NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Levodopa / Carbidopa 100/25 (100mg/25mg) tablets (Arrotex Pharmaceuticals)
Levodopa / Carbidopa 250/25 (250mg/25mg) tablets (Arrotex Pharmaceuticals)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Levodopa/carbidopa 100/25 contains 100 mg of levodopa and 25 mg of carbidopa.
Each tablet of Levodopa/Carbidopa 250/25 contains 250 mg of levodopa and 25 mg of carbidopa.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

100 mg / 25mg: Round, light yellow uncoated tablets with 'C' on one side and '19' on the other side.

250 mg / 25mg: Round, light blue uncoated tablets with 'C' on one side and '20' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

When therapeutic response to levodopa alone is irregular, and signs and symptoms of Parkinson's disease are not evenly controlled throughout the day, substitution of Levodopa/Carbidopa usually is effective in reducing fluctuations in response.

By reducing certain adverse reactions produced by levodopa alone, Levodopa/Carbidopa permits more patients to obtain adequate relief of the symptoms of Parkinson's disease.

Levodopa/Carbidopa is also indicated for patients with Parkinsonism who are taking vitamin preparations that contain pyridoxine hydrochloride (Vitamin B_6).

4.2 Dose and method of administration

Dose
The optimum daily dosage of Levodopa/Carbidopa must be determined by careful titration in each patient. Levodopa/Carbidopa tablets are available in a 1:4 ratio of carbidopa to levodopa

(Levodopa/Carbidopa 100/25) as well as a 1:10 ratio (Levodopa/Carbidopa 250/25). Tablets of the two ratios may be given separately or combined as needed to provide the optimum dosage. Please note that Levodopa/Carbidopa tablets are not scored, and should not be divided in half for dosing.

The total levodopa dose in a 24-hr period should be similar and divided accordingly, with doses given approximately every three to four hours.

General Considerations
Dosage should be titrated to the individual patient needs and this may require adjusting both the individual dose and the frequency of administration.

Studies show that the 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.

Standard antiparkinson medicines, other than levodopa alone, may be continued while Levodopa/ Carbidopa is being administered, although their dosage may have to be adjusted.

Low dose selective MAO-B inhibitors can be given with Levodopa/Carbidopa (see Section 4.3 Contraindications). Dosage adjustment of Levodopa/Carbidopa may be necessary when these agents are added to an existing Levodopa/Carbidopa treatment regimen.

Usual Initial Dose
Dosage is best initiated with one tablet of Levodopa/Carbidopa 100/25 three times a day. This dosage schedule provided 75 mg of carbidopa per day. Dosage may be increased by one tablet every day or every other day (given at intervals of 3-4 hours), as necessary, until a dosage equivalent of eight tablets of Levodopa/Carbidopa 100/25 a day is reached.

Dosage is best initiated with Levodopa/Carbidopa 100/25 in patients who have not been treated with Levodopa/Carbidopa before. Please note that, since Levodopa/Carbidopa tablets are not scored, initial dosage with Levodopa/Carbidopa 250/25 is not recommended.

If patients will be started with Levodopa/Carbidopa 250/25, the initial dose is one tablet taken once daily. However, this may not provide the optimal amount of carbidopa needed by many patients. If necessary, add 1 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.

How to Transfer Patients from Levodopa
Because both therapeutic and adverse responses occur more rapidly with Levodopa/Carbidopa than when levodopa is given, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly with Levodopa/Carbidopa 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.

Levodopa should be discontinued at least 12 hours before Levodopa/Carbidopa is started (24 hours for slow-release preparations of levodopa). A daily dosage of Levodopa/Carbidopa should be chosen that will provide approximately 20 percent of the previous levodopa daily dosage.

Patients who are taking less than 1500 mg of levodopa a day should be started on one tablet of Levodopa/Carbidopa 100/25 three or four times a day. The suggested starting dosage for most patients taking more than 1500 mg of levodopa is one tablet of Levodopa/Carbidopa 250/25 three or four times a day.

Maintenance
Therapy should be individualised and adjusted according to the desired therapeutic response. At least 70 to 100 mg of carbidopa per day should be provided for optimal inhibition of extracerebral decarboxylation of levodopa.

