

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-091

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Date of Submission: September 13, 1999



Name: Mylan Pharmaceuticals, Inc.

Name: Carbidopa and Levodopa Extended-release Tablets, 50 mg/200 mg

REVIEWING DEFICIENCIES

INSERT

1. DESCRIPTION

Delete "USP Drug release test pending."

2. CLINICAL PHARMACOLOGY

a. Pharmacodynamics

Replace "trials" with "trials" in the first sentence of the seventh paragraph.

b. Pharmacokinetics

i. Revise the second sentence of the third paragraph to read as, "...35% of the standard carbidopa and levodopa immediate-release..."

ii. In the first sentence of the sixth paragraph, add "tablets" after "immediate-release".

iii. Revise the second sentence of the sixth paragraph to read as, "...bioavailability from 50 mg/200 mg carbidopa and levodopa extended-release is..."

3. CONTRAINDICATIONS

Add a hyphen between "narrow" and "angle" in the second paragraph.

4. WARNINGS

a. Replace "lease" with "least" in the first sentence of the first paragraph.

b. Neuroleptic Malignant Syndrome (NMS)

Replace "or" with "and" in the first paragraph between "...levodopa immediate-release" and "carbidopa and levodopa..."

5. PRECAUTIONS

a. General

Revise the second paragraph to read as, "...wide-angle glaucoma may be treated cautiously with carbidopa and levodopa extended-release provided..."

b. Drug Interactions

i. Add "extended-release" after "levodopa" in the first paragraph.

ii. Add "extended-release" after "levodopa" in the third sentence of the fifth paragraph.

- c. Carcinogenesis, Mutagenesis, Impairment of Fertility

Add "equivalent to" between "(" and "8" in the second paragraph.

6. ADVERSE REACTIONS

- a. Delete "1." and "2." from the second and third paragraph respectively.
b. Replace "trials" with "trials" in the fourth paragraph.

7. DOSAGE AND ADMINISTRATION

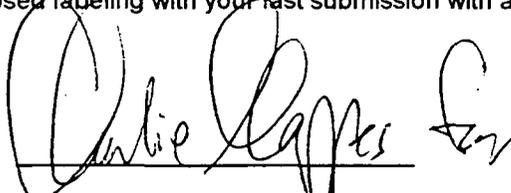
- a. Replace "Appropriate" with "Approximate" in the title of Table II.
b. Replace "From" with "from" in the Table III title.
c. Replace: "1 tab" with "200 mg"; "1 ½ tab" with "300 mg"; "2 tabs" with "400 mg"; "4 tabs" with "800 mg"; and "5 tabs" with "1000 mg" in Table III.
d. Patients Currently Treated with Levodopa Without a Decarboxylase Inhibitor
Add "50 mg/200 mg" between "of" and "carbidopa" in the last sentence of the first paragraph.
e. Patients Not Receiving Levodopa
Add "50 mg/200 mg" between "of" and "carbidopa".

Please revise your insert labeling, as described above, and submit 12 copies of final printed insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Robert L. West, M.S., R.Ph.

Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

RECORD OF TELEPHONE CONVERSATION

DATE: September 15, 1999
ANDA: 70-091
DRUG: Carbidopa and Levodopa Extended-release Tablets 50 mg/200 mg
FIRM: Mylan
CONVERSATION WITH: Andrea Miller
PHONE NUMBER: 1-800-848-0461 Ext 6869
TOPIC: Labeling Issues

The labeling review of the draft labeling submitted by Mylan on 9/13/99 for their Carbidopa and Levodopa drug product was completed and the labeling deficiencies were faxed to the firm yesterday.

Yesterday evening, Mylan faxed in their response to our labeling deficiencies. Mylan proposes to make some minor labeling changes before it enters the market and commits to making the rest of the changes at the next time of printing. Today, I informed Andrea Miller of Mylan that her commitment is acceptable since most of the labeling deficiencies were minor. According to Ms. Miller, we should have FPL by tomorrow via FedEx.

Ms. Miller said the changes that we should see in the FPL that Mylan plans to submit tomorrow should have the corrections of "trails" to "trials" in the CLINICAL PHARMACOLOGY and ADVERSE REACTIONS sections and "or" to "and" and "lease" to "least" in the WARNINGS section.

For Table II in the DOSAGE AND ADMINISTRATION section, "Appropriate" will be replaced with "Approximate" before the labeling enters the market. All other labeling deficiencies outlined in the Labeling Review of Mylan's 9/13/99 submission will be made at the next time of printing.

Koung Lee

KL 9/15/99

V:\FIRMSAM\MYLAN\TELECON\75091.091599

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 75-091

Date of Submission: September 13, 1999

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Carbidopa and Levodopa Extended-release Tablets, 50 mg/200 mg

LABELING DEFICIENCIES**INSERT****1. DESCRIPTION**

Delete "USP Drug release test pending."

