

IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PPA1151/001/002A
Case No: 2063507

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Imbat Limited

Unit L2, North Ring Business Park, Santry, Dublin 9

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Sinemet 10/100mg Tablets

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **11/06/2009**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sinemet 10/100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains carbidopa equivalent to 10 mg of anhydrous carbidopa and 100 mg levodopa.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Product imported from France:

Dappled blue, oval-shaped tablets scored and marked '647' on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Antiparkinsonian agent.

For treatment of Parkinson's disease and syndrome.

'Sinemet' is useful in relieving many of the symptoms of Parkinsonism, particularly rigidity and bradykinesia. It is frequently helpful in the management of tremor, dysphagia, sialorrhoea, and postural instability associated with Parkinson's disease and syndrome.

When response to levodopa alone is irregular, and signs and symptoms of Parkinson's disease are not controlled evenly throughout the day, substitution of 'Sinemet' usually reduces fluctuations in response. By reducing some of the adverse reactions produced by levodopa alone, 'Sinemet' permits more patients to obtain adequate relief from the symptoms of Parkinson's disease.

'Sinemet' may be given to patients with Parkinson's disease and syndrome who are taken vitamin preparations that contain pyridoxine hydrochloride (Vitamin B6).

4.2 Posology and method of administration

To be taken orally.

The optimum daily dosage of Sinemet must be determined by careful titration in each patient.

Sinemet Tablets are available in a ratio of 1:4 or 1:10 of carbidopa to levodopa to provide facility for fine dosage titration for each patient.

General Considerations

Studies show that the peripheral dopa-decarboxylase is fully inhibited (saturated) by carbidopa at doses between 70 and 100 mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting.

Standard antiparkinsonian drugs, other than levodopa alone, may be continued while Sinemet is being administered, although their dosage may have to be adjusted.

Because both therapeutic and adverse effects are seen more rapidly with Sinemet than with levodopa, patients should be carefully monitored during the dosage adjustment period. Involuntary movements, particularly blepharospasm, are a useful early sign of excess dosage in some patients.

Patients not receiving levodopa

Dosage may be best initiated with one tablet of Sinemet-Plus three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be increased by one tablet of Sinemet-62.5 or Sinemet-Plus every day or every other day, as necessary, until a dosage equivalent of eight tablets of Sinemet-Plus a day is reached.

If Sinemet-110 or Sinemet-62.5 is used, dosage may be initiated with one tablet three or four times a day. Titration upward may be required in some patients to achieve optimum dosage of carbidopa. The dosage may be increased by one tablet every day or every other day until a total of eight tablets (two tablets q.d.s.) is reached.

For patients starting with Sinemet-275, the initial dose is one-half tablet taken once or twice daily. However, this may not provide the optimal amount of carbidopa needed by many patients. If necessary, add one-half tablet every day or every other day until optimal response is reached.

Response has been observed in one day, and sometimes after one dose. Fully effective doses usually are reached within seven days as compared to weeks or months with levodopa alone.

Sinemet-62.5 or Sinemet-110 may be used to facilitate dosage titration according to the needs of the individual patient.

Patients receiving levodopa

Discontinue levodopa at least 12 hours (24 hours for slow-release preparations) before starting therapy with Sinemet. The easiest way to do this is to give Sinemet as the first morning dose after a night without any levodopa. The dose of Sinemet should be approximately 20% of the previous daily dosage of levodopa.

Patients taking less than 1,500 mg levodopa a day should be started on one tablet of Sinemet-Plus three or four times a day dependent on patient need. The suggested starting dose for most patients taking more than 1,500 mg levodopa a day is one tablet of Sinemet-275 three or four times a day.

Maintenance

Therapy with Sinemet should be individualised and adjusted gradually according to response. When a greater proportion of carbidopa is required, each tablet of Sinemet-110 may be replaced with a tablet of Sinemet-Plus or Sinemet-62.5.