When a greater proportion of carbidopa to levodopa is required, one tablet of Levodopa/Carbidopa 100/25 may be substituted. When more levodopa is required, Levodopa/Carbidopa 250/25 should be substituted for Levodopa/ Carbidopa 100/25.

If necessary, the dosage of Levodopa/Carbidopa 250/25 may be increased by one tablet every day or every other day, up to a maximum of eight tablets a day. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Maximum Recommended Dose
Eight tablets of Levodopa/Carbidopa 250/25 per day (200 mg of carbidopa and 2 g of levodopa). This is about 3 mg/kg of carbidopa, and 30 mg/kg of levodopa in a patient weighing 70 kg.

Paediatric population
See Section 4.4 Special warnings and precautions for use.

4.3 Contraindications

Non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Levodopa/Carbidopa. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Levodopa/Carbidopa. Levodopa/Carbidopa may be administered concomitantly with the manufacturer's recommended dose of a MAO inhibitor with selectivity for MAO type B (e.g. selegiline HCl) (see Section 4.5 Interactions with other medicines and other forms of interactions, *Other medicines*).

Levodopa/Carbidopa is contraindicated in patients with known hypersensitivity to any component of this medication (see Section 6.1 List of excipients), and in patients with narrow angle glaucoma.

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

4.4 Special warnings and precautions for use

Levodopa/Carbidopa is not recommended for the treatment of medicine-induced extrapyramidal reactions.

Levodopa/Carbidopa may be given to patients already receiving levodopa alone; however, the levodopa alone must be discontinued at least 12 hours before Levodopa/Carbidopa is started. Levodopa/Carbidopa should be substituted at a dosage that will provide approximately 20 percent of the previous levodopa dosage (see Section 4.2 Dose and method of administration).

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, Levodopa/Carbidopa may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa, and use of Levodopa/Carbidopa may cause a recurrence. Dosage reduction may be required. 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.

Caution should be exercised with concomitant administration of psychoactive medicines and Levodopa/ Carbidopa (see Section 4.5 Interactions with other medicines and other forms of interactions).

Levodopa/Carbidopa should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or a history of peptic ulcer disease (because of the possibility of upper gastrointestinal haemorrhage) or of convulsions.

As with levodopa, care should be exercised in administering Levodopa/Carbidopa to patients with a history of myocardial infarction who have atrial, nodal, or ventricular arrhythmia. In such patients, cardiac function should be monitored with particular care during the period of initial dosage administration and titration.

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

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of Levodopa/Carbidopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Levodopa has been associated with somnolence and episodes of sleep onset. Sudden onset of sleep

during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients should 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.

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

If general anaesthesia is required, Levodopa/Carbidopa may be continued as long as the patient is permitted to take fluids and medication by mouth. If therapy is interrupted temporarily, the usual daily dosage may be administered as soon as the patient is able to take oral medication.

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 medicines 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 Levodopa/Carbidopa for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

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

Laboratory Tests

Abnormalities in various laboratory tests have occurred with carbidopa-levodopa preparations and may occur with Levodopa/Carbidopa. These include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase (LDH), bilirubin, blood urea nitrogen, creatinine, uric acid, and positive Coombs' test.

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

Carbidopa-levodopa preparations 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.

Paediatric population

Safety and effectiveness of Levodopa/Carbidopa in infants and children have not been established, and its use in patients below the age of 18 years is not recommended.

Use in the elderly

There is wide experience in the use of levodopa and carbidopa in elderly patients (see Section 4.2 Dose and method of administration**,** *Use in hepatic impairment*). Levodopa/Carbidopa should be administered cautiously to patients with hepatic disease. Periodic evaluation of hepatic function is recommended during extended therapy.

Use in renal impairment

Levodopa/Carbidopa should be administered cautiously to patients with renal disease. Periodic evaluation of renal function is recommended during extended therapy.

4.5 Interactions with other medicines and other forms of interactions

Caution should be exercised when the following medicines are administered concomitantly with Levodopa/Carbidopa:

Antihypertensive agents:
Symptomatic postural hypotension has occurred when Levodopa/Carbidopa is added to the treatment of a patient receiving antihypertensive medicines. Therefore, when therapy with Levodopa/ Carbidopa is started, dosage adjustment of the antihypertensive medicine may be required.

