Kinson

Levodopa/Carbidopa

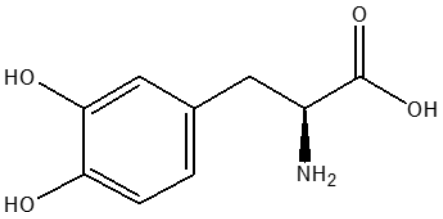
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient : Levodopa

Chemical name : (-)-3-(3,4-dihydroxyphenyl)-L-alanine

Structural formula :



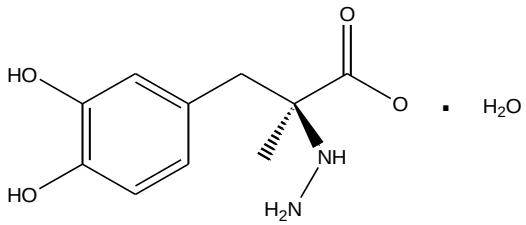
Molecular formula : $C_9H_{11}NO_4$ Molecular weight : 197.2

CAS Registry no. : 59-92-7

Active ingredient : Carbidopa

Chemical name : L ( ) 2 (3,4 dihydroxybenzyl) 2 hydrazino propionic acid monohydrate

Structural formula :



Molecular formula : $C_{10}H_{14}N_2O_4.H_2O$ Molecular weight : 244.3

CAS Registry no. : 28860-95-9

DESCRIPTION

Kinson is a combination of levodopa, the metabolic precursor of dopamine, and carbidopa, an aromatic amino acid decarboxylase inhibitor, for the treatment of Parkinson's disease and syndrome.

Levodopa, an aromatic amino acid, is a colourless crystalline compound, slightly soluble in water and insoluble in alcohol.

Carbidopa, an inhibitor of aromatic amino acid decarboxylase, is a white, crystalline compound, slightly soluble in water.

Each tablet contains 100 mg of levodopa and 25 mg of anhydrous carbidopa. The tablets also contain the following inactive ingredients: cellulose-microcrystalline, starch-maize, sodium starch glycollate, talc-purified, povidone, magnesium stearate, quinoline yellow CI 47005.

PHARMACOLOGY

Symptoms of Parkinson's disease have been related to depletion of dopamine in the corpus striatum of the brain. Levodopa, the metabolic precursor of dopamine, relieves the symptoms of Parkinson's disease presumably by being converted to dopamine in the brain. Following oral administration, levodopa is rapidly decarboxylated and converted to dopamine in extracerebral tissues and only a small amount of unchanged levodopa reaches the central nervous system. Thus, large doses of levodopa are required at frequent intervals for adequate therapeutic effect and are often attended by many adverse reactions, some of which are attributable to dopamine being formed in extracerebral tissue.

Carbidopa, which does not cross the blood-brain barrier, inhibits only extracerebral decarboxylation of levodopa, making more levodopa available for transport to the brain and conversion to dopamine. The lower dosage reduces or eliminates certain adverse reactions attributable to dopamine being formed in extracerebral tissues.

Following co-administration of levodopa and carbidopa in man, plasma levels of levodopa were markedly increased over those found when the same dosage of levodopa is given alone, while plasma levels of dopamine and homovanillic acid, two principal metabolites of levodopa, were markedly reduced.

Pyridoxine hydrochloride (vitamin B6) in oral doses of 10 mg to 25 mg have been noted to rapidly reverse the antiparkinsonian effect of levodopa. Carbidopa prevents this action of pyridoxine. In a study of patients who received 100 mg to 500 mg of pyridoxine a day whilst being treated with levodopa and carbidopa in combination, there was no reversal of therapeutic effect.

Pharmacokinetics

Metabolism of Levodopa

Levodopa is rapidly absorbed from the gastrointestinal tract and extensively metabolised. Although more than 30 metabolites may be formed, levodopa is mainly converted to dopamine and, in lesser amounts, to adrenaline and noradrenaline. These are ultimately metabolised to the principal excretion products, dopacetic acid, homovanillic acid and vanillylmandelic acid.

