

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**75-091**

**CORRESPONDENCE**



# MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

SEP 23 1999

ORIG AMENDMENT

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

## MINOR AMENDMENT

RE: CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS  
50MG/200MG  
ANDA #75-091  
RESPONSE TO AGENCY CORRESPONDENCE DATED SEPTEMBER 23, 1999

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently pending final approval, and to the comment letter pertaining to this application which was forwarded to Mylan by facsimile on September 23, 1999. In response to the comment in the September 23 letter (see Attachment A), Mylan wishes to amend this application as follows:

**FDA COMMENT:** DMF or [redacted] is deficient. Deficiencies in the DMF need to be corrected prior to approval of the ANDA.

**MYLAN RESPONSE:** Mylan acknowledges the Agency's comment regarding [redacted] and has contacted the DMF holder. Based on our discussions we have been informed that a response to the DMF deficiency has been submitted. Enclosed in Attachment B is a copy of the cover letter from [redacted] which provides documentation of the DMF holder's response.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6600 or by facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto  
Vice President  
Regulatory Affairs

FRS/tr



66-882-b  
mm

### Enclosures

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Human Resources (304) 598-5406

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(304) 598-5407  
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(304) 598-3232

38. Comments to be faxed to the applicant:

ANDA: 75-091 DRUG PRODUCT: Carbidopa and Levodopa  
Extended-release Tablets 50 mg/200 mg

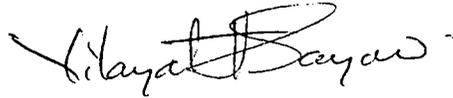
FIRM: Mylan Pharmaceuticals, Inc.

The following deficiency represents a Minor deficiency:

Chemistry Deficiency:

DMF # \_\_\_\_\_ icient. Deficiencies  
in the DMF need to be corrected prior to approval of the  
ANDA.

Sincerely yours,



Florence S. Fang  
Director  
Chemistry Division II  
Office of Generic Drugs  
Center for Drug Evaluation and Research



# MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

SEP 15 1999

NEW CORRESP

*Ne*

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

## TELEPHONE AMENDMENT

RE: CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS, 50MG/200MG  
ANDA #75-091

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently pending final approval, and to our amendment of September 8, 1999. As required in the Agency's February 26, 1999 Tentative Approval letter, our amendment of September 8 contained a statement that "--- no significant changes in the conditions outlined in this abbreviated application have been made since the date of tentative approval."

As discussed with the Office of Generic Drugs on September 15, 1999, Mylan hereby submits the following revised statement:

With the exception of changes to the prescribing information for Carbidopa and Levodopa Extended-release Tablets, 50mg/200mg, which have been addressed in a separate amendment to this application, no changes in the conditions outlined in this abbreviated application have been made since the date of tentative approval.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you have any questions or require additional information, please contact the undersigned by telephone at (304) 599-2595, ext. 6600 or by facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto  
Vice President  
Regulatory Affairs

FRS/tr

enclosures



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Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		



# MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

September 15, 1999

FPL  
ORIG AMENDMENT  
AF

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

## LABELING AMENDMENT

RE: CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS  
50MG/200MG  
ANDA #75-091

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, that is currently pending final approval. On September 13, 1999, Mylan amended this application with a draft outsert revised to incorporate recent changes in the approved labeling of the listed drug. The Office of Generic Drug's (OGD) Division of Labeling and Program Support provided comments on Mylan's draft outsert in a September 14, 1999 correspondence.

Mylan discussed the revised outsert and OGD's comments with the Division of Labeling and Program Support during a September 15, 1999 telephone call. As was discussed with the Division during the telephone call, final printed labeling was printed yesterday prior to receipt of the Division's comments. Prior to printing the outsert the following typographical errors were corrected:

1. "Trails" was corrected to "trials" throughout the outsert (three instances);
2. "Lease" was corrected to "least" in the first sentence of the first paragraph of the WARNINGS section; and
3. In the first paragraph of the WARNINGS: Neuroleptic Malignant Syndrome (NMS) section "or" was replaced with "and".

During the September 15 telephone call, Mylan and OGD agreed that Mylan will make the remainder of the requested corrections at the time of next printing except that Mylan will replace "Appropriate" with "Approximate" in the title of Table II prior to printing production quantities. The Division requested that Mylan submit the final printed outsert that was printed yesterday.

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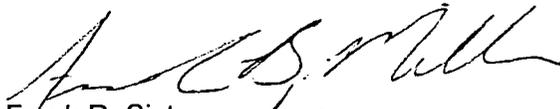


Douglas L. Sporn  
Page 2 of 2

Accordingly, twelve (12) copies of the final printed outsert (CBLVER:R5; revised September 1999) are provided in Attachment 1. As previously noted, Mylan commits to revise "Appropriate" with "Approximate" in the title of Table II prior to printing production quantities of the outsert. Mylan further commits that we will make the remainder of the corrections requested in the OGD's September 14 correspondence at the time of the next printing.

Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

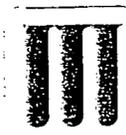


Frank R. Sisto  
Vice President  
Regulatory Affairs

ABM/fct

enclosures





# MYLAN PHARMACEUTICALS INC

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SEP 13 1999

NEW CORRESP

NC  
fx

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

## LABELING AMENDMENT

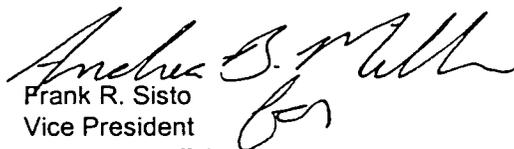
**RE: ANDA 75-091; Carbidopa and Levodopa Extended-release  
Tablets, 50 mg/200 mg**

Dear Mr. Sporn:

Reference is made to Mylan's correspondence previously submitted today, September 13, 1999, in which Mylan committed to revise the prescribing information to incorporate recent changes in the approved labeling of the listed drug. Pursuant to this commitment, Mylan wishes to amend the above-referenced application with a revised outsert. Enclosed in Attachment 2 are four (4) copies of the draft outsert CODE CBLVER:R5; revised September 1999. The labeling was revised in accordance with the approved innovator's labeling that was approved by the Agency on May 10, 1999. A copy of the innovator's labeling is provided in Attachment 1.