Antidepressants:
For patients receiving monoamine oxidase inhibitors see Section 4.3 Contraindications.

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

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

Other medicines:
Dopamine D_2 receptor antagonists (e.g. phenothiazines, butyrophenones and 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 medicines with Levodopa/Carbidopa should be carefully observed for loss of therapeutic response.

Use of Levodopa/Carbidopa with dopamine-depleting agents (e.g., reserpine and 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 (see Section 4.3 Contraindications).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Although the effects of Levodopa/Carbidopa on human pregnancy are unknown both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits (see Section 5.3 Preclinical safety data, Animal Teratology and Reproductive Studies). Therefore, use of Levodopa/Carbidopa in women of childbearing potential requires that the anticipated benefits of the medicine be weighed against possible hazards should pregnancy occur.

Breast-feeding

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 medicines are excreted in human milk and because of the potential for serious adverse reactions in infants, a decision should be made whether to discontinue nursing or to discontinue the use of Levodopa/Carbidopa, taking into account the importance of the medicine to the mother.

Fertility

See Section 5.3 Preclinical safety data, *Animal Teratology and Reproductive Studies*.

4.7 Effects on ability to drive and use machines

See Section 4.4 Special Warnings and Precautions for Use.

4.8 Undesirable effects

Adverse effects that occur frequently in patients receiving Levodopa/Carbidopa are those due to the central neuropharmacologic activity of dopamine. These reactions usually can be diminished by dosage reduction. The most common adverse effects are dyskinesias including choreiform, dystonic, and other involuntary movements and nausea. Muscle twitching and blepharospasm may be taken as early signs to consider reduction.

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

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

Cardiovascular: Cardiac irregularities and/or palpitation, orthostatic effects including hypotensive episodes, hypertension, phlebitis.

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

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

Hypersensitivity: Angioedema, urticaria, pruritus, Henoch-Schönlein purpura.

Nervous System/Psychiatric: Neuroleptic malignant syndrome (see Section 4.4 Special warnings and precautions for use), bradykinetic episodes (the "on-off" phenomenon), dizziness, somnolence including very rarely excessive daytime somnolence and sudden sleep onset episodes, paresthesia, psychotic episodes including delusions, hallucinations and paranoid ideation, depression with or without development of suicidal tendencies, dementia, dream abnormalities, agitation, confusion. Pathological (compulsive) gambling, increased libido, hypersexuality, compulsive spending/buying, and binge/compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa, including Levodopa/Carbidopa (See Section 4.4 Special warnings and precautions for use).

Respiratory: Dyspnoea.

Skin: Alopecia, rash, dark sweat.

Urogenital: Dark urine.

Rarely convulsions have occurred; however a causal relationship with Levodopa/Carbidopa has not been established.

Other Adverse Effects That Have Been Reported with Levodopa or Levodopa/Carbidopa Combinations and May Be Potential Adverse Effects with Levodopa/Carbidopa are listed below:

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

Gastrointestinal: Dyspepsia, dry mouth, bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, flatulence, burning sensation of tongue.

Investigations: Weight gain, weight loss

Metabolic: Oedema.

Skin: Flushing, increased sweating, pigmentation of teeth and skin.

Urogenital: Urinary retention, urinary incontinence, priapism.

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

Miscellaneous: Weakness, faintness, fatigue, headache, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, malignant melanoma (see Section 4.3 Contraindications).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Management of acute overdosage with Levodopa/Carbidopa is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of Levodopa/Carbidopa.

Electrocardiographic 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 medicines as well as Levodopa/Carbidopa should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

A 60 year old male patient is reported to have ingested 60 250/25 Levodopa/Carbidopa tablets. Upon hospitalisation two hours after ingestion symptoms were sinus tachycardia, nausea and vomiting. Supportive therapy was instituted and the patient was asymptomatic the following day.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopa and dopa derivatives, ATC code: N04BA02.
Antiparkinson agent.

