For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

TIDOMET CR
(Carbidopa and Levodopa Extended-Release Tablets U.S.P.)

COMPOSITION
TIDOMET CR 125
Each uncoated extended-release tablet contains: Levodopa I.P. 100 mg
Carbidopa I.P. equivalent to Carbidopa Anhydrous 25 mg

TIDOMET CR
Each uncoated extended-release tablet contains: Levodopa I.P. 200 mg
Carbidopa I.P. equivalent to Carbidopa Anhydrous 50 mg

INDICATIONS
Levodopa and Carbidopa controlled release tablet is indicated in the treatment of the Parkinson's disease.

DOSAGE AND ADMINISTRATION
Levodopa and Carbidopa controlled release tablet contains levodopa and carbidopa in a 4:1 ratio as either the 200-50 tablet or the 100-25 tablet. The daily dose of Levodopa and Carbidopa controlled release tablet must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of involuntary movements, dyskinesias or nausea. Levodopa and Carbidopa controlled release tablet may be administered as a whole, which should not be chewed or crushed. TIDOMET CR 125 may be used in combination with TIDOMET CR to facilitate the optimum dosage.

Initial Dosage
Patients currently treated with conventional carbidopa-levodopa preparations:
The dosage with Levodopa and Carbidopa controlled release tablet should be substituted at an amount that provides approximately 10% more levodopa per day, although this may need to be increased to a dosage that provides up to 30% more levodopa per day depending upon clinical response. The interval between doses of Levodopa and Carbidopa controlled release tablet should be 4 to 8 hours during the waking day.

The guidelines for the initial conversion from conventional Levodopa and Carbidopa controlled release tablet preparations to Levodopa and Carbidopa controlled release tablets is given below:

Conventional Release Levodopa and Carbidopa Preparation	**Controlled Release Levodopa and Carbidopa Preparation**
Total daily dose of Levodopa	**Suggested dosage regimen**
300-400 mg	200mg b.i.d.
500-600 mg	300mg b.i.d. or 200mg t.i.d.
700-800 mg	A total of 800mg in 3 or more divided doses
900-1000 mg	A total dose of 1000mg in 3 or more divided doses

Patients currently treated with levodopa without a decarboxylase inhibitor:
Levodopa must be discontinued at least twelve hours before therapy with Levodopa and Carbidopa controlled release tablet is started. Levodopa and Carbidopa controlled release tablet should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. In patients with mild to moderate disease, the initial dose is usually 1 tablet of Levodopa and Carbidopa controlled release tablet b.i.d.

Patients not receiving levodopa:
In patients with mild to moderate disease, the initial recommended dose is 1 tablet of TIDOMET CR 125 b.i.d. Initial dosage should not be given at intervals of less than 6 hours.

Titration
Following initiation of therapy, doses and dosing intervals may be increased or decreased depending upon therapeutic response. Most patients have been adequately treated with doses of Levodopa and carbidopa, that provide 400 to 1600mg of levodopa per day, administered as divided doses at intervals ranging from 4 to 8 hours during the waking day. Higher doses of Levodopa and carbidopa, (2400mg or more of levodopa per day) and shorter intervals (less than 4 hours) have been used, but are not usually recommended. An interval of at least 3 days between dosage adjustments is recommended.

CONTRAINDICATIONS
Non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Carbidopa and Levodopa. These inhibitors must be discontinued at least two weeks before starting Carbidopa and Levodopa. Carbidopa and Levodopa may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g. selegiline hydrochloride).

Carbidopa and Levodopa 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.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Carbidopa and Levodopa is not recommended for the treatment of drug-induced extrapyramidal reactions.

Carbidopa and Levodopa 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 gastrointestinal haemorrhage).

Care should be exercised when Carbidopa and Levodopa 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, Carbidopa and Levodopa 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 Carbidopa and Levodopa is substituted. These reactions are thought to be due to increased brain dopamine following administration of levodopa, and use of Carbidopa and Levodopa 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 Carbidopa and Levodopa should be carefully observed, particularly in patients who are also receiving neuroleptics.

Concomitant administration of psychoactive 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, haematopoetic, cardiovascular and renal function are recommended during extended therapy.