When single test doses of radioactive levodopa are given to fasting patients with Parkinson's disease, plasma levels of radioactivity peak at 0.5 to 2 hours and remain measurable for 4 to 6 hours. At peak levels, about 30% of the radioactivity appears as catecholamines, 15% as dopamine and 10% as dopa. The radioactive compounds are rapidly excreted in the urine, one-third of the dose appearing in the urine in 2 hours. 80 to 90% of urinary metabolites are phenylcarboxylic acids, principally homovanillic acid. Over 24 hours, 1 to 2% of recovered radioactivity is dopamine and less than 1% is adrenaline, noradrenaline and unchanged levodopa.

Metabolism of Carbidopa

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 2 to 4 hours in the subjects and in 1.5 to 5 hours in the patients. Approximately equal quantities were excreted in the urine and the faeces by both groups.

A comparison of the urinary metabolites in healthy subjects and patients indicated that carbidopa is metabolised to the same degree in both. Urinary excretion of unchanged drug was essentially complete in 7 hours and represented 35% of the total urinary radioactivity. Only metabolites were present thereafter.

Among the metabolites excreted by humans are α-methyl-3-methoxy-4-hydroxy-phenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid. These accounted for approximately 14% and 10%, respectively, of the radioactive metabolites excreted. Two minor metabolites were also found. One was identified as 3,4-dihydroxyphenylacetone and the other tentatively identified as N-methylcarbidopa. They each accounted for less than 5% of the urinary metabolites. Unchanged carbidopa is also present in urine. No conjugates were found.

Effect of Carbidopa on Levodopa Metabolism

Carbidopa consistently increased plasma levels of levodopa by statistically significant amounts, as measured against placebo, in healthy subjects. This has been demonstrated when carbidopa is given before levodopa and when the 2 drugs are given simultaneously. In one study, pre-treatment with carbidopa increased plasma levels of a single dose of levodopa about 5 times and extended the duration of measurable plasma concentrations of levodopa from 4 to 8 hours. When the 2 drugs 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 pretreated 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 3 times by carbidopa. Plasma and urinary dopamine and homovanillic acid were both decreased by carbidopa pre-treatment.

INDICATIONS

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

CONTRAINDICATIONS

Monoamine oxidase inhibitors (MAOIs) and Kinson should not be given concomitantly. MAOIs must be discontinued at least 2 weeks prior to initiating therapy with Kinson. Kinson may be administered concomitantly with the manufacturer's recommended dose of a MAO inhibitor with selectivity for MAO type B, e.g. selegiline (see **INTERACTIONS WITH OTHER MEDICINES: Other Drugs**).

Kinson is contraindicated in patients with known hypersensitivity to this drug or any component of this medication, and in patients with narrow angle glaucoma.

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

PRECAUTIONS

Kinson may be given to patients already receiving levodopa alone; however, the levodopa must be discontinued 12 hours before Kinson is started. Kinson should be substituted at a dosage that will provide approximately 20% of the previous levodopa daily dosage (see **DOSAGE AND ADMINISTRATION**). Patients taking Kinson should be instructed not to take additional levodopa unless prescribed.

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

All patients should be monitored carefully for the development of mental changes, depression with suicidal tendencies, or other serious antisocial behaviour.

Dyskinesia 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 dyskinesia may require dosage reduction.

Patients with a history of severe involuntary movements or psychotic episodes when treated with levodopa alone, should be observed carefully when Kinson is substituted. These reactions are thought to be due to increased brain dopamine following administration of levodopa, and use of Kinson may cause a recurrence.

If concomitant administration of psychoactive drugs is necessary, such drugs should be administered with caution and patients carefully observed for loss of antiparkinsonian effect.

Patients with a history of convulsions should be treated with caution.

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.

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

Care should be exercised in administering Kinson to patients who have atrial, nodal or ventricular arrhythmia. In such patients, cardiac function should be monitored continuously during the period of initial dosage adjustment.

Symptomatic postural hypotension has been reported occasionally. Therefore, Kinson should be given cautiously to patients taking antihypertensive drugs. When Kinson is started, dosage adjustment of the antihypertensive drug may be required. (For patients receiving pargyline, see **CONTRAINDICATIONS** on MAOIs.)