2. CLINICAL PHARMACOLOGY**a. Pharmacodynamics**

Replace "trials" with "trials" in the first sentence of the seventh paragraph.

b. Pharmacokinetics

- i. Revise the second sentence of the third paragraph to read as, "...35% of the standard carbidopa and levodopa immediate-release..."
- ii. In the first sentence of the sixth paragraph, add "tablets" after "immediate-release".
- iii. Revise the second sentence of the sixth paragraph to read as, "...bioavailability from 50 mg/200 mg carbidopa and levodopa extended-release is..."

3. CONTRAINDICATIONS

Add a hyphen between "narrow" and "angle" in the second paragraph.

4. WARNINGS**a. Replace "lease" with "least" in the first sentence of the first paragraph.****b. Neuroleptic Malignant Syndrome (NMS)**

Replace "or" with "and" in the first paragraph between "...levodopa immediate-release" and "carbidopa and levodopa..."

5. PRECAUTIONS**a. General**

Revise the second paragraph to read as, "...wide-angle glaucoma may be treated cautiously with carbidopa and levodopa extended-release provided..."

b. Drug Interactions

- i. Add "extended-release" after "levodopa" in the first paragraph.
- ii. Add "extended-release" after "levodopa" in the third sentence of the fifth paragraph.

- c. Carcinogenesis, Mutagenesis, Impairment of Fertility

Add "equivalent to" between "(" and "8" in the second paragraph.

6. ADVERSE REACTIONS

- a. Delete "1." and "2." from the second and third paragraph respectively.
b. Replace "trials" with "trials" in the fourth paragraph.

7. DOSAGE AND ADMINISTRATION

- a. Replace "Appropriate" with "Approximate" in the title of Table II.
b. Replace "From" with "from" in the Table III title.
c. Replace: "1 tab" with "200 mg"; "1 ½ tab" with "300 mg"; "2 tabs" with "400 mg"; "4 tabs" with "800 mg"; and "5 tabs" with "1000 mg" in Table III.
d. Patients Currently Treated with Levodopa Without a Decarboxylase Inhibitor
Add "50 mg/200 mg" between "of" and "carbidopa" in the last sentence of the first paragraph.
e. Patients Not Receiving Levodopa
Add "50 mg/200 mg" between "of" and "carbidopa".

Please revise your insert labeling, as described above, and submit 12 copies of final printed insert labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- A. Do you have 12 Final Printed Labels and Labeling? Yes (I have verified 12 copies in the original jacket)

CONTAINER LABELS: 100's & 500's

PROFESSIONAL PACKAGE INSERT LABELING:

- B. REVISIONS NEEDED POST-APPROVAL:

- C. BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Sinemet CR 25/200

NDA Number: 19-856

NDA Drug Name: Sinemet CR

NDA Firm: Merck, Sharp & Dome

Date of Approval of NDA Insert and supplement #:

NDA 19-856/S-001/S-006/S-007/S-009/S-012 approved May 10, 1999

Has this been verified by the MIS system for the NDA?

Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Sinemet

FOR THE RECORD:

1. Review based on the labeling of the listed drug Sinemet CR; approved May 10, 1999.

2. Mylan is the manufacturer. No outside firms used (p 6175, vol 1.2).

3. Patent/Exclusivities:

There are two patents for this drug product. Patent 4900755 and 4832957 which both expire on May 23, 2006. Mylan has filed Paragraph IV Certification.

4. Both the NDA and the ANDA are scored. The tablet description is accurate as stated in the HOW SUPPLIED section (p 6529, vol 1.3).

5. Storage/dispensing recommendations:

NDA: (insert and container) Store in a tightly closed container. Avoid temperatures above 30°C (86°F).

ANDA: (container) Dispense in a tight container as defined in the USP using a child-resistant closure. Keep container tightly closed. DO NOT STORE ABOVE 30°C (86°F).
(insert) Dispense in a tight container as defined in the USP using a child-resistant closure. Keep container tightly closed.

USP: Not the subject of a USP monograph.

Sinemet (carbidopa and levodopa immediate-release tablets) is the subject of a USP monograph. The storage recommendations for it as listed in the USP: Preserve in well-closed, light-resistant containers. We previously asked Purepac's unapproved ANDA 74-669 to end their dispensing statement ... in a tight, light-resistant container. Upon discussion with J. Grace we will not ask Mylan to add "light-resistant" to its dispensing statement since the innovator does not.

