NDA 17-555/S-036,S-037,S-038,S-039,S-040,S-045,S-050,S-051
NDA 17-555/S-055

DuPont Pharmaceuticals Company
Attention: Robert A. Barto
Regulatory Affairs Manager
Chestnut Run Plaza, MR 2134
974 Centre Road
Wilmington, DE 19805

Dear Mr. Barto:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sinemet (carbidopa-levodopa) 10/100 mg, 25/100 mg, 25/250 mg Tablets.

S-055
This supplement, submitted January 19, 2000 and received January 20, 2000, provides for the addition of "bullous lesions" and "increased libido" as adverse events.

We have completed the review of this supplement and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the labeling text provided. Accordingly, this supplemental application is approved effective on the date of this letter. The final printed labeling (FPL) must be identical to the package insert submitted January 19, 2000

We have reviewed the content of the following supplements and note that these changes have either been incorporated or superceded by the approval of S-055. Therefore, the supplement applications listed below will be retained in our files with no further action.

Supplement	**Letter Date**	**Receipt Date**
036	May 18, 1988	May 23, 1988
037	August 3, 1988	August 8, 1988
038	August 4, 1988	August 8, 1988
039	November 1, 1989	November 3, 1989
040	May 1, 1990	May 3, 1990
045	August 7, 1996	August 12, 1996
050	February 27, 1998	March 2, 1989
051	January 15, 1999	January 19, 1999

These "Changes Being Effected" supplemental new drug applications provide for:

S036
This supplement provides for revisions under WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS editorially, under DESCRIPTION and HOW SUPPLIED to list the 25-100 tablet strength before the 10-100, and under ADVERSE REACTIONS to add "malignant melanoma".

S037
This supplement provides for an updated package circular in the new format containing current medical opinion concerning the treatment of Parkinson's Disease with carbidopa-levodopa preparations.

S038
This supplement provides a replacement for the labeling provided in S037.

S039
This supplement provides a response to our June 21, 1989 letter requesting changes to labeling under CONTRAINDICATIONS regarding concomitant use of Sinemet with monoamine oxidase type B inhibitors.

S040
This supplement provides for revised labeling components prepared in Du Pont trade dress for use by Du Pont Pharmaceuticals to market Sinemet Tablets in the United States.

S045
This supplement provides for revisions to labeling to comply with labeling regulations as listed in 21 CFR 201.57, to add or strengthen safety information, and to achieve consistency with the prescription information of Lodosyn (carbidopa) and Sinemet CR (carbidopa – levodopa).

S050
This supplement provides for labeling changes to the CONTRAINDICATION section of labeling information for consistency with Sinemet CR and Lodosyn, addition to PRECAUTION SECTION regarding Isoniazid, addition of hypersensitivity to ADVERSE REACTIONS section, and a change in the tablet description in the HOW SUPPLIED section.

S051
This supplement provides for clarification of bioavailability of carbidopa from Sinemet, to add or strengthen safety information, to achieve consistency with the prescription information, and to update the company logo.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

We recommend that you submit supplements for Sinemet and Sinemet CR. These supplemental applications should contain for review current labeling with revised descriptions of the results of the carcinogenicity and reproduction studies . Doses (in mg/kg/day) should be listed for each study, and related to the maximum recommended human dose on a mg/m^2 basis. Human dose calculations should be based on 60 kg.

Additionally, the Overdosage sections should be updated to provide information on overdose experience in humans. If human data are available, it is recommended that the animal data be removed from labeling. If no human data are available, rewrite the animal portion of the section to provide minimum lethal doses (mg/kg) and comparisons to the maximum recommended dose in humans on a mg/m^2 basis.

Lastly, neither the labeling for Sinemet or for Sinemet CR contain any information on mutagenicity. There have been at least four published studies on the mutagenic potential of L-dopa:

Martinez A, Urios A, Blanco M. *Mutat Res* 467(1):41-53, 2000.
Glatt H. *Mutat Res* 238(3): 235-243, 1990.
McGregor DB, Riach CG, Brown A *et al. Environ Mol Mutagen* 11(4):523-544, 1988.
Suter W, Matter-Jaeger I. Mutat Res 137(1):17-28,1984.

These results suggest some genotoxic potential for L-dopa; therefore, they should be discussed in labeling.

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Russell Katz
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