CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

17-555/S-069

Trade Name: Sinemet Tablets

Generic Name: Carbidopa-Levodopa

Sponsor: Bristol-Meyers Squibb Company

Approval Date: December 31, 2008

Indications: For the treatment of symptoms of idiopathic Parkinson's disease (paralysis agitans), post-encephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-555/S-069

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-555/S-069

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 17-555/S-069

Bristol-Myers Squibb Company
Attention: Marianne Frost
Associate Director, Global Regulatory Affairs
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Frost:

Please refer to your supplemental new drug application dated July 16, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sinemet® (carbidopa/levodopa) Tablets.

We also refer to the amendment dated February 11, 2008.

This supplemental new drug application provides for the addition of information regarding melanoma and impulse control disorder to the PRECAUTIONS section of the package insert.

We completed our review of this application and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 17-555/S-069**." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Stacy Metz, Regulatory Project Manager, at (301) 796-2139.

Sincerely,

{See appended electronic signature page}

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

Enclosure: labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
12/31/2008 08:21:05 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-555/S-069

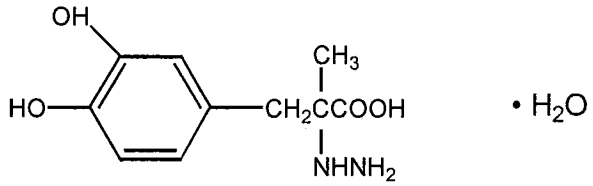
LABELING

SINEMET®
(CARBIDOPA-LEVODOPA)
TABLETS

DESCRIPTION

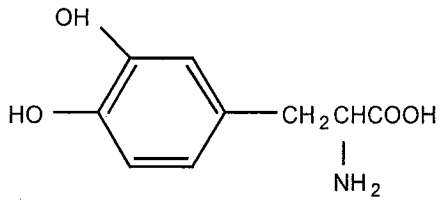
SINEMET* (Carbidopa-Levodopa) is a combination of carbidopa and levodopa for the treatment of Parkinson's disease and syndrome.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (—)-L-α-hydrazino-α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$, and its structural formula is:



Tablet content is expressed in terms of anhydrous carbidopa which has a molecular weight of 226.3.

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (—)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_9H_{11}NO_4$, and its structural formula is:



SINEMET is supplied as tablets in three strengths:

SINEMET 25-100, containing 25 mg of carbidopa and 100 mg of levodopa.

SINEMET 10-100, containing 10 mg of carbidopa and 100 mg of levodopa.

SINEMET 25-250, containing 25 mg of carbidopa and 250 mg of levodopa.

Inactive ingredients are cellulose, magnesium stearate, and starch. SINEMET 10-100 and 25-250 Tablets also contain FD&C Blue 2. SINEMET 25-100 Tablets also contain D&C Yellow 10 and FD&C Yellow 6.

CLINICAL PHARMACOLOGY

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Its characteristic features include resting tremor, rigidity, and bradykinetic movements. Symptomatic treatments, such as levodopa therapies, may permit the patient better mobility.

Mechanism of Action

Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

Pharmacodynamics

When levodopa is administered orally, it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect, and these may often be accompanied by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.

Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet.

Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system.

The incidence of levodopa-induced nausea and vomiting is less with SINEMET than with levodopa. In many patients, this reduction in nausea and vomiting will permit more rapid dosage titration.

Since its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain.

Pharmacokinetics

Carbidopa reduces the amount of levodopa required to produce a given response by about 75% and, when administered with levodopa, increases both plasma levels and the plasma half-life of levodopa, and decreases plasma and urinary dopamine and homovanillic acid.

The plasma half-life of levodopa is about 50 minutes, without carbidopa. When carbidopa and levodopa are administered together, the half-life of levodopa is increased to about 1.5 hours. At steady state, the bioavailability of carbidopa from SINEMET tablets is approximately 99% relative to the concomitant administration of carbidopa and levodopa.