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

If general anaesthesia is required, therapy with Carbidopa and Levodopa 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, Carbidopa and Levodopa may be restarted as soon as oral medication can be taken at the same daily dosage as before.

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population (approximately 26 fold higher). It is unclear whether the increased risk observed was due to Parkinson's disease, or other factors such as drugs used to treat Parkinson's disease. Therefore patients and providers

are advised to monitor for melanomas on a regular basis when using Carbidopa and Levodopa for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Laboratory Tests
Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of Carbidopa and Levodopa 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 Carbidopa and Levodopa and levodopa alone.

Carbidopa and Levodopa 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.

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with carbidopa/ levodopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS.

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Carbidopa and Levodopa. Review of treatment is recommended if such symptoms develop.

DRUG INTERACTION
Caution should be exercised when the following drugs are administered concomitantly with Carbidopa and Levodopa.

Antihypertensive agents
Postural hypotension can occur when Carbidopa and Levodopa 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.

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 Carbidopa and Levodopa should be carefully observed for loss of therapeutic response.

Use of Carbidopa and Levodopa with dopaminedepleting agents (e.g., tetrabenazine) or other drugs known to deplete monoamine stores is not recommended.

Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone.

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

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

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

PREGNANCY AND LACTATION

Pregnancy
Although the effects of Carbidopa and Levodopa 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 Carbidopa and Levodopa 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 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 breastfeeding or discontinue the use of Carbidopa and Levodopa, taking into account the importance of the drug to the mother.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Individual responses to medication may vary and certain side effects that have been reported with Carbidopa and Levodopa 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.

UNDESIRABLE EFFECTS

Side effects that occur frequently with Carbidopa and Levodopa are those due to the central neuro-pharmacological 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.

Gastro-intestinal: vomiting, gastrointestinal bleeding, development of duodenal ulcer, diarrhoea, dark saliva.

Haemotologic: leucopenia, haemolytic and nonhaemolytic anaemia, thrombocytopenia, agranulocytosis.

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

Nervous System/Psychiatric: neuroleptic malignant syndrome, bradykinetic episodes (the "onoff" 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 Carbidopa and Levodopa has not been established.

Other side effects that have been reported with levodopa or levodopa/carbidopa combinations and may be potential side effects with Carbidopa and Levodopa 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, gait abnormalities and Dopamine Dysregulation Syndrome.

Description of selected adverse reactions
Dopamine Dysregulation Syndrome (DDS) is an addictive disorder seen in some patients treated with carbidopa/ levodopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias.

Impulse control disorders
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Carbidopa and Levodopa.

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.

OVERDOSE

Treatment
Management of acute over dosage with Carbidopa and Levodopa is basically the same as management of acute over dosage with levodopa; however pyridoxine is not effective in reversing the actions of Carbidopa and Levodopa. ECG monitoring should be instituted, and the patient carefully observed for the possible development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as Carbidopa and Levodopa should be taken into consideration. To date, no experience has been reported with dialysis, and hence its value in the treatment of over dosage is not known.
The terminal half-life of levodopa is about two hours in the presence of carbidopa.

PHARMACOLOGICAL PROPERTIES

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.

Carbidopa and Levodopa 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 Carbidopa and Levodopa usually reduces fluctuations in response. By reducing some of the adverse reactions produced by levodopa alone, Carbidopa and Levodopa permits more patients to obtain adequate relief from the symptoms of Parkinson's disease.

Pharmacokinetic properties

Following oral dosing levodopa, in the absence of decarboxylase inhibitor, is rapidly but variably absorbed from the gastrointestinal tract. t 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 3% 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.

Preclinical safety data
Carbidopa and Levodopa is well established in medical use. Preclinical data is broadly consistent with clinical experience.

EXPIRY DATE
Do not use later than the date of expiry.

STORAGE
STORE AT A TEMPERATURE NOT EXCEEDING 30ºC,PROTECTED FROM LIGHT AND MOISTURE.

PACKAGING INFORMATION
3 BLISTER STRIPS OF 10 TABLETS EACH.

DIRECTION FOR USE
Swallow whole tablet, do not crush or chew. Keep out of reach of children.

MARKETED BY

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IN/TIDOMET 100,200,25,50mg/JUN-18/03/PI