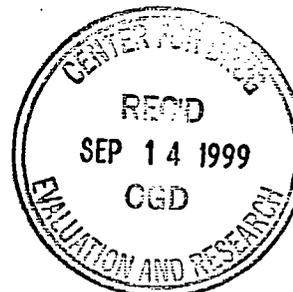
This correspondence is submitted in duplicate. Should you require additional information or have any questions regarding this correspondence, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

  
Frank R. Sisto  
Vice President  
Regulatory Affairs

ABM/dn

Enclosure



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*File: 15-091*

**MYLAN PHARMACEUTICALS INC**

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

**NDA ORIG AMENDMENT**

**FAX COVER**

*N/AF*

DATE: September 13, 1999

TO: Mr. Douglas L. Sporn, Director, Office of Generic Drugs - Desk Copy -  
Mr. Robert West, Director, Division of Labeling and Program Support - Desk Copy ✓  
Mr. Peter Rickman, Deputy Director, Division of Labeling and Program Support - Desk Copy

FROM: Frank R. Sisto, Vice President  
Regulatory Affairs Department  
Mylan Pharmaceuticals Inc.

RE: CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS  
50MG/200MG  
ANDA #75-091

Following is a desk copy of the amendment to the above referenced application which provides revised  
outsert labeling. Hard copy of this amendment is being submitted to the ANDA this evening by overnight  
courier.

Regards,

*Frank R. Sisto*  
Frank R. Sisto

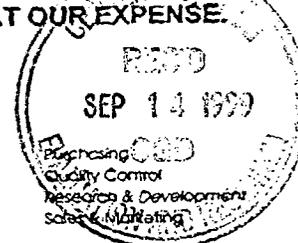
PHONE - (800) 826-9526 Ext. 6600 or 6807

FAX - (304) 285-6407

Number of pages including this sheet 56

**CONFIDENTIALITY NOTICE**

THIS FACSIMILE TRANSMISSION COVER SHEET, AND ANY DOCUMENTS WHICH MAY ACCOMPANY IT, CONTAIN INFORMATION WHICH IS INTENDED ONLY FOR THE USE OF THE INDIVIDUAL OR ENTITY TO WHICH IT IS ADDRESSED, AND WHICH MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND/OR OTHERWISE EXEMPT FROM DISCLOSURE UNDER APPLICABLE LAW. IF THE READER OF THIS MESSAGE IS NOT THE INTENDED RECIPIENT OF THE EMPLOYEE OR AGENT RESPONSIBLE FOR DELIVERING THE MESSAGE TO THE INTENDED RECIPIENT, ANY DISCLOSURE, DISSEMINATION, DISTRIBUTION, COPYING OR OTHER USE OF THIS COMMUNICATION OR ITS SUBSTANCE IS PROHIBITED. IF YOU HAVE RECEIVED THIS COMMUNICATION IN ERROR, PLEASE CALL US COLLECT TO ARRANGE FOR THE DESTRUCTION OF THE COMMUNICATION OR ITS RETURN TO US AT OUR EXPENSE. THANK YOU.



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# MYLAN PHARMACEUTICALS INC

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SEP 13 1999

Office of Generic Drugs, CDER, FDA  
 Douglas L. Sporn, Director  
 Document Control Room  
 Metro Park North II  
 7500 Standish Place, Room 150  
 Rockville, MD 20855-2773

## LABELING AMENDMENT

**RE: ANDA 75-091; Carbidopa and Levodopa Extended-release  
 Tablets, 50 mg/200 mg**

Dear Mr. Sporn:

Reference is made to Mylan's correspondence previously submitted today, September 13, 1999, in which Mylan committed to revise the prescribing information to incorporate recent changes in the approved labeling of the listed drug. Pursuant to this commitment, Mylan wishes to amend the above-referenced application with a revised outsert. Enclosed in Attachment 2 are four (4) copies of the draft outsert CODE CBLVER:R5; revised September 1999. The labeling was revised in accordance with the approved innovator's labeling that was approved by the Agency on May 10, 1999. A copy of the innovator's labeling is provided in Attachment 1.

This correspondence is submitted in duplicate. Should you require additional information or have any questions regarding this correspondence, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

  
 Frank R. Sisto  
 Vice President  
 Regulatory Affairs

ABM/dn

Enclosure

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# MYLAN PHARMACEUTICALS INC

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SEP 13 1999

NEW CORRESP

NC

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn, Director  
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Metro Park North II  
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Rockville, MD 20855-2773

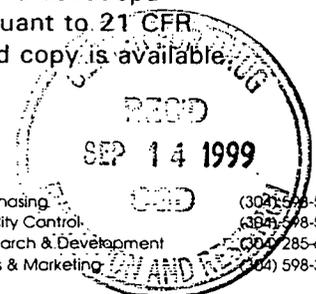
RE: CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS,  
50MG/200MG  
ANDA #75-091

Dear Mr. Sporn:

On December 31, 1998, Mylan amended the above referenced Abbreviated New Drug Application to provide information and data to support approval of an additional product strength, namely Carbidopa and Levodopa Extended-release Tablets, 25mg/100mg. On February 29, 1999, Mylan was granted tentative approval of the ANDA as originally submitted on March 31, 1997, referencing only the product strength provided for in the original application, namely Carbidopa and Levodopa Extended-release Tablets, 50mg/200mg.

