# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Carbidopa and Levodopa Crescent 25 mg/100 mg tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains carbidopa monohydrate equivalent to 25 mg carbidopa and 100 mg levodopa.

For the full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Tablet.

Round shaped light yellow coloured tablet, with ‘C” on one side and “19” on other side of tablet. The tablet dimensions are 8.00 ± 0.2mm.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For the treatment of Parkinson’s disease and syndrome.

### 4.2 Posology and method of administration

Posology

The optimum daily dosage of Carbidopa and Levodopa Crescent must be determined by careful titration in each patient.

Carbidopa and Levodopa Crescent Tablets are available in two strengths (25 mg/100 mg and 12.5 mg/50 mg) 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 Carbidopa and Levodopa is being administered, although their dosage may have to be adjusted.
Because both therapeutic and adverse effects are seen more rapidly with Carbidopa and 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.

**Patients not receiving levodopa**
Dosage may be best initiated with one tablet of Carbidopa and Levodopa Crescent 25 mg/100 mg three times a day. This dosage schedule provides 75 mg of carbidopa per day. Dosage may be increased by one tablet of Carbidopa and Levodopa Crescent 12.5 mg/50 mg or Carbidopa and Levodopa Crescent 25 mg/100 mg every day or every other day, as necessary, until a dosage equivalent of eight tablets of Carbidopa and Levodopa Crescent 25 mg/100 mg a day is reached.

If Carbidopa and Levodopa Crescent 12.5 mg/50 mg Tablets are used, dosage may be initiated with one tablet three or four times a day. Titration upward may be required in some patients to achieve optimum dosage of carbidopa. The dosage may be increased by one tablet every day or every other day until a total of eight tablets (two tablets q.d.s.) is reached.

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.

Carbidopa and Levodopa Crescent 12.5 mg/50 mg Tablets may be used to facilitate dosage titration according to the needs of the individual patient.

**Patients receiving levodopa**

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

Patients taking less than 1,500 mg levodopa a day should be started on one tablet of Carbidopa and Levodopa Crescent 25 mg/100 mg three or four times a day dependent on patient need. The suggested starting dose for most patients taking more than 1,500 mg levodopa a day is one tablet of Carbidopa and Levodopa Crescent 25 mg/250 mg three or four times a day.

**Maintenance**
Therapy with Carbidopa and Levodopa Crescent should be individualised and adjusted gradually according to response.

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 Carbidopa and Levodopa Crescent from levodopa

combined with another decarboxylase inhibitor, discontinue dosage at least 12 hours before Carbidopa and Levodopa Crescent is started. Begin with a dosage of Carbidopa and Levodopa Crescent 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 Carbidopa and Levodopa is introduced, although dosage may have to be adjusted in line with manufacturers recommendations.

*Paediatric population*
The safety and efficacy of Carbidopa and Levodopa in children 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

For oral use.

If a tablet breaks when it is removed from the packaging, it should only be consumed if the whole dose can be taken. If it cannot, the pieces of the broken tablet should be discarded and another tablet taken from the packaging.

Administration of a partial dose may result in worsening of symptoms

## 4.3 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). (See section 4.5 'Interaction with other medicinal products and other forms of interaction'.)
Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Carbidopa and Levodopa is contraindicated in patients with narrow-angle glaucoma.

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

Use in patients with severe psychoses.

See also section 4.6 'Fertility, pregnancy and lactation'.

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

As with levodopa, periodic evaluation of hepatic, 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 intra-ocular pressure is well controlled and the patient monitored carefully for changes in intra-ocular pressure during therapy.

If general anaesthesia is required, therapy with 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 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 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 and levodopa.
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 Carbidopa and Levodopa . Review of treatment is recommended if such symptoms develop

## 4.5 Interaction with other medicinal products and other forms of 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 (see first paragraph of section 4.3 'Contraindications' for patients receiving MAOIs).

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

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

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

Dopamine $D_2$ 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 Carbidopa and Levodopa should be carefully observed for loss of therapeutic response.

Use of Carbidopa and Levodopa with dopamine-depleting 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 (see section 4.3 'Contraindications').

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).

## 4.6 Fertility, 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
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 and 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 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 or serious injury or death (e.g. operating machines), until such recurrent episodes and somnolence have resolved (see also section 4.4 'Special warnings and precautions for use').

## 4.8 Undesirable effects

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

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

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

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

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

*Haemotologic*: leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis.

*Hypersensitivity*: angioedema, urticaria, pruritus, Henoch-Schonlein purpura. Infections and Infestations: urinary tract infections (very common).

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

*Respiratory*: dyspnoea.

*Skin*: alopecia, rash, dark sweat.

*Urogenital*: dark urine.

Rarely, convulsions have occurred; however, a causal relationship with 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 and 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 (see also section 4.4).

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 (see section 4.4. 'Special warnings and precautions for use').

*Skin*: flushing, increased sweating.

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

*Urogenital*: urinary retention, urinary incontinence, priapism.

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

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 at 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 Carbidopa and Levodopa is basically the same as management of acute overdosage 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 anti-arrhythmic 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 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: Anti-Parkinson drugs
ATC code: N04BA02

Mechanism of action
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.

Pharmacodynamics 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

## 5.2 Pharmacokinetic properties

Absorption

Following oral dosing levodopa, in the absence of decarboxylase inhibitor, is rapidly but variably absorbed from the gastro-intestinal 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 gastro-intestinal 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

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

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Crospovidone XL

Yellow iron oxide (E172)

Pregelatinised Starch

Pregelatinized maize starch

Microcrystalline cellulose-102

Magnesium stearate

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

2 years

## 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

## 6.5 Nature and contents of container

Carbidopa and Levodopa Crescent tablets are available in Alu-Alu blister Packs.

Pack sizes: 20,30,50,60,90,100,120,180, and 200 tablets.
Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

No special requirements

## 7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
Key House
Sarum Hill, Basingstoke
RG21 8SR
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0953

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/05/2025

## 10 DATE OF REVISION OF THE TEXT

01/05/2025