SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-Careldopa 25 mg/100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg carbidopa (as monohydrate) and 100 mg levodopa.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Mottled yellow, round, flat-bevelled tablet, 9.1 mm in diameter, plain and breakline on each side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For treatment of Parkinson’s disease and syndrome.

4.2 Posology and method of administration

The optimum daily dosage of Co-Careldopa must be determined by careful titration in each patient.

Co-Careldopa 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 Co-Careldopa is being administered, although their dosage may have to be adjusted.

Because both therapeutic and adverse effects are seen more rapidly with carbidopa/levodopa 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.

Posology

Patients not receiving levodopa

Dosage may be best initiated with one tablet of Co-Careldopa 25 mg/100 mg three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be increased by half a tablet or 1 tablet every day or every other day, as necessary, until a dosage equivalent of eight tablets of Co-Careldopa 25 mg/100 mg 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.

Patients receiving levodopa

Discontinue levodopa at least 12 hours (24 hours for slow-release preparations) before starting therapy with Co-Careldopa. The easiest way to do this is to give Co-Careldopa as the first morning dose after a night without any levodopa. The dose of Co-Careldopa 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 25 mg carbidopa and 100 mg levodopa and 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 25 mg carbidopa and 250 mg levodopa and three or four times a day.

Maintenance

Therapy with Co-Careldopa should be individualised and adjusted gradually according to response. When a greater proportion of carbidopa is required,

each tablet of Co-Careldopa 100 mg/10 mg may be replaced with a tablet of Co-Careldopa 100 mg/25 mg.

When more levodopa is required, a tablet with 25 mg carbidopa and 250 mg levodopa should be given three or four times a day. If necessary, the dosage may of Co-Careldopa 250 may be increased by one tablet every day or 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 Co-Careldopa from levodopa combined with another decarboxylase inhibitor, discontinue dosage at least 12 hours before Co-Careldopa is started. Begin with a dosage of Co-Careldopa 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 Co-Careldopa is introduced, although dosage may have to be adjusted in line with manufacturers recommendations.

Paediatric population

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

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.

Method of administration
Oral use.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Levodopa/carbidopa should not be given when administration of a sympathomimetic compound is contraindicated.
- Non-selective monoamine oxidase (MAO) inhibitors and selective MAO-type-A inhibitors. These inhibitors must be discontinued at least two weeks before starting Co-Careldopa.Co-Careldopa 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 section 4.5).
- Narrow-angle glaucoma.

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

4.4 Special warnings and precautions for use

Co-Careldopa can be administered to patients already receiving levodopa alone. However, the treatment with levodopa alone should be discontinued at least 12 hours (24 hours for slow-release preparations) prior to start of treatment with Co-Careldopa. The substitution with Co-Careldopa should be at a dose equivalent to approximately 20% of the levodopa dose used before(see section 4.2).

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, Co-Careldopa may cause involuntary movements and mental disturbances. Patients with a history of severe involuntary movements or psychotic episodes when treated with levodopa alone or combination of levodopa and a decarboxylase inhibitor should be observed carefully when Co-Careldopa is substituted. These reactions are thought to be due to increased brain dopamine following administration of levodopa, and use of Co-Careldopa may cause a recurrence.
A reduction of dosage may be required.

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.

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

Care should be exercised when levodopa/carbidopa 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 and dosage adjustments.

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

Levodopa/carbidopa is not recommended in the treatment of drug-induced extrapyramidal reactions and in the treatment of Huntington’s chorea.

<u>Abrupt withdrawal</u>
A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes and elevated serum creatine phosphokinase has been reported with the abrupt withdrawal of antiparkinsonian agents. Therefore, any abrupt dosage reduction or withdrawal of Co-Careldopa should be carefully observed, particularly in patients who are also receiving neuroleptics.

Dopamine dysregulation syndrome (DDS)
Dopamine dysregulation syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with levodopa/carbidopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS (see also section 4.8).

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 Co-Careldopa. Review of treatment is recommended if such symptoms develop.

Somnolence and episodes of sudden sleep onset
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.

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

General anaesthesia
If general anaesthesia is required, therapy with levodopa/carbidopa 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, levodopa/carbidopa may be restarted as soon as oral medication can be taken at the same daily dosage as before.

Melanoma
Epidemiological studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population (approximately 2-6 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 levodopa/carbidopa 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 levodopa/carbidopa 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 levodopa/carbidopa and levodopa alone.
Co-Careldopa 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 levodopa/carbidopa:

Antihypertensive agents
Postural hypotension can occur when levodopa/carbidopa 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 and levodopa/carbidopa (for patients receiving monoamine oxidase A inhibitors, see section 4.3).

Anticholinergic agents
Anticholinergic agents may act synergistically with levodopa to decrease tremor and this interaction is often used to therapeutic advantage; however they can exacerbate abnormal involuntary movements. They may impair the effect of levodopa due to a delayed absorption.

Iron
Studies demonstrate a decrease in the bioavailability of carbidopa and/or levodopa when it is ingested with ferrous sulphate or ferrous gluconate. Reductions of 30 % to 50 % in the AUC of levodopa and more than 75 % in the AUC of carbidopa have been observed.