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatinine 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.

If general anaesthesia is required, therapy with Kinson 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.

Kinson should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease. Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function are recommended during extended therapy.

As with levodopa, there is a possibility of upper gastrointestinal haemorrhage in patients with a history of peptic ulcer.

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

Compulsive behaviour

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 (such as pathological gambling, hypersexuality, increased libido, compulsive spending/buying, and binge eating, medication use and

punding (repetitive purposeless activity)) has been reported in patients taking dopamine agonists for the treatment of Parkinson's disease, especially at high doses. Review of treatment is recommended if such symptoms develop. Prescribers, patients and caregivers should be alert to the possibility of such behaviour, which may have serious financial and social consequences.

Use in Pregnancy (Category B3)

Although the effects of Kinson on human pregnancy and lactation are unknown, levodopa caused visceral and skeletal malformations in rabbits at doses of 125 and 250 mg/kg/day. With combinations of levodopa and carbidopa in doses ranging from 250/50 to 500/100 mg/kg/day there was no evidence of teratogenicity in mice, but in rabbits visceral and skeletal malformations occurred similar to those seen with levodopa alone. Carbidopa alone showed no evidence of teratogenicity in mice and rabbits at doses up to 120 mg/kg/day.

Combinations of levodopa and carbidopa in doses up to 100/10 mg/kg/day had no adverse effects of the reproductive performance of male or female rats or on the growth and survival of the pups.

Therefore, use of Kinson in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards, should pregnancy occur.

Use in Lactation

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, Kinson should not be used by breastfeeding mothers. A decision should be made either to discontinue breastfeeding or to discontinue Kinson.

Paediatric Use

The safety of Kinson in patients under 18 years of age has not been established.

Effects on Ability to Drive and Operate Machinery

Patients being 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.

INTERACTIONS WITH OTHER MEDICINES

Caution should be exercised when the following drugs are administered concomitantly with Kinson:

Antihypertensive agents

Symptomatic postural hypotension has occurred when levodopa/decarboxylase inhibitor combinations were added to the treatment regimen of patients receiving some antihypertensive drugs. Therefore, when therapy with Kinson is started, dosage adjustment of the antihypertensive drug may be required.

Antidepressants

For patients receiving monoamine oxidase inhibitors, see **CONTRAINDICATIONS**. There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and levodopa-carbidopa preparations.

MAOIs and Kinson should not be given concomitantly (see **CONTRAINDICATIONS**). The MAOIs must be discontinued at least 2 weeks prior to initiating therapy with Kinson.

Iron

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

Other drugs

Dopamine D_2-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 Kinson should be observed carefully for loss of therapeutic response.

Use of Kinson 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 levodopa/carbidopa may be associated with severe orthostatic hypotension not attributable to levodopa/carbidopa alone (see **CONTRAINDICATIONS**).

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

Effects on Laboratory Tests

Abnormalities in laboratory tests may include elevations of blood urea nitrogen, creatinine, SGOT, SGPT, LDH, bilirubin, alkaline phosphatase or protein bound iodine. More commonly, levels of blood urea nitrogen and uric acid are lower during the administration of Kinson than with levodopa.

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

Levodopa-carbidopa 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 glycosuria.

Positive Coombs' tests have been reported both with Kinson and with levodopa alone, but haemolytic anaemia is rare.

ADVERSE EFFECTS

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

Other serious side effects are mental changes, including paranoid ideation and psychotic episodes including delusions, hallucinations; depression with or without development of suicidal tendencies; and dementia. A common, but less serious side effect is nausea.

Less frequent side effects are cardiac irregularities and/or palpitations, orthostatic effects including hypotensive episodes, bradykinetic episodes (the “on-off” phenomenon), anorexia, vomiting, somnolence and dizziness.

Gastrointestinal bleeding, development of duodenal ulcer, hypertension, phlebitis, leucopoenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis, chest pain, dyspnoea and paraesthesia have occurred rarely.

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

Haemolytic anaemia is extremely rare.