In clinical pharmacologic studies, simultaneous administration of carbidopa and levodopa produced greater urinary excretion of levodopa in proportion to the excretion of dopamine than administration of the two drugs at separate times.

Pyridoxine hydrochloride (vitamin B_6), in oral doses of 10 mg to 25 mg, may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine; therefore, SINEMET can be given to patients receiving supplemental pyridoxine (vitamin B_6).

INDICATIONS AND USAGE

SINEMET is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), post-encephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication. SINEMET is indicated in these conditions to permit the administration of lower doses of levodopa with reduced nausea and vomiting, with more rapid dosage titration, with a somewhat smoother response, and with supplemental pyridoxine (vitamin B_6).

In some patients a somewhat smoother antiparkinsonian effect results from therapy with SINEMET than with levodopa. However, patients with markedly irregular ("on-off") responses to levodopa have not been shown to benefit from SINEMET.

Although the administration of carbidopa permits control of parkinsonism and Parkinson's disease with much lower doses of levodopa, there is no conclusive evidence at present that this is beneficial other than in reducing nausea and vomiting, permitting more rapid titration, and providing a somewhat smoother response to levodopa.

Certain patients who responded poorly to levodopa have improved when SINEMET was substituted. This is most likely due to decreased peripheral decarboxylation of levodopa which results from administration of carbidopa rather than to a primary effect of carbidopa on the nervous system.

Carbidopa has not been shown to enhance the intrinsic efficacy of levodopa in parkinsonian syndromes.

In considering whether to give SINEMET to patients already on levodopa who have nausea and/or vomiting, the practitioner should be aware that, while many patients may be expected to improve, some do not. Since one cannot predict which patients are likely to improve, this can only be determined by a trial of therapy. It should be further noted that in controlled trials comparing SINEMET with levodopa, about half of the patients with nausea and/or vomiting on levodopa improved spontaneously despite being retained on the same dose of levodopa during the controlled portion of the trial.

CONTRAINDICATIONS

Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with SINEMET. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET. SINEMET may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g., selegiline HCl) (see **PRECAUTIONS: Drug Interactions**).

SINEMET is contraindicated in patients with known hypersensitivity to any component of this drug, and in patients with narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, SINEMET should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS

When SINEMET (Carbidopa-Levodopa) is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least twelve hours before therapy with SINEMET (Carbidopa-Levodopa) is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See DOSAGE AND ADMINISTRATION section before initiating therapy.

The addition of carbidopa with levodopa in the form of SINEMET reduces the peripheral effects (nausea, vomiting) due to decarboxylation of levodopa; however, carbidopa does not decrease the adverse reactions due to the central effects of levodopa. Because carbidopa permits more levodopa to reach the brain and more dopamine to be formed, certain adverse CNS effects, e.g., dyskinesias (involuntary movements), may occur at lower dosages and sooner with SINEMET than with levodopa alone.

Levodopa alone, as well as SINEMET, is associated with dyskinesias. The occurrence of dyskinesias may require dosage reduction.

As with levodopa, SINEMET may cause mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering SINEMET to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with SINEMET may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

Neuroleptic Malignant Syndrome (NMS)

Sporadic cases of a symptom complex resembling NMS have been reported in association with dose reductions or withdrawal of therapy with SINEMET. Therefore, patients should be observed carefully when the dosage of SINEMET is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia. Neurological findings, including muscle rigidity, involuntary movements, altered consciousness, mental status changes; other disturbances, such as autonomic dysfunction, tachycardia, tachypnea, sweating, hyper- or hypotension; laboratory findings, such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin have been reported.

The early diagnosis of this condition is important for the appropriate management of these patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (e.g., pneumonia, systemic infection, etc.) is essential. This may be especially complex if the clinical presentation includes both serious medical illness and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) intensive symptomatic treatment and medical monitoring and 2) treatment of any concomitant serious medical problems for which specific treatments are available. Dopamine agonists, such as bromocriptine, and muscle relaxants, such as dantrolene, are often used in the treatment of NMS, however, their effectiveness has not been demonstrated in controlled studies.