Selegiline
Concomitant therapy with selegiline and levodopa/carbidopa may be associated with severe orthostatic hypotension not attributable to levodopa/carbidopa alone (see section 4.3).

Sympathomimetic agents
Concomitant administration of levodopa/carbidopa with sympathomimetics may potentiate their effects, and the dose of the sympathomimetic agents may need to be reduced.

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. metoclopramide, phenothiazines, butyrophenones, and risperidone), benzodiazepines 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 levodopa/carbidopa should be carefully observed for loss of therapeutic response.

Use of levodopa/carbidopa with dopamine-depleting agents (e.g. reserpine tetrabenazine) or other drugs known to deplete monoamine stores is not recommended.

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Although the effects of carbidopa/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 levodopa/carbidopa in women of childbearing potential requires that the anticipated benefits of the drug 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 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 carbidopa/levodopa, 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 such as sleepiness, dizziness and confusion have been reported with levodopa/carbidopa which 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 section 4.4).

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

Adverse reactions from clinical trials and post-marketing experience are per System Organ Class and per frequency. The frequency is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data)

System Organ Class / Frequency	**Adverse Drug Reaction**
Infections and infestations	
Very common	Urinary tract infections
Blood and lymphatic system disorders	
Rare	Leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia
Very rare	Agranulocytosis
Metabolism and nutrition disorders	
Common	Anorexia
Uncommon	Weight gain or loss
Psychiatric disorders	
Common	Hallucinations, insomnia, euphoria, depression with or without development of suicidal tendencies, dementia, sense of stimulation, dream abnormalities, , confusion,
Rare	Agitation, anxiety, decreased mental acuity, disorientation, increased libido, psychotic episodes including delusions and paranoid ideation
Not known	Dopamine dysregulation syndrome
Nervous system disorders	
Common	Dizziness, dyskinesia including choreiform, dystonic and other involuntary movements, bradykinetic episodes (the 'on-off' phenomenon), syncope
Uncommon	Ataxia, increased hand tremor
Rare	Headache, numbness, convulsions[1], malignant neuroleptic syndrome, paraesthesia, falling, gait abnormalities, trismus, blepharospasm, activation of latent Horner's syndrome
Very rare	Somnolence (very rarely associated with excessive daytime somnolence and sudden sleep onset episodes)

Eye disorders	
Rare	Diplopia, blurred vision, dilated pupils, oculogyric crises
Cardiac disorders	
Common	Cardiac irregularities and/or palpitations
Vascular disorders	
Common	Orthostatic effects including hypotensive episodes
Uncommon	Hypertension
Rare	Phlebitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Hoarseness
Rare	Dyspnoea, abnormal breathing patterns
Gastrointestinal disorders	
Common	Nausea, vomiting, dry mouth, bitter taste
Uncommon	Constipation, diarrhoea, sialorrhoea, dysphagia, flatulence
Rare	Dyspepsia, abdominal pain and distress, dark saliva, bruxism, hiccups, gastrointestinal bleeding, burning sensation of the tongue, development of duodenal ulcer
Skin and subcutaneous tissue disorders	
Uncommon	Oedema
Rare	Angioedema, urticaria, pruritus, flushing, Henoch-Schonlein purpura, alopecia, rash, increased sweating, dark sweat
Not known	Malignant melanoma (see sections 4.3 and 4.4)
Musculoskeletal, connective tissues, and bone disorders	
Uncommon	Muscle cramp
Not known	Muscle twitching
Renal and urinary disorders	
Uncommon	Dark urine
Rare	Urinary retention, urinary incontinence
Reproductive system and breast disorders	
Rare	Priapism
General disorders and administration site conditions	
Common	Fatigue, faintness
Uncommon	Chest pain, asthenia, malaise, hot flushes, weakness

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

Description of selected adverse reactions

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 Co-Careldopa (see section 4.4).

Dopamine Dysregulation Syndrome (DDS)

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder seen in some patients treated with levodopa/carbidopa. 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 (see also section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard, or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

In case of overdose, general supportive measures should be taken along with immediate gastric lavage if the drug has been taken recently. Intravenous fluids must be administered proficiently and the airways must be kept open. 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 levodopa/carbidopa 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

Pharmacotherapeutic group: dopaminergic agents; levodopa and decarboxylase inhibitor

ATC Code: N04BA02

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.

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

Although pyridoxine hydrochloride (vitamin B6) is known to accelerate the peripheral conversion of levodopa to dopamine, carbidopa inhibits this action.

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 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In reproductive toxicity studies both levodopa and the combination of levodopa/carbidopa have caused visceral and skeletal malformations in rabbits.
The potential risk for humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised maize starch

Maize starch

Microcrystalline cellulose

Quinoline yellow aluminium lake (E104)

Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Bottles: 4 years

Blisters: 3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

HDPE bottles with metal screw cap: 100, 500 and 1000 tablets.

HDPE bottles with child resistant tamper evident screw cap: 100 tablets

Cardboard boxes with PVC/aluminium blister strips: 20, 30, 50, 60, 100 and 200 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited, Ridings Point, Whistler Drive, Castleford, WF10 5HX, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0784

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