When more levodopa is required, Sinemet-275 should be substituted at a dosage of one tablet three or four times a day. If necessary, the dosage of Sinemet-275 may be increased by half to one tablet every other day to a maximum of eight tablets a day. Experience with a total daily dosage greater than 200 mg carbidopa is limited.

Patients receiving levodopa with another decarboxylase inhibitor

When transferring a patient to Sinemet from levodopa combined with another decarboxylase inhibitor, discontinue dosage at least 12 hours before Sinemet is started. Begin with a dosage of Sinemet that will provide the same amount of levodopa as contained in the other levodopa/decarboxylase inhibitor combination.

Patients receiving other antiparkinsonian agents

Current evidence indicates that other antiparkinsonian agents may be continued when Sinemet is introduced, although dosage may have to be adjusted in line with manufacturers recommendations.

Use in children

The safety of Sinemet in patients under 18 years of age has not been established and its use in patients below the age of 18 is not recommended.

Use in the elderly

There is wide experience in the use of this product in elderly patients. The recommendations set out above reflect the clinical data derived from this experience.

4.3 Contraindications

Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with Sinemet. These inhibitors must be discontinued at least two weeks before starting 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 hydrochloride). (See 4.5 'Interaction with other medicinal products and other forms of interaction'.)

Sinemet is contraindicated in patients with narrow-angle glaucoma and in patients with known hypersensitivity to any component of this medication.

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

Use in patients with severe psychoses.

See also 4.6 'Pregnancy and lactation'.

4.4 Special warnings and precautions for use

Sinemet is not recommended for the treatment of drug-induced extrapyramidal reactions.

Sinemet should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease (because of the possibility of upper gastro-intestinal haemorrhage).

Care should be exercised when Sinemet is administered to patients with a history of myocardial infarction who have residual atrial nodal, or ventricular arrhythmias. Cardiac function should be monitored with particular care in such patients during the period of initial dosage adjustment.

Levodopa has been associated with somnolence and episodes of sudden sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely.

Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with levodopa. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

All patients should be monitored carefully for the development of mental changes, depression with suicidal tendencies, and other serious antisocial behaviour. Patients with current psychoses should be treated with caution.

Dyskinesias may occur in patients previously treated with levodopa alone because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed. The occurrence of dyskinesias may require dosage reduction.

As with levodopa, Sinemet may cause involuntary movements and mental disturbances. Patients with a history of severe involuntary movements or psychotic episodes when treated with levodopa alone should be observed carefully when Sinemet is substituted. These reactions are thought to be due to increased brain dopamine following administration of levodopa, and use of Sinemet may cause a recurrence. A syndrome resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes and increased serum creatine phosphokinase has been reported with the abrupt withdrawal of antiparkinsonian agents. Therefore, any abrupt dosage reduction or withdrawal of Sinemet should be carefully observed, particularly in patients who are also receiving neuroleptics.

Concomitant administration of psycho-active drugs such as phenothiazines or butyrophenones should be carried out with caution, and the patient carefully observed for loss of antiparkinsonian effect. Patients with a history of

convulsions should be treated with caution.

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

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

If general anaesthesia is required, therapy with Sinemet may be continued for as long as the patient is permitted to take fluids and medication by mouth. If therapy has to be stopped temporarily, Sinemet may be restarted as soon as oral medication can be taken at the same daily dosage as before.

Laboratory Tests

Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of Sinemet than with levodopa. Transient abnormalities include elevated levels of blood urea, AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase.

Decreased haemoglobin, haematocrit, elevated serum glucose and white blood cells, bacteria and blood in the urine have been reported.

Positive Coombs' tests have been reported, both with Sinemet and levodopa alone.

Sinemet may cause a false positive result when a dipstick is used to test for urinary ketone; and this reaction is not altered by boiling the urine. The use of glucose oxidase methods may give false negative results for glycosuria.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be exercised when the following drugs are administered concomitantly with Sinemet.

Antihypertensive agents

Postural hypotension can occur when Sinemet is added to the treatment of patients already receiving antihypertensive drugs. Dosage adjustment of the antihypertensive agent may be required.

