# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Carbidopa/Levodopa Orion 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.

White or off-white, round tablet, 10 mm in diameter which is scored and marked "LC 100" on one side. The tablet can be divided into equal doses.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Carbidopa/Levodopa Orion is indicated for the treatment of Parkinson's disease in adults.

### 4.2 Posology and method of administration

Posology
The optimal carbidopa/levodopa dosage should be determined individually by careful titration. The ratio of carbidopa and levodopa in Carbidopa/Levodopa Orion tablets is 1:4 (Carbidopa/Levodopa Orion 25 mg/100 mg and Carbidopa/Levodopa Orion 12.5 mg/50 mg).

For doses not practicable with this medicinal product, please refer to other authorized medicinal products containing levodopa and carbidopa.
*General considerations:* The dosage should be adjusted to individual patient needs. This may require adjusting both the individual dose and the frequency of administration.

Studies show that carbidopa inhibits the function of peripheral dopadecarboxylase at daily doses of about 70–100 mg. Patients receiving smaller carbidopa doses than this are more likely to experience nausea and vomiting.

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

*The usual initial dose:* The recommended initial dose is one Carbidopa/Levodopa Orion 25 mg/100 mg tablet three times daily. The daily dose of carbidopa is then 75 mg. The dosage may be increased by adding one tablet to the regimen every day or every other day as necessary, until the total daily dose is equivalent to eight Carbidopa/Levodopa Orion 25 mg/100 mg tablets.

Carbidopa/Levodopa Orion 12.5 mg/50 mg tablets may be used to facilitate adjusting the dose to individual patient needs.

If Carbidopa/Levodopa Orion 12.5 mg/50 mg tablets are used, treatment may be initiated by administering one tablet three or four times daily. However, this may not provide the optimal amount of carbidopa many patients need. The dose may be increased by one tablet every day or every other day until the total dose is eight tablets (two tablets four times daily).

Response has been observed within one day, occasionally already after one dose. A fully effective dose is usually reached within seven days. This takes weeks or months when levodopa is used alone.

*Maintenance therapy:* Treatment should be adjusted individually and according to the desired therapeutic response. A carbidopa dose of at least 70–100 mg/day is needed for optimal inhibition of peripheral dopa-decarboxylation of levodopa.

If necessary, the dosage of Carbidopa/Levodopa Orion 25 mg/100 mg tablets 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.

*Discontinuation of treatment:* If treatment with Carbidopa/Levodopa Orion must be discontinued temporarily, eg before anaesthesia, the usual daily dose should be reinstated as soon as oral medication is possible.

*Paediatric population*
The safety and efficacy in children have not been established, and therefore Carbidopa/Levodopa Orion is not recommended for children aged under 18 years.

Method of administration
Orally

**4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

The use of non-selective monoamineoxidase inhibitors (MAOIs) is contraindicated in connection with the use of carbidopa/levodopa. The use of MAOIs must be discontinued at least two weeks before initiating carbidopa/levodopa therapy. Carbidopa/levodopa may be used concomitantly with selective MAO-B inhibitors (e.g. selegiline hydrochloride) at doses recommended by the manufacturers of these medicines (see section 4.5 *Other medicines*).

Conditions in which adrenergics are contraindicated, e.g. pheochromocytoma, hyperthyroidism, Cushing's syndrome, severe cardiovascular diseases.

Carbidopa/levodopa must not be administered to patients with narrow-angle glaucoma.

As levodopa may activate malignant melanoma, carbidopa/levodopa must not be administered to patients with suspicious undiagnosed skin lesions or a history of melanoma.

**4.4 Special warnings and precautions for use**

Carbidopa/levodopa is not recommended for the treatment of medicine-induced extrapyramidal symptoms.

As with levodopa, carbidopa/levodopa may cause involuntary movements and psychiatric disorders. These effects are assumed to be due to the increased dopamine concentrations in the brain, and continuing carbidopa/levodopa therapy may cause recurrence of the symptoms. Dose reduction may be necessary in such cases. All patients should be carefully monitored for signs of mental changes, early depression and associated suicidal tendencies. Caution should be exercised when treating patients with a history of psychosis or with current psychosis.

Caution should be exercised in concomitant use of psychopharmaceuticals and carbidopa/levodopa tablets (see section 4.5).

Caution should be exercised when using carbidopa/levodopa in patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrinological disease, or a history of peptic ulcer (due to the risk of upper gastrointestinal bleeding), or convulsions.

As with levodopa, caution should be exercised when administering carbidopa/levodopa to patients with a history of recent myocardial infarction who have atrial, ventricular or nodal arrhythmias. In such cases, cardiac function should be monitored with particular care at the start of therapy and during dose adjustment.

Carbidopa/levodopa may be used with caution in patients with chronic open-angle glaucoma, provided that intraocular pressure is well controlled and is monitored carefully for any changes during therapy.