Other side effects that have been reported include:

Body as a whole:	Syncope.
Nervous system:	Ataxia, increased hand tremor, muscle twitching, muscle cramps, trismus, activation of latent Horner's syndrome, oculogyric crises.
Psychiatric:	Confusion, insomnia, nightmares and dream abnormalities, hallucinations, delusions, agitation, anxiety, euphoria, lethargy, sedation, increased libido. Levodopa is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.
Gastrointestinal:	Dry mouth, bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, epigastric and abdominal pain and distress, constipation, diarrhoea, flatulence, burning sensation of tongue, difficulty in swallowing, dark saliva.
Hypersensitivity:	Angioedema, urticaria, pruritus, Henoch-Schönlein purpure.
Investigations:	Weight gain, weight loss
Metabolism and nutrition disorders:	Oedema, anorexia.
Integumentary:	Flushing, increased sweating, dark sweat, rash, hair loss, bad odour.
Genitourinary:	Urinary retention, urinary incontinence, dark urine, priapism, haematuria.
Special senses:	Diplopia, blurred vision, dilated pupils.
Miscellaneous:	Weakness, faintness, fatigue, headache, hoarseness, malaise, hot flushes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome, malignant melanoma (see **CONTRAINDICATIONS**).

Other side effects that have been associated with controlled release formulations and may therefore be potential side effects with immediate release formulations such as Kinson are:

Gastrointestinal: Dyspepsia.

Nervous system/psychiatric: Asthenia, decreased mental acuity, disorientation, falling, gait abnormalities.

Postmarketing Data:

In post marketing use, pathological (compulsive) gambling, increased libido, hypersexuality, compulsive spending/buying, and binge/compulsive eating have been reported with dopamine agonists and/or other dopaminergic treatments, and in patients treated with levodopa, including Kinson (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

The optimum daily dosage of Kinson must be determined by careful titration in each patient. Kinson tablets are available in a 1:4 ratio of carbidopa to levodopa (25 mg/100 mg).

General Considerations

Dosage should be titrated to 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 daily. 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 Kinson is being administered, although dosage may have to be adjusted.

Usual Initial Dosage

Dosage is best initiated with one tablet of Kinson 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 equivalent of eight tablets of Kinson a day 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 Kinson than when levodopa is given, patients should be monitored closely during the dose adjustment period. Specifically, involuntary movements will occur more rapidly with Kinson 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 Kinson is started (24 hours for slow release preparations of levodopa). A daily dosage of Kinson should be chosen that will provide approximately 20% 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 Kinson 25/100 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.

Usually 3 tablets daily. Dosage may be increased by one tablet every day or every other day, as necessary, up to a maximum of 8 tablets daily. Experience with total daily dosages of carbidopa greater than 200 mg is limited. For dosage beyond this recommendation, other brands of levodopa/carbidopa may have to be used. (Patients may require more levodopa but no advantage will be gained by increasing the amount of carbidopa above 200 mg/day).

Most patients can be maintained on 3 to 6 tablets a day and none should receive more than 8 tablets a day. No advantage will be gained by increasing the dosage of carbidopa beyond that provided by 8 tablets of Kinson. Patients may require additional levodopa. Dosage ranges recommended should usually not be exceeded.

Adjustment in the dosage of Kinson may be necessary.

Patients taking Kinson should be instructed not to take additional levodopa unless prescribed.

OVERDOSAGE

Treatment

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

In the event of overdosage, general supportive measures should be employed. 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 Kinson should be taken into consideration. To date, no experience has been reported with dialysis; hence its value in overdosage is not known.

In case of overdose, immediately contact the Poisons Information Centre on 13 11 26 for advice.

PRESENTATION AND STORAGE CONDITIONS

Kinson, Levodopa 100 mg with carbidopa 25 mg tablet: yellow, marked "LC" breakline "2" on one side, "□" on the reverse; 100 tablet bottle pack.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Alphapharm Pty Limited

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

ABN 93 002 359 739

www.alphapharm.com.au

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

11/07/1994

DATE OF MOST RECENT AMENDMENT

29/05/2015

Kinson_pi\may15/00