Antidepressants

Rarely, reactions including hypertension and dyskinesia have been reported with the concomitant use of tricyclic antidepressants. (*See first paragraph of 4.3 Contraindications for patients receiving MAOIs*).

Anticholinergics

Anticholinergics may affect the absorption and thus the patient's response.

Iron

Studies demonstrate a decrease in the bioavailability of carbidopa and/or levodopa when it is ingested with ferrous sulphate or ferrous gluconate.

Other drugs

To date there has been no indication of interactions that would preclude concurrent use of standard antiparkinsonian drugs.

Dopamine D₂ receptor antagonists (e.g. phenothiazines, butyrophenones, and risperidone) and isoniazid, may reduce the therapeutic effects of levodopa. 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.

Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone (*See 4.3 'Contraindications'*)

Since levodopa competes with certain amino acids, the absorption of Sinemet may be impaired in some patients on a high protein diet.

The effect of simultaneous administration of antacids with Sinemet on the bioavailability of levodopa has not been studied.

Sinemet may be given to patients with Parkinson's disease and syndrome who are taking vitamin preparations that contain pyridoxine hydrochloride (Vitamin B6).

4.6 Pregnancy and lactation

Pregnancy

Although the effects of Sinemet on human pregnancy are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Therefore, the use of Sinemet in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards should pregnancy occur.

Breast-feeding mothers

It is not known whether carbidopa or levodopa is excreted in human milk. In a study of one nursing mother with Parkinson's disease, excretion of levodopa in human breast milk was reported. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in infants, a decision should be made whether to discontinue breast-feeding or discontinue the use of Sinemet, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Individual responses to medication may vary and certain side effects that have been reported with Sinemet may affect some patients' ability to drive or operate machinery. Patients treated with levodopa and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines), until such recurrent episodes and somnolence have resolved (*see also section 4.4 'Special warnings and precautions for use'*).

4.8 Undesirable effects

Side effects that occur frequently with Sinemet are those due to the central neuropharmacological activity of dopamine. These reactions can usually be diminished by dosage reduction. The most common are dyskinesias including choreiform, dystonic and other involuntary movements and nausea. Muscle twitching and blepharospasm may be taken as early signs to consider dosage reduction.

Other side effects reported in clinical trials or in post-marketing experience include:

Body as a whole: syncope, chest pain, anorexia.

Cardiovascular: cardiac irregularities and/or palpitations, orthostatic effects including hypotensive episodes, hypertension, phlebitis.

Gastrointestinal: vomiting, gastrointestinal bleeding, development of duodenal ulcer, diarrhoea, dark saliva.

Haematologic: leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis.

Hypersensitivity: angioedema, urticaria, pruritus, Henoch-Schonlein purpura.

Nervous System/Psychiatric: neuroleptic malignant syndrome (*see 4.3 'Contraindications'*), bradykinetic episodes (the "on-off" phenomenon), dizziness, paraesthesia, psychotic episodes including delusions, hallucinations and paranoid ideation, depression with or without development of suicidal tendencies, dementia, dream abnormalities, agitation, confusion, increased libido. Levodopa is associated with somnolence and has been associated very rarely with

excessive daytime somnolence and sudden sleep onset episodes.

Respiratory: dyspnoea.

Skin: alopecia, rash, dark sweat.

Urogenital: dark urine.

Rarely convulsions have occurred; however, a causal relationship with Sinemet has not been established.

Other side effects that have been reported with levodopa or levodopa/carbidopa combinations and may be potential side effects with Sinemet include:

Gastro-intestinal: dyspepsia, dry mouth, bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, flatulence, burning sensation of the tongue.

Metabolic: weight gain or loss, oedema.

Nervous System/Psychiatric: asthenia, decreased mental acuity, disorientation, ataxia, numbness, increased hand tremor, muscle cramp, trismus, activation of latent Horner's syndrome, insomnia, anxiety, euphoria, falling and gait abnormalities.

Skin: flushing, increased sweating,

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

Urogenital: urinary retention, urinary incontinence, priapism.