PRECAUTIONS

General

As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided the intraocular pressure is well-controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Dopaminergic agents, including levodopa, may be associated with somnolence and very rarely episodes of sudden onset of sleep. In some cases, these episodes may occur without awareness or warning during daily activities. Patients must be informed of this and advised to exercise caution while driving or operating machines while being treated with dopaminergic agents, including levodopa. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines (see **Information for Patients**).

Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using SINEMET for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Information for Patients

The patient should be informed that SINEMET is an immediate-release formulation of carbidopa-levodopa that is designed to begin release of ingredients within 30 minutes. It is important that SINEMET be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa-levodopa preparations, without first consulting the physician.

Patients should be advised that sometimes a 'wearing-off' effect may occur at the end of the dosing interval. The physician should be notified if such response poses a problem to lifestyle.

Patients should be advised that occasionally, dark color (red, brown, or black) may appear in saliva, urine, or sweat after ingestion of SINEMET. Although the color appears to be clinically insignificant, garments may become discolored.

The patient should be advised that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation. Excessive acidity also delays stomach emptying, thus delaying the absorption of levodopa. Iron salts (such as in multivitamin tablets) may also reduce the amount of levodopa available to the body. The above factors may reduce the clinical effectiveness of the levodopa or carbidopa-levodopa therapy.

Patients should be alerted to the possibility of sudden onset of sleep during daily activities, in some cases without awareness or warning signs, when they are taking dopaminergic agents, including levodopa. Patients should be advised to exercise caution while driving or operating machinery and that if they have experienced somnolence and/or sudden sleep onset, they must refrain from these activities. (See **PRECAUTIONS: General.**)

There have been reports of patients experiencing intense urges to gamble, increased sexual urges, and other intense urges, and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease, including SINEMET. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with SINEMET. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges, or other intense urges while taking SINEMET. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking SINEMET.

Laboratory Tests

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

SINEMET may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Cases of falsely diagnosed pheochromocytoma in patients on carbidopa-levodopa therapy have been reported very rarely. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on levodopa or carbidopa-levodopa therapy.

Drug Interactions

Caution should be exercised when the following drugs are administered concomitantly with SINEMET (Carbidopa-Levodopa).

Symptomatic postural hypotension occurred when SINEMET was added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with SINEMET is started, dosage adjustment of the antihypertensive drug may be required.

For patients receiving MAO inhibitors (Type A or B), see **CONTRAINDICATIONS**. Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone (see **CONTRAINDICATIONS**).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and SINEMET.

Dopamine D_2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone) and isoniazid may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET should be carefully observed for loss of therapeutic response.

Iron salts may reduce the bioavailability of levodopa and carbidopa. The clinical relevance is unclear.

Although metoclopramide may increase the bioavailability of levodopa by increasing gastric emptying, metoclopramide may also adversely affect disease control by its dopamine receptor antagonistic properties.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year bioassay of SINEMET, no evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa.

In reproduction studies with SINEMET, no effects on fertility were found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa.

Pregnancy

Pregnancy Category C. No teratogenic effects were observed in a study in mice receiving up to 20 times the maximum recommended human dose of SINEMET. There was a decrease in the number of live pups delivered by rats receiving approximately two times the maximum recommended human dose of carbidopa and approximately five times the maximum recommended human dose of levodopa

during organogenesis. SINEMET caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa/levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa/levodopa to 20 times/10 times the maximum recommended human dose of carbidopa/levodopa.

There are no adequate or well-controlled studies in pregnant women. It has been reported from individual cases that levodopa crosses the human placental barrier, enters the fetus, and is metabolized. Carbidopa concentrations in fetal tissue appeared to be minimal. Use of SINEMET in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child.