Mechanism of action
Levodopa/Carbidopa is a combination of carbidopa, MSD, an aromatic amino acid decarboxylase inhibitor, and levodopa, MSD, the metabolic precursor of dopamine, for the treatment of Parkinson's

disease and syndrome.

Levodopa relieves the symptoms of Parkinson's disease by being decarboxylated to dopamine in the brain. Carbidopa, which does not cross the blood-brain barrier, inhibits the extracerebral decarboxylation of levodopa, making more levodopa available for transport to the brain and subsequent conversion to dopamine.

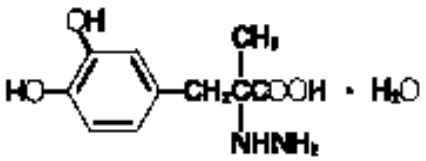
Levodopa/Carbidopa improves overall therapeutic response as compared to levodopa. Levodopa/Carbidopa provides effective long-lasting levodopa plasma levels at doses that are approximately 80 percent lower than those needed with levodopa alone.

While pyridoxine hydrochloride (Vitamin B_6) is known to accelerate the peripheral metabolism of levodopa to dopamine, carbidopa prevents this action.

The carbidopa component of Levodopa/Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g. dyskinesias, may occur at lower dosages and sooner during therapy with Levodopa/Carbidopa than with levodopa.

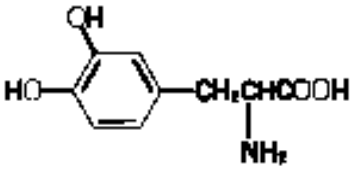
Chemistry

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



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

Levodopa, MSD, 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-alpha-amino-beta- (3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_3H_{11}NO_4$ and its structural formula is:



5.2 Pharmacokinetic properties

Onset of Action With Usual Doses of Levodopa/Carbidopa - Response has been observed in one day and sometimes after one dose. Fully effective doses usually are reached within seven days.

Half Life Carbidopa, Levodopa, Carbidopa/Levodopa - The plasma half-life of levodopa is about 50

minutes. When carbidopa and levodopa are administered together, the half-life of levodopa is increased to about one and one half hours.

Carbidopa pharmacokinetics

Absorption

Following an oral dose of radioactive labelled carbidopa to healthy subjects and to patients with Parkinson's disease, maximum plasma levels of radioactivity were reached in two to four hours in the normal subjects and in one and one half to five hours in the patients.

Biotransformation and elimination

Following an oral dose of radioactive labelled carbidopa to healthy subjects and to patients with Parkinsons disease approximately equal quantities were excreted in the urine and the faeces by both groups. Comparison of urinary metabolites in healthy subjects and patients indicated that carbidopa is metabolised to the same degree in both. Urinary excretion of unchanged carbidopa was essentially complete in seven hours and represented 35 percent of the total urinary radioactivity. Only metabolites were present thereafter. No hydrazines were found.

Among the metabolites excreted by humans are α-methyl-3-methoxy-4-hydroxyphenyl- propionic acid and α-methyl-3,4 dihydroxyphenyl- propionic acid. These accounted for approximately 14 and 10 percent, respectively, of the radioactive metabolites excreted. Two minor metabolites were found.

One was identified as 3,4 dihydroxyphenyl-acetone and the other tentatively identified as N-methylcarbidopa. They each accounted for less than five percent of the urinary metabolites. Unchanged carbidopa also is present in the urine. No conjugates were found.

Levodopa pharmacokinetics

Absorption, biotransformation and elimination

Levodopa is rapidly absorbed from the gastrointestinal tract and extensively metabolised. Although more than 30 metabolites may be formed, it is converted mainly to dopamine, epinephrine and norepinephrine, and eventually to dihydroxy-phenylacetic acid, homovanillic acid, and vanilmandelic acid. 3-0-methyldopa appears in the plasma and cerebrospinal fluid. Its significance is not known.