Miscellaneous: weakness, faintness, fatigue, headache, hoarseness, malaise, hot flushes, sense of stimulation, bizarre breathing patterns, malignant melanoma (*see 4.3 'Contraindications'*).

4.9 Overdose

Treatment

Management of acute overdosage with Sinemet is basically the same as management of acute overdosage with levodopa; however pyridoxine is not effective in reversing the actions of Sinemet. ECG monitoring should be instituted, and the patient carefully observed for the possible development of arrhythmias; if required, appropriate anti-arrhythmic 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, and hence its value in the treatment of overdosage is not known.

The terminal half-life of levodopa is about two hours in the presence of carbidopa.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Levodopa is a precursor of dopamine, and is given as replacement therapy in Parkinson's disease.

Carbidopa is a peripheral dopa decarboxylase inhibitor. It prevents metabolism of levodopa to dopamine in the peripheral circulation, ensuring that a higher proportion of the dose reaches the brain, where dopamine acts. A lower dose of levodopa can be used, reducing the incidence and severity of side effects.

Sinemet is useful in relieving many of the symptoms of parkinsonism, particularly rigidity and bradykinesia. It is frequently helpful in the management of tremor, dysphagia, sialorrhoea, and postural instability associated with Parkinson's disease and syndrome.

When response to levodopa alone is irregular, and signs and symptoms of Parkinson's disease are not controlled evenly throughout the day, substitution of Sinemet usually reduces fluctuations in response. By reducing some of the adverse reactions produced by levodopa alone, Sinemet permits more patients to obtain adequate relief from the symptoms of Parkinson's disease.

5.2 Pharmacokinetic properties

Following oral dosing levodopa, in the absence of decarboxylase inhibitor, is rapidly but variably absorbed from the gastrointestinal tract. It has a plasma half life of about 1 hour and is mainly converted by decarboxylation to dopamine, a proportion of which is converted to noradrenaline. Up to 30 % is converted to 3-O-methyldopa which has a half life of 9 to 22 hours. About 80 % of levodopa is excreted in the urine within 24 hours mainly as homovanillic acid and dihydroxyphenylactic acid. Less than 1 % is excreted unchanged.

Once in the circulation it competes with other neutral amino acids for transport across the blood brain barrier. Once it has entered the striatal neurones it is decarboxylated to dopamine, stored and released from presynaptic neurones. Because levodopa is so rapidly decarboxylated in the gastrointestinal tract and the liver, very little unchanged drug is available for transport into the brain. The peripheral decarboxylation reduces the therapeutic effectiveness of levodopa but is responsible for many of its side effects. For this reason levodopa is usually administered together with a peripheral decarboxylase inhibitor such as carbidopa, so that lower doses may be given to achieve the same therapeutic effect.

Carbidopa in the absence of levodopa, is rapidly but incompletely absorbed from the gastrointestinal tract following oral dosing. Following an oral dose approximately 50% is recorded in the urine, with about 30 % of this as unchanged drug. It does not cross the blood brain barrier but crosses the placenta and is excreted in breast milk. Turnover of the drug is rapid and virtually all unchanged drug appears in the urine within 7 hours.

Carbidopa inhibits the peripheral decarboxylation of levodopa to dopamine but as it does not cross the blood brain barrier, effective brain levels of dopamine get produced with lower levels of levodopa therapy reducing the peripheral side effects, noticeably nausea and vomiting and cardiac arrhythmias.

5.3 Preclinical safety data

Sinemet is well established in medical use. Preclinical data is broadly consistent with clinical experience. (*For reproductive toxicity , see section 4.6 'Pregnancy and Lactation'.*)

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
 Pregelatinised maize starch
 Microcrystalline cellulose
 Magnesium stearate
 Indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

PVC/Al blisters in a cardboard carton containing 100 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Imbat Limited
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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1151/1/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 June 2004
Date of last renewal: 11 June 2009

10 DATE OF REVISION OF THE TEXT

August 2010