Nursing Mothers

In a study of one nursing mother with Parkinson's disease, excretion of levodopa in human breast milk was reported. Therefore, caution should be exercised when SINEMET is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Use of the drug in patients below the age of 18 is not recommended.

ADVERSE REACTIONS

The most common adverse reactions reported with SINEMET have included dyskinesias, such as choreiform, dystonic, and other involuntary movements and nausea.

The following other adverse reactions have been reported with SINEMET:

Body as a Whole: chest pain, asthenia.

Cardiovascular: cardiac irregularities, hypotension, orthostatic effects including orthostatic hypotension, hypertension, syncope, phlebitis, palpitation.

Gastrointestinal: dark saliva, gastrointestinal bleeding, development of duodenal ulcer, anorexia, vomiting, diarrhea, constipation, dyspepsia, dry mouth, taste alterations.

Hematologic: agranulocytosis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia.

Hypersensitivity: angioedema, urticaria, pruritus, Henoch-Schonlein purpura, bullous lesions (including pemphigus-like reactions).

Musculoskeletal: back pain, shoulder pain, muscle cramps.

Nervous System/Psychiatric: psychotic episodes including delusions, hallucinations, and paranoid ideation, neuroleptic malignant syndrome (see **WARNINGS**), bradykinetic episodes ("on-off" phenomenon), confusion, agitation, dizziness, somnolence, dream abnormalities including nightmares, insomnia, paresthesia, headache, depression with or without development of suicidal tendencies, dementia, pathological gambling, increased libido including hypersexuality, impulse control symptoms. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

Respiratory: dyspnea, upper respiratory infection.

Skin: rash, increased sweating, alopecia, dark sweat.

Urogenital: urinary tract infection, urinary frequency, dark urine.

Laboratory Tests: decreased hemoglobin and hematocrit; abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen (BUN), Coombs test; elevated serum glucose; white blood cells, bacteria, and blood in the urine.

Other adverse reactions that have been reported with levodopa alone and with various carbidopa-levodopa formulations, and may occur with SINEMET are:

Body as a Whole: abdominal pain and distress, fatigue.

Cardiovascular: myocardial infarction.

Gastrointestinal: gastrointestinal pain, dysphagia, sialorrhea, flatulence, bruxism, burning sensation of the tongue, heartburn, hiccups.

Metabolic: edema, weight gain, weight loss.

Musculoskeletal: leg pain.

Nervous System/Psychiatric: ataxia, extrapyramidal disorder, falling, anxiety, gait abnormalities, nervousness, decreased mental acuity, memory impairment, disorientation, euphoria, blepharospasm (which may be taken as an early sign of excess dosage; consideration of dosage reduction may be made at this time), trismus, increased tremor, numbness, muscle twitching, activation of latent Horner's syndrome, peripheral neuropathy.

Respiratory: pharyngeal pain, cough.

Skin: malignant melanoma (see also **CONTRAINDICATIONS**), flushing.

Special Senses: oculogyric crises, diplopia, blurred vision, dilated pupils.

Urogenital: urinary retention, urinary incontinence, priapism.

Miscellaneous: bizarre breathing patterns, faintness, hoarseness, malaise, hot flashes, sense of stimulation.

Laboratory Tests: decreased white blood cell count and serum potassium; increased serum creatinine and uric acid; protein and glucose in urine.

OVERDOSAGE

Management of acute overdosage with SINEMET is the same as management of acute overdosage with levodopa. Pyridoxine is not effective in reversing the actions of SINEMET.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as SINEMET should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

Based on studies in which high doses of levodopa and/or carbidopa were administered, a significant proportion of rats and mice given single oral doses of levodopa of approximately 1500-2000 mg/kg are expected to die. A significant proportion of infant rats of both sexes are expected to die at a dose of 800 mg/kg. A significant proportion of rats are expected to die after treatment with similar doses of carbidopa. The addition of carbidopa in a 1:10 ratio with levodopa increases the dose at which a significant proportion of mice are expected to die to 3360 mg/kg.