6. Other differences between Purepac's unapproved ANDA 74-669 and this application, Mylan's 75-091:
 - a. The first line of the ADVERSE REACTIONS section was changed from "In controlled clinical trials,..." to "It has been reported in controlled clinical trials,..." in ANDA 74-669. We have NOT asked Mylan to do this.
 - b. We have asked Mylan to delete the phrase "extended-release" from the PRECAUTIONS-General (1 instance) and the Drug Interactions subsections. We did not do this with the Purepac application.
7. The RLD markets a container size of 100s and a unit-dose carton of 100s.
The ANDA wishes to market sizes of 100s and 500s.
8. The 100s have a CRC (p 6338, vol 1.2). Both the 100s and the 500s container sizes are made of beige, opaque HDPE (light-resistant) (pp 6316, 6325, vol 1.2).
9. The listing of inactive ingredients is accurate.
(p 6006, vol 1.1).

Date of Review: September 14, 1999

Date of Submission: September 13, 1999

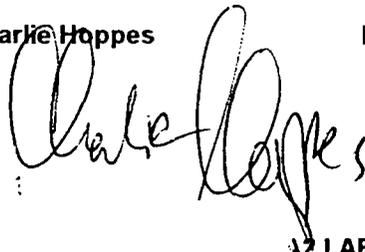
Primary reviewer: Koung Lee

Date: 9/14/99

Team Leader: Charlie Hoppes

Date:

cc:



9/14/99

12.LABELING

RECORD OF TELEPHONE CONVERSATION

DATE: July 14, 1998

PRODUCT NAME: Carbidopa/Levodopa

ANDA/AADA NUMBER: 75-091

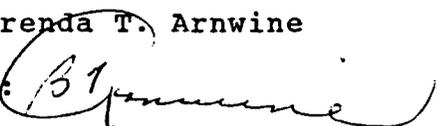
FIRM NAME: Mylan

NAME AND TITLE OF PERSON WITH
WHOM CONVERSATION HELD: Frank Sisto

TELEPHONE: (304) 599-2595 Ext 6600

MINUTES OF CONVERSATION: Mr. Sisto called requesting clarification on question #1 of our deficiency letter dated 7/7/98. We had raised concerns regarding the time frames indicated in the application to complete the granulation/drying /milling and blending of the bulk drug product. Mr. Sisto indicated that the firm was planning to follow our suggested time frame of 4 weeks which would eliminate our request to supply stability data on the product stored in bulk for 3 months. I told him that would be fine and that also eliminated the need to answer question #2 which requested additional data on the bulk drum. Mr. Sisto thanked me and we ended the conversation.

NAME OF OGD REPRESENTATIVE: Brenda T. Arnwine

SIGNATURE OF OGD REPRESENTATIVE: 

DIVISION/BRANCH: Div Chem II/Br 5

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-091 Date of Submission: February 6, 1998

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Carbidopa and Levodopa Extended-release
Tablets, 50 mg/200 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

A. Do you have 12 Final Printed Labels and Labeling? Yes (I have verified 12 copies in the original jacket)

CONTAINER LABELS: 100's & 500's

Satisfactory in FPL as of 2/6/98 submission

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in FPL as of 2/6/98 submission

B. REVISIONS NEEDED POST-APPROVAL:

1. GENERAL

Replace "Caution:..." statement with "Rx only".

2. CONTAINER - 100's & 500's

a. See FTR #5 on "light-resistant container" issue.

b. Encourage to add the statement "This is bulk package and not intended for dispensing" as appears on the innovator's container labels of 100's bottle.

C. BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Sinemet® CR 25/200

NDA Number: 19-856

NDA Drug Name: Sinemet® CR

NDA Firm: Merck, Sharp & Dome

Date of Approval of NDA Insert and supplement #: May 30, 1991/No labeling supplement approved

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance?
No

Basis of Approval for the Container Labels: Sinemet®

FOR THE RECORD:

1. Review based on the labeling of the listed drug Sinemet® CR; approved May 30, 1991. The first review for unapproved ANDA 74-669 (Purepac) was also used for guidance. There are currently no approved ANDAs for this drug product.

2. Mylan is the manufacturer. No outside firms used (p 6175, vol 1.2).

3. Patent/Exclusivities:

There are two patents for this drug product. Patent 4900755 and 4832957 which both expire on May 23, 2006. Mylan has filed Paragraph IV Certification.

4. Both the NDA and the ANDA are scored. The tablet description is accurate as stated in the HOW SUPPLIED section (p 6529, vol 1.3).

5. Storage/dispensing recommendations:

NDA: (insert and container) Store in a tightly closed container. Avoid temperatures above 30°C (86°F).

ANDA: (container) Dispense in a tight container as defined in the USP using a child-resistant closure. Keep container tightly closed. DO NOT STORE ABOVE 30°C (86°F). (insert) Dispense in a

tight container as defined in the USP using a child-resistant closure. Keep container tightly closed.

USP: Not the subject of a USP monograph.