In light of the fact that the December 31, 1998 amendment for the lower strength product has not yet been reviewed and that patent litigation pertaining to the higher strength product has been resolved, as evidenced in our amendment dated September 8, 1999, Mylan would like to secure approval for Carbidopa and Levodopa Extended-release Tablets, 50mg/200mg. In order for this to take place and pursuant to 21 CFR 314.99 and 314.65, Mylan hereby requests the withdrawal of our December 31, 1998 amendment pertaining to the manufacture, packaging, testing and labeling of Carbidopa and Levodopa Extended-release Tablets, 25mg/100mg. With the withdrawal of this amendment, ANDA 75-091 will only provide for the manufacture and marketing of Carbidopa and Levodopa Extended-release Tablets, 50mg/200mg. As provided for in 21 CFR 314.99 and 314.65, this request for withdrawal is made without prejudice to future refiling. Subsequent to approval of the ANDA for Carbidopa and Levodopa Extended-release Tablets, 50mg/200mg, Mylan intends to supplement the application with a request to re-activate the review of the December 31, 1998 submission pertaining to the lower strength product.

As a result of the requested withdrawal, Mylan commits to revise the prescribing information for this product to delete reference to the lower 25mg/100mg product strength in the TITLE, DESCRIPTION and HOW SUPPLIED sections. These revisions will be made before commercial distribution. In addition the prescribing information will also be revised prior to commercial distribution to include changes in the approved labeling of the listed drug (approved by the Agency on May 10, 1999). The revised prescribing information providing for Carbidopa and Levodopa Extended-release Tablets, 50mg/200mg, will be submitted to the application pursuant to 21 CFR 314.20(c): Special Supplement - Changes Being Effectuated, as soon as final printed copy is available.



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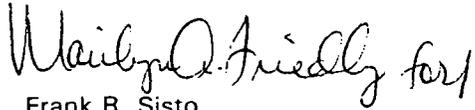
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Douglas L. Sporn  
Page 2 of 2

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this correspondence, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office:

This correspondence is submitted in duplicate. Should you require additional information or have any questions regarding this correspondence, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

A handwritten signature in cursive script that reads "Frank R. Sisto for".

Frank R. Sisto  
Vice President  
Regulatory Affairs

FRS/dn



# MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

September 8, 1999

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

*Discussed approval status of this  
ANDA with Peter Richman on 9/9/99.  
Approval of multiple strengths in  
this ANDA will require further  
discussion.*  
*MS 9/10/99*

## PATENT AMENDMENT

RE: CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS ~~ANDA ORIG AMENDMENT~~  
50MG/200MG  
ANDA #75-091

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently pending final approval. With regard to this application Mylan submitted an amendment on December 15, 1998 which provided documentation evidencing the filing of a lawsuit by Merck & Co., Inc. This lawsuit was filed on June 24, 1997 in the United States District Court for the Eastern District of Pennsylvania. Mylan was granted Summary Judgement in this action on September 22, 1998 and Merck filed an appeal with respect to said decision. The United States Court of Appeals for the Federal Circuit affirmed the district court's decision on September 3, 1999, a copy of which is attached for your reference.

Mylan understands that Purepac/Faulding was the first to file for the 50mg/200mg strength of Carbidopa and Levodopa Extended-release Tablets. In addition, Mylan is aware that Purepac subsequently withdrew its application for this product. While Mylan would enjoy being eligible for a 180-day market exclusivity period as the second filer, we recognize that such a position may not be consistent with the Agency's past practice or the stated position in the proposed revision to the 180-day exclusivity provisions. In that regard we understand that with the withdrawal of a first-to-file applicant's ANDA no applicant is deemed eligible for the 180-day exclusivity period. Mylan simply seeks the most expeditious approval possible and is not concerned that it may not be eligible for exclusivity for the higher strength product.

Based on the withdrawal by Purepac/Faulding of their ANDA for Carbidopa and Levodopa Extended-release Tablets, 50mg/200mg and the September 3, 1999 decision from the United States Court of Appeals, Mylan believes there is no statutory bar which would hinder approval of this application. In addition, as required by the tentative approval letter, this amendment provides notification that no significant changes in the conditions outlined in this abbreviated application have been made since the date of tentative approval.



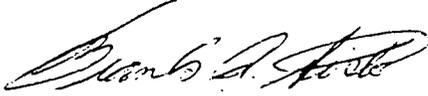
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- |                        |                |                           |                |                        |                |
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Douglas L. Sporn  
Page 2 of 2

Should you have any questions regarding this amendment or require additional information, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,



Frank R. Sisto  
Vice President  
Regulatory Affairs

FRS/tlr

enclosures



# MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

AUG 11 1998

ANDA ORIG AMENDMENT

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

N/Ac

## MAJOR AMENDMENT

RE: CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS,  
50MG/200MG  
ANDA #75-091  
RESPONSE TO AGENCY LETTER DATED JULY 07, 1998

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to the comments from the Agency pertaining to this application which were provided to Mylan in a facsimile dated July 7, 1998. In response to the Agency's comments of July 7, Mylan wishes to amend this application as follows.

### A. REGARDING CHEMISTRY ISSUES

Page (s) 2

Contain Trade Secret,  
Commercial/Confidential  
Information and are not  
releasable.