DOSAGE AND ADMINISTRATION

The optimum daily dosage of SINEMET must be determined by careful titration in each patient. SINEMET tablets are available in a 1:4 ratio of carbidopa to levodopa (SINEMET 25-100) as well as 1:10 ratio (SINEMET 25-250 and SINEMET 10-100). Tablets of the two ratios may be given separately or combined as needed to provide the optimum dosage.

Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100 mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting.

Usual Initial Dosage

Dosage is best initiated with one tablet of SINEMET 25-100 three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be increased by one tablet every day or every other day, as necessary, until a dosage of eight tablets of SINEMET 25-100 a day is reached.

If SINEMET 10-100 is used, dosage may be initiated with one tablet three or four times a day. However, this will not provide an adequate amount of carbidopa for many patients. Dosage may be increased by one tablet every day or every other day until a total of eight tablets (2 tablets q.i.d.) is reached.

How to Transfer Patients from Levodopa

Levodopa must be discontinued at least twelve hours before starting SINEMET (Carbidopa-Levodopa). A daily dosage of SINEMET should be chosen that will provide approximately 25% of the previous levodopa dosage. Patients who are taking less than 1500 mg of levodopa a day should be started on one tablet of SINEMET 25-100 three or four times a day. The suggested starting dosage for most patients taking more than 1500 mg of levodopa is one tablet of SINEMET 25-250 three or four times a day.

Maintenance

Therapy should be individualized and adjusted according to the desired therapeutic response. At least 70 to 100 mg of carbidopa per day should be provided. When a greater proportion of carbidopa is required, one tablet of SINEMET 25-100 may be substituted for each tablet of SINEMET 10-100. When more levodopa is required, SINEMET 25-250 should be substituted for SINEMET 25-100 or SINEMET 10-100. If necessary, the dosage of SINEMET 25-250 may be increased by one-half or one tablet every day or every other day to a maximum of eight tablets a day. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Because both therapeutic and adverse responses occur more rapidly with SINEMET than with levodopa alone, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly with SINEMET than with levodopa. The occurrence of involuntary movements may require dosage reduction. Blepharospasm may be a useful early sign of excess dosage in some patients.

Addition of Other Antiparkinsonian Medications

Standard drugs for Parkinson's disease, other than levodopa without a decarboxylase inhibitor, may be used concomitantly while SINEMET is being administered, although dosage adjustments may be required.

Interruption of Therapy

Sporadic cases of a symptom complex resembling Neuroleptic Malignant Syndrome (NMS) have been associated with dose reductions and withdrawal of SINEMET. Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET is required, especially if the patient is receiving neuroleptics. (See **WARNINGS**.)

If general anesthesia is required, SINEMET may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the patient should be observed for symptoms resembling NMS, and the usual daily dosage may be administered as soon as the patient is able to take oral medication.

HOW SUPPLIED

SINEMET 25-100 Tablets are yellow, oval, uncoated tablets, that are scored and coded "650" on one side and "SINEMET" on the other side. They are supplied as follows:

NDC 0056-0650-68 bottles of 100

SINEMET 10-100 Tablets are dark dapple-blue, oval, uncoated tablets, that are scored and coded "647" on one side and "SINEMET" on the other side. They are supplied as follows:

NDC 0056-0647-68 bottles of 100

SINEMET 25-250 Tablets are light dapple-blue, oval, uncoated tablets, that are scored and coded "654" on one side and "SINEMET" on the other side. They are supplied as follows:

NDC 0056-0654-68 bottles of 100

Storage

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). Protect from light.