Sinemet (carbidopa and levodopa immediate-release tablets) is the subject of a USP monograph. The storage recommendations for it as listed in the USP: Preserve in well-closed, light-resistant containers. We previously asked Purepac's unapproved ANDA 74-669 to end their dispensing statement ... in a tight, light-resistant container. Upon discussion with J. Grace we will not ask Mylan to add "light-resistant" to its dispensing statement since the innovator does not.

6. Other differences between Purepac's unapproved ANDA 74-669 and this application, Mylan's 75-091:
 - a. The first line of the ADVERSE REACTIONS section was changed from "In controlled clinical trials,..." to "It has been reported in controlled clinical trials,..." in ANDA 74-669. We have NOT asked Mylan to do this.
 - b. We have asked Mylan to delete the phrase "extended-release" from the PRECAUTIONS-General (1 instance) and the Drug Interactions subsections. We did not do this with the Purepac application.
7. The RLD markets a container size of 100s and a unit-dose carton of 100s.

The ANDA wishes to market sizes of 100s and 500s.
8. The 100s have a CRC (p 6338, vol 1.2). Both the 100s and the 500s container sizes are made of beige, opaque HDPE (light-resistant) (pp 6316, 6325, vol 1.2).
9. The listing of inactive ingredients is accurate. (p 6006, vol 1.1).
10. The bio review is pending. Single-dose fasting, post-prandial and steady state *in vivo* bio studies have been done. The bio reviewer, Z. Wahba, has been notified that since this drug product is scored and extended-release - it will need a suitable dissolution study. The firm has submitted data for the requested dissolution study, but not reviewed by the Agency, yet.

Date of Review: May 8, 1998

Date of Submission: February 6,
1998

Primary Reviewer: Chan Park

Date:

Chan Park
5/15/98

Team Leader: Charlie Hoppes

Date:

Charlie Hoppes

5/17/98

CC:

91AP.L

Sherrif

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 75-091 Date of Submission: March 13, 1997

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Carbidopa and Levodopa Extended-release
Tablets, 50 mg/200 mg

Labeling Deficiencies:

1. CONTAINER 100s and 500s

Satisfactory in draft.

2. INSERT

- a. DESCRIPTION

- i. Revise the first sentence of paragraph 1 to read:

Carbidopa and levodopa extended-release tablets are for the treatment...

- ii. Revise the molecular weights of carbidopa and anhydrous carbidopa to read:

244.25 and 226.23 respectively.

- iii. Revise the molecular weight of levodopa to read:

197.19

- iv. Paragraph 4, first sentence.

...in water, with a... (add comma).

- v. Paragraph 5

- A). First sentence

Each extended-release tablet, for oral administration, contains 50 mg...

B). Second sentence

- 1). In addition, each tablet contains the following inactive ingredients:
- 2). ...FD&C Blue #2 Aluminum Lake, FD&C Red #40 Aluminum Lake, hydroxypropyl...

vi. Add the following as the last paragraph of this section:

USP Drug release test pending.

b. CLINICAL PHARMACOLOGY

i. Pharmacodynamics, paragraph 7, sentence 1 -
Each tablet contains...

ii. Pharmacokinetics, paragraph 3 -
...50 mg/200 mg carbidopa... (2 instances)

c. CONTRAINDICATIONS

Paragraph 2 - ...narrow angle... (delete hyphen)

d. PRECAUTIONS

i. General - second paragraph
Delete "extended-release"

ii. Information for Patients

A). Paragraph 1, sentence 1 -

...extended-release tablets are a...

B). Paragraph 5, sentence 1 -

...extended-release tablets is...

iii. Drug Interactions

Delete "extended-release" from this subsection (3 instances).

iv. Carcinogenesis, Mutagenesis, Impairment of Fertility - Paragraph 2, last sentence -

Delete "equivalent to".

v. Pediatric Use - Delete the bold print from the word "Safety".

e. ADVERSE REACTIONS

Number the first 2 paragraphs following TABLE I as 1. and 2. respectively.

f. OVERDOSAGE

Last paragraph, sentence 1 - ...1500 to 2000...

g. DOSAGE AND ADMINISTRATION

i. Paragraph 1

A). Sentence 1

...extended-release tablets contain...

B). Last sentence

...extended-release tablets may...

ii. Initial Dosage: Patients Currently Treated with Conventional Carbidopa-Levodopa Preparations, Paragraph 1, last sentence -

...should be 4 to 8 hours...

iii. TABLE II

Replace "200 mg" with "1 tab".

iv. Patients Currently Treated With Levodopa Without A Decarboxylase Inhibitor, Last sentence -

...extended-release tablets b.i.d.

v. Patients Not Receiving Levodopa -

...extended-release tablets b.i.d.

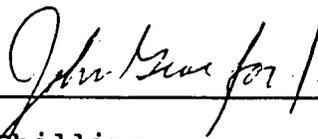
h. HOW SUPPLIED

...other side of the tablet. (rather than table).

Please revise your insert labeling, as instructed above, and submit final print container labels and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research