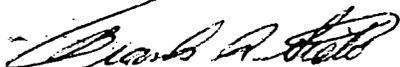
8/11 198

A copy of the Agency correspondence dated July 7, 1998 is included in Attachment 2, for the convenience of the reviewer.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

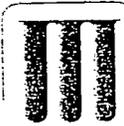
Sincerely,



Frank R. Sisto  
Vice President  
Regulatory Affairs

FRS/tlr

enclosures



# MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

FEB 6 1998

ORIG AMENDMENT

N/A

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**MAJOR AMENDMENT**

RE: CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS,  
50MG/200MG  
ANDA #75-091  
RESPONSE TO AGENCY CORRESPONDENCE DATED JULY 7, 1997

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Application identified above and to the comments from the Agency which were provided to Mylan in a telefax dated July 7, 1997. In response to the Agency's comments, Mylan wishes to amend this application with the following:

**REGARDING CHEMISTRY ISSUES:**

Page (s) 7

Contain Trade Secret,  
Commercial/Confidential  
Information and are not  
releasable.

2/6/98

**REGARDING LABELING ISSUES:**

**MYLAN RESPONSE:** Attachment Q contains twelve (12) copies of the following final printed bottle labels and outsert for Carbidopa and Levodopa Extended-release Tablets, 50 mg/200 mg:

BOTTLE LABELS

Code RM0094A - Bottles of 100 Tablets  
Code RM0094B - Bottles of 500 Tablets

OUTSERT

Code CBLVER:R1 , Revised February 1997

The enclosed labeling incorporates the revisions requested in the Agency's letter of July 7, 1997. A copy of this letter is provided in Attachment O for the convenience of the reviewer.

In order to facilitate the review of this labeling, Attachment P contains a side-by-side comparison of the final printed outsert (CBLVER:R1) to the outsert that was previously submitted. It is noted that prior to approval of this application, the agency reserves the right to request further changes in the Mylan labeling based upon the changes in the approved labeling of the listed drug or upon further review of the application.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical section this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,



Frank R. Sisto  
Executive Director  
Regulatory Affairs

FRS/tlm

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# MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

DEC 31 1998

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

FPL  
AC

RE: CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS, 50MG/200MG  
ANDA 75-091  
AMENDMENT TO PROVIDE FOR THE ADDITION OF 25MG/100MG TABLETS

Dear Mr. Sporn:

The enclosed amendment to the pending application referenced above for Carbidopa and Levodopa Extended-release Tablets, 50mg/200mg, provides for the inclusion of one additional dosage strength (25mg/100mg tablets).

Carbidopa and Levodopa Extended-release Tablets, 25mg/100mg will be manufactured, tested, packaged and labeled by Mylan Pharmaceuticals Inc. in Morgantown, WV following the procedures for the 50mg/200mg tablets, as currently provided in the ANDA. The two dosage strengths are compositionally proportional. The amounts of the ingredients, both active and inactive, in the 25mg/100mg strength are one-half (1/2) the amount of the corresponding ingredients in the 50mg/200mg strength tablet. The bioequivalence of the 50mg/200mg product to the reference listed drug (Sinemet®CR Tablets, 50mg/200mg) was demonstrated in a single-dose fasting *in vivo* bioequivalence study, a single-dose post-prandial *in vivo* bioequivalence study and a multiple-dose steady-state *in vivo* bioequivalence study pursuant to the Office of Generic Drugs' September 9, 1993 Bioguidance for Oral Extended (controlled) Release Dosage Forms. These studies were provided in the original ANDA for the 50mg/200mg product which was submitted March 13, 1997 (ANDA #75-091) and which is currently under review.

Based on the compositional proportionality of the 25mg/100mg to the 50mg/200mg product and the proven bioequivalence of the 50mg/200mg product, only a fasting bioequivalence study was conducted with the 25mg/100mg product pursuant to the Office of Generic Drugs' September 9, 1993 Bioguidance for Oral Extended (Controlled) Release Dosage Forms.

Much of the information included in this amendment has been submitted and reviewed by the Agency in support of the 50mg/200mg product. Revisions based on Agency observations for the 50mg/200mg product have been applied to the 25mg/100mg product, where applicable. As such and to aid in the review, commentary will be provided identifying when previously submitted information exists.

This amendment consists of a total of 17 volumes.

Archival Copy - 7 volumes.

Review Copy - 8 volumes.

Technical Section For Chemistry - 3 volumes.

Technical Section For Pharmacokinetics - 5 volumes. JAN 04 1999

Analytical Methods - 2 extra copies; 1 volume each.

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[G:\PROJECT\ANDA\CARBIDOPA-LEVODOPA-ER-TABS-25\_100MG\SECTIONS-01THRU07.WPD

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Adeline  
1-15-98

Douglas L. Sporn  
Page 2 of 2

As required by 21 CFR 314.96(b) we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this amendment.

This amendment is submitted in duplicate. All correspondence regarding this amendment should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310, or via facsimile at (304) 285-6407.