Manufactured by:
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

Marketed by:

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

[Co. Print Code]
Printed in USA
Rev TBD

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-555/S-069

MEDICAL REVIEW(S)

Labeling Change Review

Topic: Proposed labeling changes regarding gambling, hypersexuality and other uncontrollable urges

Drug	**Sponsor**	**Submission Date**
Symmetrel (amantadine) NDA#017-118	Endo	11/29/06
Apokyn (apomorphine) NDA#021-264	Vernalis	11/30/06
Azilect (rasagaline) NDA#021-641	Teva	2/1/07
(b) (4)	(b) (4)	(b) (4)
Comtan (entacapone) NDA#020-796	Orion	11/14/06
Mirapex (pramipexole) NDA#020-667	Boehringer Ingelheim	2/13/07
Requip (ropinirole) NDA#020-658	GlaxoSmithKline	11/7/06
Eldepryl (selegiline) NDA 19-334, NDA#020-647	Somerset	11/7/06
Stalevo (levodopa, carbidopa, entacapone) NDA#021-485	Orion	12/14/06
Tasmar (tolcapone) NDA#020-697	Valeant	4/10/07
Sinemet CR (carbidopa-levodopa) NDA#19-856	Bristol Myers Squibb	5/31/07
Sinemet (carbidopa-levodopa) NDA#017-555	Bristol Myers Squibb	7/16/07

Reviewer: Gerard Boehm, MD, MPH
Date Completed: 10/5/07

Background

Following a review of the medical literature and spontaneous post marketing reports (see memo dated 6/27/06), the Division of Neurology Products (DNP) requested that the package inserts for the class of medications used to treat Parkinson's disease be amended to include language about impulsive behaviors. The Division requested the following language be placed in the Information for Patients subsection of the PRECAUTIONS labeling section:

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Labeling Review
The Responses to the Division's labeling change request have varied. Some sponsors have agreed to the Division's proposal, other sponsors agreed to some of the Division's proposed language with revisions, and other sponsors rejected the Division's proposal.

Agreeing to the Proposed Labeling Changes
The sponsor's agreed to the Division's labeling language request for the following products: Stalevo, Apokyn, Symmetrel, Eldepryl, Sinemet CR, Sinemet, and Tasmar.

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8 Pages Immediately Following Withheld - b(4) Draft Labeling

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FDA Literature Update

Since my initial review of this topic over a year ago, several articles have been published regarding impulsive behavior and Parkinson's disease treatments. I searched PubMed using the terms Parkinson's disease, impulsive, gambling, and sex. I excluded identified review articles and case reports from further consideration. I reviewed the remaining articles that described event risks for cohorts of treated patients. I summarize some of that information in the following paragraphs.

Weintraub et al[1] investigated frequency of compulsive gambling, buying, and sexual behaviors in a convenience sample of 272 patients with idiopathic PD from 2 university associated movement disorder clinics. The authors excluded patients taking anticholinergics, MAO inhibitors, and there were no no bromocriptine or apomorphine users in the group. Established patients were interviewed using a screening battery of

open ended questions. Those screened positive were later called and administered the MIDI. Medical records were reviewed to identify medications taken when the patient was most symptomatic with an impulse control disorder. The authors reported that 21 patients screened positive, 2 of these did not meet MIDI criteria and 1 could not be reached for follow up. The authors reported the following event prevalences:

> Active ICD: 4% (n=11); anytime ICD: 6.6% (n=18)
> Active compulsive gambling: 2.2% (n=6); any time compulsive gambling: 2.6% (n=7)
> Active compulsive sexual behavior: 2.6% (n=7); any time compulsive sexual behavior: 2.6% (n=7)

Thirteen subjects reported a history of impulse control disorders prior to PD onset including 5 of the 18 subjects in the anytime ICD group identified above. For all 5 of these subjects, the ICD experienced prior to PD onset was the same ICD experienced after their PD diagnosis.

