99

ANDA 75-091

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated March 13, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Carbidopa and Levodopa Extended-release Tablets, 50 mg/200 mg.

Reference is also made to your amendments dated June 6, 1997; and January 23, June 19, July 23, August 11, and December 15, 1998.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product), and is therefore subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product referenced in your application is subject to a periods of patent protection which expire on June 16, 2006, (patent 4,900,755 [the '755 patent] and patent 4,832,957 [the '957 patent]). Your application contains patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, sale, or offer for sale of this drug product will not infringe on either of these patents, or that the patents are invalid or unenforceable. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately unless an action is brought before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received. However, you have notified the Agency that litigation is underway in the United States District Court for the Eastern District of Pennsylvania involving a challenge to the patents (Merck & Co., Inc. v. Mylan Pharmaceuticals Inc., Civil Action No. 97-CV-4241). You have also informed the agency that Mylan was granted Summary Judgement in the above litigation, but that the decision is currently being

appealed by Merck and Co. Therefore, final approval of this application cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(I), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,
 - b. the date of court decision [505(j)(5)(B)(iii) (I), (II), or (III)], which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,
 - c. the patents have expired, and
2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. Your amendment must provide:

1. a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the district court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and
2. a. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or
- b. a statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application or to the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Kassandra Sherrod, Project Manager, at (301) 827-5849, for further instructions.

Sincerely yours,



2/22/99

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research