Sincerely,



Frank R. Sisto  
Vice President  
Regulatory Affairs

FRS/tlr



# MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4

*This is an amendment!*  
*J*

JUL 23 1998

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

NEW CORRESP

NC/Bio

## BIOEQUIVALENCE AMENDMENT (BIOEQUIVALENCE AND CMC INFORMATION ENCLOSED)

RE: CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS,  
50MG/200MG  
ANDA #75-091  
RESPONSE TO AGENCY CORRESPONDENCE DATED JULY 9, 1998

Dear Mr. Sporn:

Reference is made to the ANDA identified above, which is currently under review, and to the July 9, 1998 letter pertaining to this application which was forwarded to Mylan from the Office of Generic Drugs' Division of Bioequivalence. In response to the July 9 correspondence, Mylan wishes to amend the application as follows:

### A. REGARDING BIOEQUIVALENCE ISSUES:

**FDA COMMENT 1.** The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 50 rpm. Based on the submitted data, the following tentative specifications are recommended for Carbidopa and Levodopa:

#### Whole Tablet

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

#### Half Tablet

- 0.5 hour NL
- 1.0 hour N
- 2.5 hours
- 4 hours

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JUL 25 1998

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R:\ANDA\CARBIDOPA LEVODOPA\BIO-AGENCY LETTER\_070998.WPD

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

**MYLAN RESPONSE:** The dissolution testing requested by the Division of Bioequivalence will be incorporated into Mylan's stability and quality control programs as of the date of this amendment. Mylan has revised the finished product specifications, dissolution procedure, and post-approval stability protocol for Carbidopa and Levodopa Extended-release Tablets, 50mg/200mg to incorporate the requested changes in the procedure and specifications for dissolution. These revised documents are provided in Attachments 1, 2, and 3, respectively.

For the purpose of routine quality control release and stability testing Mylan will only conduct dissolution testing on whole tablets. Dissolution specifications have, therefore, only been included for whole tablets. This has been discussed with personnel in both OGD's Division of Bioequivalence and Division of Chemistry II. It is understood that, if tested, the dissolution of the half tablets will meet the same specifications as the whole tablet.

It is also acknowledged and understood that the bioequivalency comments expressed in the letter dated July 9, 1998 are preliminary and may be revised after review of the entire application.

For your reference, a copy of the Agency correspondence dated July 9, 1998 is enclosed in Attachment 4.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,



Frank R. Sisto  
Vice President  
Regulatory Affairs

FRS/tlr

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JUL 9 1998

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75-091            APPLICANT: Mylan Pharmaceutical Inc.

DRUG PRODUCT: Carbidopa and Levodopa, 50 mg/200 mg extended release  
(ER) Tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 50 rpm. Based on the submitted data, the following tentative specifications are recommended for Carbidopa and Levodopa:

Whole Tablet

0.5 hour  
1.0 hour  
2.5 hours  
4 Hours

Half Tablet

0.5 hour  
1.0 hour  
2.5 hours  
4 Hours

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm.D.  
Director Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75-091

APPLICANT: Mylan Pharmaceutical Inc.

DRUG PRODUCT: Carbidopa and Levodopa, 50 mg/200 mg extended release (ER) Tablets

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus II (paddle) at 50 rpm. Based on the submitted data, the following tentative specifications are recommended for Carbidopa and Levodopa:

Whole Tablet

0.5 hour  
1.0 hour  
2.5 hours  
4 Hours

Half Tablet

0.5 hour  
1.0 hour  
2.5 hours  
4 Hours

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm.D.  
Director Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research



# MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

Submitted Via Facsimile on June 19, 1998

JUN 19 1998

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

AB

## BIOEQUIVALENCE TELEPHONE AMENDMENT

RE: CARBIDOPA & LEVODOPA EXTENDED-RELEASE TABLETS,  
50MG/200MG  
ANDA 75-091  
RESPONSE TO AGENCY TELEPHONE CALL OF JUNE 09, 1998

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Application identified above which is currently under review and to the June 09, 1998 telephone call from the Division of Bioequivalence in which half-tablet dissolution profile data for the reference product were requested. The lot of innovator drug product which was used to conduct the bioequivalence studies submitted in support of this application has expired. Therefore, as requested by the Agency, half-tablet dissolution profile data for a representative lot of the reference listed drug (Sinemet®) are enclosed.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this telephone amendment as submitted to the Office of Generic Drugs has been forwarded to the FDA's Baltimore District Office.

This amendment is being transmitted via facsimile on this date followed by hard copy submitted in duplicate via Federal Express. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto  
Vice President  
Regulatory Affairs

FRS/tlr

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JUN 22 1998

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RE: CARBIDOPA-LEVODOPA AGENCY CALL DATED JUNE 09, 1998

JUL 7 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-091    APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Carbidopa and Levodopa Extended-release Tablets,  
50 mg/200 mg.

The deficiencies presented below represent MAJOR Deficiencies.

A. Deficiencies:

1. The proposed time delays between phases of manufacturing are not acceptable. We recommend a 8 week time delay for the completion of granulation/drying/milling and blending. We also notice your intention to store the bulk product in drums inside double bags. Please note that bulk stability of the product needs to be established for 3 months, at ambient conditions using the proposed drums, before it will be granted. Hence we recommend a 4 week time frame for compression and packaging into the approved 100 and 500 count packaging configurations. Also, amend the application with bulk stability data for up to 3 months in the fiber drums/polyethylene bags, in order to store the samples in bulk for up to three months.
2. We notice from the COAs for fiber drum and bags that the bulk product may be stored in this configuration for up to 3 months. Please provide USP <671> testing results (for this configuration).
3. Upon verifications of your methods, the Baltimore District Lab has the following comments:
  1. It is not necessary to dilute the 30 and 60 minutes dissolution samples.
  2. The resolution solution for the related compounds method should include the Carbidopa impurities (FP-CDLDER-RC-M). Although, the method states to inject them separately, they should be included in the resolution solution in order to insure that they are all resolved.
  3. The related compounds method, (FP-CDLDER-RC-M), submitted by the firm to CDER is different from the related compounds method submitted to the district laboratory. It was also observed that both of these methods have the same dates and approval dates (2/25/97 and 2/28/97). The differences are observed in the formula given for calculation. You need to use the following statements and formula for calculating the related compounds:

A peak matching the retention time of methyldopa and/or 3-0- methylcarbidopa will be calculated upon levodopa standard response using the equation:

Carbidopa impurities % =  
(Includes methyldopa and 3-O-methylcarbidopa)

$$\frac{\text{Impurity response} \times \text{Levodopa std con. Mg.mL} \times \text{ATW gm/tab} \times \text{XD.F.ml} \times 100}{\text{Avg. Levodopa std.resp} \times \text{Sample wt.g} \times \text{Carbidopa dose mg}}$$

Levodopa and other impurities such as those matching the retention times of . . . . . and 3- . . . . . should use the following calculation:

Levodopa and other impurities % =

$$\frac{\text{Levodopa Impurity response} \times \text{X}}{\text{Avg. Levodopa std.resp}}$$

Sincerely yours,



Frank O. Holcombe, Jr., Ph.D.  
Director  
Division of Chemistry II  
Office of Generic Drugs  
Center for Drug Evaluation and Research



# MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

JAN 23 1998

## BIOEQUIVALENCE AMENDMENT BIOEQUIVALENCE DATA ENCLOSED

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

RE: CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS, 50MG/200MG  
ANDA 75-091  
RESPONSE TO AGENCY CORRESPONDENCE DATED DECEMBER 12, 1997

Dear Mr. Sporn:

Reference is made to the ANDA identified above, which is currently under review, and to the Agency's correspondence from the Division of Bioequivalence which was forwarded to Mylan by facsimile on December 12, 1997. In response to the December 12<sup>th</sup> correspondence, Mylan wishes to amend this application as follows:

### REGARDING BIOEQUIVALENCE ISSUES:

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

**FDA COMMENT 1.** Please submit complete dissolution profiles data generated in different buffers media (such as citric acid or phosphate buffers), in the pH ranges: 1-1.5, 4-4.5, 6-6.5, and 7-7.5. The rotation basket (rpm) should be as follow: at 50 rpm and 75 rpm (paddle); and 100 rpm (basket). The sampling schedule as follow: 1, 2, 4 hours, and every two hours thereafter, until of the drug is released. You are advised to refer to the Division of Bioequivalence guidance 'Oral Extended (Control) Release Dosage Forms' dated September 09, 1993.

**MYLAN RESPONSE:** As requested by the Agency and pursuant to the Division of Bioequivalence guidance, entitled 'Oral Extended (Control) Release Dosage Forms' dated September 9, 1993, dissolution profiles have been generated in 0.1 N HCl for Mylan's Carbidopa and Levodopa Extended-release Tablets, 50mg/200mg and Sinemet® CR Tablets, 50mg/200mg using paddles at 75 rpm as well as baskets at 100 rpm. Dissolution profiles generated in 0.1 N HCl with paddles at 50 rpm for the Mylan product and innovator product are provided in Mylan's ANDA

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JAN 26 1998

[RD LIBANDA CARBIDOPA-LEVODOPA AGENCY-LETTER-DATED-121297

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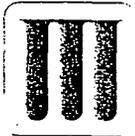
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# MYLAN PHARMACEUTICALS INC

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JAN 23 1998

## BIOEQUIVALENCE AMENDMENT BIOEQUIVALENCE DATA ENCLOSED

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

RE: CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS, 50MG/200MG  
ANDA 75-091  
RESPONSE TO AGENCY CORRESPONDENCE DATED DECEMBER 12, 1997

Dear Mr. Sporn:

Reference is made to the ANDA identified above, which is currently under review, and to the Agency's correspondence from the Division of Bioequivalence which was forwarded to Mylan by facsimile on December 12, 1997. In response to the December 12<sup>th</sup> correspondence, Mylan wishes to amend this application as follows:

### REGARDING BIOEQUIVALENCE ISSUES:

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

**FDA COMMENT 1.** Please submit complete dissolution profiles data generated in different buffers media (such as citric acid or phosphate buffers), in the pH ranges:  
The rotation basket (rpm) should be as follow: at 50 rpm and 75 rpm (paddle); and 100 rpm (basket). The sampling schedule as follow: 1, 2, 4 hours, and every two hours thereafter, until of the drug is released. You are advised to refer to the Division of Bioequivalence guidance 'Oral Extended (Control) Release Dosage Forms' dated September 09, 1993.

**MYLAN RESPONSE:** As requested by the Agency and pursuant to the Division of Bioequivalence guidance, entitled 'Oral Extended (Control) Release Dosage Forms' dated September 9, 1993, dissolution profiles have been generated in 0.1 N HCl for Mylan's Carbidopa and Levodopa Extended-release Tablets, 50mg/200mg and Sinemet® CR Tablets, 50mg/200mg using paddles at 75 rpm as well as baskets at 100 rpm. Dissolution profiles generated in 0.1 N HCl with paddles at 50 rpm for the Mylan product and innovator product are provided in Mylan's ANDA

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#75-091 (pages 6440-6447) for Carbidopa and Levodopa Extended-release Tablets, 50mg/200mg. Sampling of these dissolution analyses was performed at 30 minutes, 1 hour, 2 hours, 2 ½ hours, and 4 hours. In all cases if the drug was released at 4 hours for the Mylan formulation. Attachment A contains these data as well as the current dissolution procedure which has been updated pursuant to a major deficiency letter from the Agency dated July 7, 1997 which requested that the stability of dissolution standard and sample preparations be determined. The study results indicate that the standard and sample preparations are stable for about (2) days and additional instructions are now included in the procedure to caution the analyst to that effect.

Mylan has not performed dissolution testing of Carbidopa and Levodopa Extended-release Tablets in dissolution media at pH values greater than 4.0 since Carbidopa has been observed to degrade under these conditions.