All 18 patients who experienced ICDs were taking a dopamine agonist at the time they were symptomatic. For the seven that subsequently became asymptomatic, 4 had their symptoms resolve after discontinuation of the dopamine agonist, 2 had their symptoms resolve after reduction of the dopamine agonist dose, and 1 patient's symptoms resolved with counseling.

From a logistic regression analysis, DA use and history of ICD symptoms prior to PD diagnosis were significant predictors of an active ICD. The authors found no difference in ICD risk for ropinirole, pramipexole, or pergolide.

Voon et al[2] screened consecutive PD patients presenting to a Toronto movement disorders clinic over a 3 month period. The authors excluded patients with atypical PD, patients with dementia within 1 year of motor symptom onset, and patients that couldn't complete the questionnaire. The authors used a modified South Oaks Gambling screen for pathological gambling (PG), Lejoyeux's compulsive shopping (CS) questionnaire, and a specifically designed hypersexuality (HS) questionnaire. Positive screens were assessed by a psychiatrist.

The authors reported that 75% (297/396) of patients adequately completed the screen. Fifty-five patients had positive screens and were interviewed by phone (PG 16, HS 32, CS 7). Four HS patients and 1 CS patient could not be reached. The authors determined that 19 patients had misinterpreted the screen (PG3, HS 14, and CS2). Two patients refused assessment (both HS). Thirty patients were assessed (PG12, HS 14, CS4) and 4 patients could not be assessed due to distance/failure to show. The authors reported the following prevalence results: HS, CS, or PG: 6.1% (18/297); HS: 2.4% (7/297); CS: 0.7% (2/297); and PG: 3.4% (10/297). The authors also reported that the lifetime prevalence for PD patients taking DAs was 7.2% for PG, 7.2% for HS and 1.4% for CS. The authors compared the PG gambling prevalence in their PD patients to an estimate of lifetime prevalence (1%) from a study conducted in Ontario, Canada.

The authors reported that the impulsive events were more common on DAs than levodopa. The authors did not find difference in risk among the DAs. HS was associated with male sex, and early PD onset.

Pontone et al[3] studied 66 men and 34 women <=65 years old with idiopathic PD that attended outpatient clinics, or participated in research programs or community outreach programs. The investigators excluded patients with current substance abuse, psychotic disorder, or neurosurgical treatment for PD. At baseline, patients had a clinical psychiatric interview (SCID), a Neuropsychiatric interview, MMSE, and Hoehn and Yahr assessment.

The investigators identified 6 men and 3 women with ICDs. The investigators found that the ICD group was more likely to have symptoms of depressed mood, irritability, appetite changes, and disinhibition. All patients with ICDs were taking DAs (pramipexole, ropinirole) and at the time of ICD onset were taking DAs combined with L-dopa. In the non-ICD group 38% of patients were taking DAs and L-dopa. The investigators found a statistical association for ICDs only with pramipexole.

Voon et al[4] examined risk factors among PD patients with PG. This study examined data for PD patients with PG that were identified from a Toronto movement disorders clinic (study population described in previous publications from these investigators). This study used 2 comparison groups. The first comparison group consisted of consecutive PD patients that agreed to participate in the study (excluding those patients with PG, HS, CS, or compulsive dopaminergic medication use). The second comparison group for this investigation was comprised of the patients without PG (from the investigators' original prevalence study).

The investigators compared 21 PD patients with PG to 42 newly selected controls and to 286 patients without PG from the original prevalence study (3 patients overlapped the 2 control groups). The investigators reported that when compared to controls, patients with PG were younger, were younger at onset of PD, had higher novelty seeking, had higher risks for medication induced mania or hypomania, had impaired Barret impulsivity scale scores (assesses planning), and had higher rates of personal or family history of alcohol use disorders. Sex, Hoehn and Yahr stage and levodopa dose equivalents were not different between the groups. The investigators noted that the novelty seeking differences in this study were due to lower scores among controls (cases had scores similar to general population). PG was associated with adjunctive DA use but not with DA monotherapy. The investigators found a trend toward higher DA dose in the PG group when compared to the larger control group but not the smaller group.