When single test doses of radioactive levodopa are given to fasting patients with Parkinson's disease, plasma levels of radioactivity peak in one-half to two hours and remain measurable for four to six hours. At peak levels, about 30 percent of the radioactivity appears as catecholamines, 15 percent as dopamine, and 10 percent as dopa. Radioactive compounds are rapidly excreted in the urine, one-third of the dose appearing in two hours. Eighty to ninety percent of urinary metabolites are phenylcarboxylic acids, principally homovanillic acid. Over 24 hours, one to two percent of recovered radioactivity is dopamine, and less than one percent is epinephrine, norepinephrine, and unchanged levodopa.

Levodopa/Carbidopa pharmacokinetics Effect of Carbidopa on Levodopa Metabolism

In healthy subjects carbidopa increased plasma levels of levodopa by statistically significant amounts, as measured against placebo. This has been demonstrated when carbidopa is given before levodopa and when the two medicines are given simultaneously. In one study, pre- treatment with carbidopa

increased plasma levels of a single dose of levodopa about five times and extended the duration of measurable plasma concentrations of levodopa from four hours to eight hours. When the two medicines were given simultaneously in other studies, similar results were obtained.

In a study in which a single dose of stem-labelled levodopa was given to patients with Parkinson's disease who had been pre-treated with carbidopa, there was an increase in the half-life of total plasma radioactivity derived from the levodopa, from 3 to 15 hours. The proportion of radioactivity remaining as unmetabolised levodopa was increased at least three times by carbidopa. Plasma and urinary dopamine and homovanillic acid were both decreased by carbidopa pre-treatment.

5.3 Preclinical safety data

Animal Toxicology

Animal Teratology, and Reproductive Studies

Carbidopa showed no evidence of teratogenicity in mice or rabbits at doses of 120 mg/kg/day. Levodopa produced visceral and skeletal malformations in rabbits at doses of 125 and 250 mg/kg/day.

With combinations of carbidopa and levodopa, in doses ranging from 25/250 to 100/500 mg/kg/day, there was no evidence of teratogenicity in mice, but in rabbits visceral and skeletal malformations occurred which were quantitatively and qualitatively similar to those seen with levodopa alone.

Carbidopa had no effect on the mating performance, fertility or survival of the young when administered orally to rats at doses of 30, 60, or 120 mg/kg/day. The highest dose caused a moderate decrease in body weight gain in males.

The administration of carbidopa/levodopa at dose levels of 10/20, 10/50 or 10/100 mg/kg/day did not adversely affect the fertility of male or female rats, their reproductive performance, or the growth and survival of their young.

Carcinogenesis

There were no significant differences between treated and control rats with respect to mortality or neoplasia in a 96 week study of carbidopa at oral doses of 25, 45, or 135 mg/kg/day.

Combinations of carbidopa and levodopa (10/20, 10/50 and 10/100 mg/kg/day) were given orally to rats for 106 weeks. No effect on mortality or incidence and type of neoplasia was seen when compared to concurrent controls.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Levodopa/Carbidopa 100/25 tablets contain the following excipients:
Crospovidone
Microcrystalline cellulose

Magnesium stearate
Pregelatinised maize starch
Quinoline yellow aluminium lake

Levodopa/Carbidopa 25/250 tablets contain the following excipients:
Crospovidone
Microcrystalline cellulose
Magnesium stearate
Pregelatinised maize starch
Indigo carmine aluminium lake.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters: 36 months
Bottles: 12 months

6.4 Special precautions for storage

Keep tightly closed in a cool place protected from sunlight. Store below 25°C. Store in a tightly closed container.

6.5 Nature and contents of container

Levodopa/Carbidopa 100mg/25mg tablets containing 100 mg of levodopa & 25 mg of carbidopa is supplied in Blister (Aluminium/Aluminium) packs containing 10, 20 or 100 tablets or HDPE bottles of 100 tablets.

Levodopa/Carbidopa 250mg/25mg tablets containing 250 mg of levodopa & 25 mg of carbidopa is supplied in Blister (Aluminium/Aluminium) packs containing 10, 20 or 100 tablets or HDPE bottles of 100.

6.6 Special precautions for disposal and other handling

Any unused material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Arrotex Pharmaceuticals (NZ) Limited
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Phone: +64 3 4779 669

9 DATE OF FIRST APPROVAL

23 September 2021

10 DATE OF REVISION OF THE TEXT

23 September 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information