Review of literature received through the Freedom of Information Act regarding the reference product, Sinemet® CR Tablets, indicates that the innovator had observed either poor solubility or poor solution stability of their Carbidopa and Levodopa Tablets during dissolution testing using water or phosphate buffer at a pH of 6.9. The instability of Carbidopa in solutions at pH values greater than 4.0 is further supported by Mylan's Intentional Degradation study presented in Mylan's application (ANDA #75-091, pages 6675-6720) in which exposure of Carbidopa to phosphate buffer solutions at a pH of 4.0 yields significant decomposition of this drug substance. Since the degradation of Carbidopa occurs in solutions with a pH value greater than 4.0, performing dissolution testing under these conditions will not yield a practical and reproducible quality control test.

**FDA COMMENT 2.** Since carbidopa and levodopa ER tablets are scored, therefore, dissolution profiles for half tablets are required in an addition to whole tablets.

**MYLAN RESPONSE:** Mylan has performed half tablet dissolution testing of the 50mg/200mg Carbidopa and Levodopa Extended-release Tablets. Dissolution profiles were generated using 0.1 N HCl, as the medium with paddles at 50 rpm. Dissolution profiles were generated based upon a sampling schedule of 30 minutes, 60 minutes, 120 minutes, 150 minutes and 240 minutes. These half tablet dissolution profiles have been provided in Attachment B. The data indicate that the rate of dissolution of half tablets is similar to that of whole tablets.

**FDA COMMENT 3.** The dissolution specifications for the test product will be established based on acceptable submitted dissolution data.

**MYLAN RESPONSE:** Mylan acknowledges that the dissolution specifications for the test product will be established based upon acceptable submitted dissolution data.

Douglas L. Sporn  
Page 3 of 3

For the convenience of the reviewer, a copy of the Agency correspondence dated December 12, 1997 is enclosed in Attachment C.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,



Frank R. Sisto  
Executive Director  
Regulatory Affairs

FRS/tlm

enclosures



June 25, 1997

Office of Generic Drugs  
United States Food and Drug Administration  
Center for Drug Evaluation & Research  
HFD 600, Metropark North-2  
Room 286  
7500 Standish Place  
Rockville, Maryland 20855

RECEIVED

JUN 25 1997

GENERIC DRUGS

Attention: Douglas L. Sporn

Re: Notice of Filing of Patent Infringement  
Action Relating to Mylan ANDA 75-091

Dear Mr. Sporn:

*Sporn*  
This letter is to give notice that Merck & Co., Inc., owner of U.S. Patent Nos. 4,900,755 and 4,832,957, yesterday instituted an action for infringement of those patents against Mylan Pharmaceuticals Inc. ("Mylan") as a result of Mylan's filing of the above-identified abbreviated new drug application ("ANDA"). Consistent with the requirements of 21 C.F.R. § 314.107(f)(2), the following information is provided:

(i) Mylan's abbreviated new drug application number is, according to Mylan's notice of certification to Merck, ANDA 75-091.

(ii) The ANDA applicant is Mylan Pharmaceuticals Inc. and the ANDA drug product is "Carbidopa: Levodopa Tablets; Extended Release; 50 mg; 200 mg" containing the active ingredients Carbidopa (50 mg) and Levodopa (200 mg).

(iii) The established name of Merck's drug product covered by the above patents, which are Orange Book listed, is SINEMET® CR.

(iv) An action for patent infringement against Mylan was filed in the U.S. District Court for the Eastern District of Pennsylvania on June 24, 1997, C.A. No. 97-4241. This action was filed within 45 days of Merck's receipt of Mylan's notice of

DIVISION OFFICE WEST POINT, PENNSYLVANIA 19486 JUN 25 1997

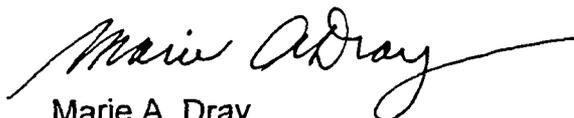
RECEIVED  
GENERIC DRUGS

RE: Notice of Filing of Patent Infringement

Page 2

certification, dated May 9, 1997, submitted to Merck pursuant to Section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act.

Sincerely,

A handwritten signature in cursive script that reads "Marie A. Dray". The signature is written in black ink and is positioned above the printed name.

Marie A. Dray

Senior Director  
Regulatory Agency Relations



June 25, 1997

Office of Generic Drugs  
United States Food and Drug Administration  
Center for Drug Evaluation & Research  
HFD 600, Metropark North-2  
Room 286  
7500 Standish Place  
Rockville, Maryland 20855

RECEIVED

JUN 25 1997

GENERIC DRUGS

Attention: Douglas L. Sporn

Re: Notice of Filing of Patent Infringement  
Action Relating to Mylan ANDA 75-091

Dear Mr. Sporn:

*Part*  
This letter is to give notice that Merck & Co., Inc., owner of U.S. Patent Nos. 4,900,755 and 4,832,957, yesterday instituted an action for infringement of those patents against Mylan Pharmaceuticals Inc. ("Mylan") as a result of Mylan's filing of the above-identified abbreviated new drug application ("ANDA"). Consistent with the requirements of 21 C.F.R. § 314.107(f)(2), the following information is provided:

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DIVISION OFFICE: WEST POINT, PENNSYLVANIA 19486

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RE: Notice of Filing of Patent Infringement

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Marie A. Dray

Senior Director  
Regulatory Agency Relations

DEC 12 1997 1,1

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-091

APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Carbidopa and Levodopa, 50 mg/200 mg ER Tablets

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. Please submit complete dissolution profiles data generated in different buffers media (such as citric acid or phosphate buffers), in the pH ranges: 1-1.5, 4-4.5, 6-6.5 and 7-7.5. The rotation basket (rpm) should be as follow: at 50 rpm and 75 rpm (paddle); and 100 rpm (basket). The sampling schedule as follow: 1, 2, 4 hours, and every two hours thereafter, until of the drug is released. You are advised to refer to the Division of Bioequivalence guidance 'Oral Extended (Control) Release Dosage Forms' dated September 09, 1993.
2. Since carbidopa and levodopa ER tablets are scored, therefore, dissolution profiles for half tablets are required in an addition to whole tablets.
3. The dissolution specifications for the test product will be established based on acceptable submitted dissolution data.