Ondo and Lai[5] interviewed consecutive patients taking DAs for PD (n=207), RLS (n=89), or both (n=4) about changes in gambling, spending, sexual activity, or other impulsive activities subsequent to starting DAs. The investigators also determined the prevalence of pathological gambling for this group.

The investigators reported that 19.9% (59/300) of the interviewed patients reported increased impulsive behavior after starting DAs. This total included 30 patients with increased gambling, 26 with increased spending, 11 with increased sexual activity, and 1 with traveling. PD patients had a higher prevalence of increased impulsive activity (24.6%, 51/207) compared to RLS patients (8.6%, 8/89). The investigators reported that 3.4% (7/207) of PD patients experienced pathological gambling compared to no RLS patients. The investigators found a relationship between impulsive activity and younger age, larger doses of DAs, and PD. The relationship between impulsive activity and PD was no longer significant when controlling for dose of DA.

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[redacted]

[1] Weintraub D, Siderowf AD, Potenza MN, Goveas J, Morales KH, Duda JE, Moberg PJ, Stern MB. Association of dopamine agonist use with impulse control disorders in Parkinson disease. Arch Neurol. 2006 Jul;63(7):969-73.

[2] Voon V, Hassan K, Zurowski M, deSouza M, Thomsen T, Fox S, Lang AE, Miyasaki J. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. Neurology. 2006 Oct 10;67(7):1254-7. Epub 2006 Sep 6.

[3] Pontone G, Williams JR, Bassett SS, Marsh L. Clinical features associated with impulse control disorders in Parkinson's disease. Neurology. 2006 Oct 10;67(7):1118-9.

[4] Voon V, Thomsen T, Miyasaki JM, deSouza M, Shafro A, Fox SH, Duff-Canning S, Lang AE, Zurowski M. Factors associated with dopaminergic drug-related pathological gambling in Parkinson disease. Arch Neurol. 2007 Feb;64(2):212-6.

[5] Ondo WG, Lai D. Predictors of impulsivity and reward seeking behavior with dopamine agonists. Parkinsonism Relat Disord. 2007 Aug 14; [Epub ahead of print]

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/s/

Jerry Boehm
10/5/2007 07:56:28 AM
MEDICAL OFFICER

Alice T. Hughes
10/11/2007 10:43:29 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-555/S-069

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 17-555/S-069
NDA 19-856/S-025

Bristol-Myers Squibb Company
Attention: Marianne Frost
Associate Director, Global Regulatory Sciences
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Frost:

Please refer to your New Drug Applications (NDAs) submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Sinemet (carbidopa / levodopa) Tablets and Sinemet CR (carbidopa / levodopa) Sustain-Release Tablets.

We reviewed your supplement in response to our October 6, 2006, request to add information regarding intense urges to gamble, increased sexual urges, and other intense urges to the labeling for Sinemet and Sinemet CR. Our review has led us to make additional changes to the proposed labeling. We request that the following labeling changes be submitted to your supplement to furnish adequate information for the safe and effective use of the drug. Please resubmit your labels with these changes to your supplements within 7 days of the date on this letter:

In the **Information for Patients** subsection of the **PRECAUTIONS** section of the labeling add:

> There have been reports of patients experiencing intense urges to gamble, increased sexual urges, other intense urges, and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease, including Sinemet. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with Sinemet. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges or other intense urges while taking Sinemet. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Sinemet.

We also ask that you add the adverse event terms "pathological gambling", "increased libido including hypersexuality", and "impulse control symptoms" to the **ADVERSE REACTIONS - Postmarketing Reports** subsection of labeling.

We feel that the proposed labeling language accurately reflects the currently available information regarding the relationship between intense urges and the medications used to treat Parkinson's disease.

The portion of your supplement that provides for the addition of information regarding melanoma is acceptable and should remain in the label.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
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