Sincerely yours,



Dale Conner, Pharm.D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

38. Chemistry Comments to be Provided to the Applicant

JUL 7 1997

ANDA: 75-091    APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Carbidopa and Levodopa Extended-release Tablets, 50 mg/200 mg.

The deficiencies presented below represent MAJOR Deficiencies.

A. Deficiencies:

1. Please provide copies of Certificates of Analysis for the in-house reference standards for Carbidopa and Levodopa if they are employed in routine analysis.
2. We notice from the information given on pages 6287 and 6295 that parameters such as blend uniformity, bulk density and moisture are measured and are assigned specifications. However, the blank production records do not include testing statements for moisture or bulk density of granulation. Please identify when these tests are performed clearly and include them in the production records.
3. We observe that the entire manufacturing and packaging operations were performed within a 2 week time period. During routine production, what type of holding time(s) are established between different stages of manufacture?
4. Please provide us a COA from the supplier (3M) and your test data for the Safe Gard 100 inner seal. Since these are in actual contact with the product, please include the test for buffering capacity as per USP 23 <661> requirements.
5. For the methods \_\_\_\_\_ and \_\_\_\_\_ please include the following in your system suitability parameters: Tailing factors limit and number of plates for the analytical column.
6. We notice your statement on page 6504 regarding contacting USP for the Levodopa impurities method. When do you plan to develop a USP monograph of this method through submission to PF?
7. We notice that the specification for friability is included and examined for the exhibited batch (page 6298). However, it is not included as an in-process specification on page 6291. We request that you revise this and submit Friability = \_\_\_\_\_ as a specification.
8. The assay method validation needs to include evaluation of robustness, a new element USP XXIII has included to investigate the working limits of any analytical method.

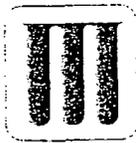
9. Stability of standards and samples needs to be documented for both the assay and dissolution experiments. Are samples stored past a 24 hour period of preparation? What is the stability of the solutions? Please include stability evaluation to establish time limits for sample analyses (assay, dissolution and content uniformity).
  10. Are any filters employed in the assay, dissolution sample preparation? If so please identify them and include filter validation data.
  11. Please provide PDA spectra and/or peak purity measurement UV spectra for the forced degradation samples. We could not locate this information in the ANDA.
  12. For the dissolution experiment, please provide individual values with %RSDs obtained during stability.
  13. We notice from the protocol that Methyldopa (See page 6729) is to be reported as one of the related substances/degradants. However, its results are not found in any of the stability reports. Does it mean that it is not found (< LOD) or is it added to total impurities? Please amend your stability data sheets.
  14. We notice from the date of assay that both the ambient and accelerated samples are analyzed at least 2 months after they are pulled. Samples have to be analyzed within a reasonable amount of time (2 weeks). Please provide us a rationale for this delay in stability sample analysis.
- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
1. Since this drug product is not covered by an official monograph in the USP, the analytical methods must be validated by an FDA field laboratory prior to the approval of the application. Samples will be requested by the FDA at an appropriate time.
  2. The dissolution specifications for this product will be reviewed by the Division of Bioequivalence. The chemistry review will cover only the validation portion and data submitted (release and stability).

Sincerely yours,



Frank O. Holcombe, Jr., Ph.D.  
Director  
Division of Chemistry II  
Office of Generic Drugs  
Center for Drug Evaluation and Research





# MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

MAR 13 1997

ELECTRONIC DATA ENCLOSED  
BIOEQUIVALENCE DATA ENCLOSED

*Harvey*  
*4/21/97*

Office of Generic Drugs, CDER, FDA  
Douglas L. Sporn Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

RE: CARBIDOPA AND LEVODOPA EXTENDED-RELEASE TABLETS,  
50MG/200MG

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None

Established Name: Carbidopa and Levodopa Extended-release Tablets

This application consists of a total of 35 volumes.

Archival Copy - 16 volumes.

Review Copy - 17 volumes.

Technical Section For Chemistry - 3 volumes.

Technical Section For Pharmacokinetics - 14 volumes.

Analytical Methods - 2 extra copies; 1 volume each.

NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a data diskette for the bioequivalence studies conducted in support of this application. An electronic data set, using the Office of Generic Drug's new EVA software program, is currently being prepared and will be submitted as an amendment to this application as soon as it becomes available.

This application provides for the manufacture of Carbidopa and Levodopa Extended-release Tablets, 50mg/200mg. All operations in the manufacture, packaging, and labeling of the drug product are performed by Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730.

As required by 21 CFR 314.94(d)(5) we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310, or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto  
Executive Director  
Regulatory Affairs

MAR 13 1997

MAR 14 1997

Department - Fax Numbers  
Accounting  
Administration  
Business Development  
Human Resources

(304) 285-6403  
(304) 599-7284  
(304) 599-7284  
(304) 598-5406

FRS/tlm

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Label Control  
Legal Services  
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Medical Unit

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(304) 598-5445

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Research & Development  
Sales & Marketing

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(304) 598-5407  
(304) 285-6409  
(304) 598-3232