A syndrome resembling neuroleptic malignant syndrome, involving muscle stiffness, increased body temperature, mental changes and increased serum creatine kinase levels, has been observed in connection with abrupt discontinuation of anti-parkinson medication. Therefore the patient's condition should be carefully monitored if the dosage of carbidopa/levodopa is reduced abruptly or the treatment is discontinued, especially if the patient is using neuroleptics.

*Day-time somnolence and sleep episodes:* Somnolence and sleep episodes have been observed in connection with the use of levodopa (see section 4.8). Sudden sleep episodes during the day, in some cases without awareness or preceding symptoms, have been reported in very rare cases. Patients should be informed about this and advised to exercise caution when driving a motor vehicle or operating machinery during levodopa therapy. Patients who have experienced somnolence and/or sudden sleep episodes should avoid driving a motor vehicle and operating machinery.

As with levodopa, regular monitoring of hepatic, haematopoietic, cardiovascular and renal function is recommended during long-term therapy (see section 4.8).

If general anaesthesia is required, carbidopa/levodopa therapy may be continued for as long as oral ingestion of fluids and medicines is permitted. If the treatment is interrupted, administration of the normal daily dose may be continued as soon as the patient is able to take medicines by mouth.

*Melanoma:* Epidemiological studies have shown that the risk of developing melanoma is higher (2- to approximately 6-fold) in patients with Parkinson's disease than in the general population. It has not been investigated whether the increased risk is due to Parkinson's disease or other factors, such as medicines used for the treatment of Parkinson's disease.

Due to the reasons mentioned above, the patient and the healthcare team are advised to monitor the patient's skin often and regularly for any signs of melanoma when the patient is using carbidopa/levodopa for any indication. In an ideal situation, an expert (such as a dermatologist) should examine the patient's skin at times.

Dopamine dysregulation syndrome (DDS) is an addictive disorder diagnosed in some patients treated with the combination of carbidopa and levodopa, and results in excessive use of the product. Before treatment initiation, patients and their carers must be warned about the risk of DDS (see also section 4.8).

*Impulse control disorders:* The patient's condition should be regularly monitored to detect any impulse control disorders (see section 4.8). Patients and their carers should be informed that behavioural symptoms associated with impulse control disorders (such as pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating) may occur in patients using a dopamine agonist or another levodopa-containing dopaminergic
medicine such as carbidopa/levodopa. Treatment re-assessment is recommended if such symptoms occur.

*Orthostatic hypotension:* Carbidopa/levodopa may induce orthostatic hypotension. Therefore carbidopa/levodopa should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension (see also sections 4.5 and 4.8).

Excipient
This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

**4.5 Interaction with other medicinal products and other forms of interaction**

Caution should be exercised when using carbidopa/levodopa in combination with the following medicines:

*Antidepressants*
Monoamineoxidase inhibitors are contraindicated in patients treated with carbidopa/levodopa (see section 4.3). In some rare cases, concomitant use of carbidopa/levodopa and tricyclic antidepressants has been associated with adverse effects, such as hypertension and movement disorders.

*Antihypertensives*
Symptomatic postural hypotension has occurred when carbidopa/levodopa has been added to the treatment regimen of patients receiving antihypertensives. Therefore, the dosage of the antihypertensive medicine may have to be adjusted when carbidopa/levodopa therapy is started.

*Iron products*
Studies have shown that the bioavailability of carbidopa and/or levodopa has decreased when taken with ferrous sulfate or ferrous gluconate.
Therefore, administration of carbidopa/levodopa and iron preparations should be separated by the longest possible interval in time.

*Anticholinergics*
Anticholinergics may act synergistically with levodopa to decrease tremor. However, combined use may exacerbate abnormal involuntary movements. Anticholinergics may decrease the effects of levodopa by delaying its absorption. An adjustment of the dose of carbidopa/levodopa may be needed.

*COMT inhibitors (tolcapone, entacapone)*
Concomitant use of COMT (Catechol-O-Methyl Transferase) inhibitors and carbidopa/levodopa can increase the bioavailability of levodopa. The dose of carbidopa/levodopa may need adjustment.

*Other medicines*
*D2 dopamine receptor antagonists*
D2 dopamine receptor antagonists (e.g. phenothiazines, butyrophenones and risperidone) and isoniazide may reduce the therapeutic effects of levodopa. In addition, phenytoin and papaverine have been found to reverse the beneficial effects of levodopa in the treatment of Parkinson's disease. Patients receiving these medicines concomitantly with carbidopa/levodopa therapy should be monitored carefully for any loss of therapeutic response.

Carbidopa/Levodopa Orion may be given to patients with parkinsonism who are taking vitamin preparations that contain pyridoxine hydrochloride (Vitamin B6).

Amantadine has synergic effect with levodopa and may increase levodopa related adverse events. An adjustment of the dose of carbidopa/levodopa may be needed.

Sympathicomimetics may increase cardiovascular adverse events related to levodopa.

Concomitant use of medicines (such as reserpine and tetrabenazine) causing deficiency of dopamine and other monoamines is not recommended with carbidopa/levodopa.

*Serious orthostatic hypotension*
Serious orthostatic hypotension has been associated with concomitant use of selegiline and a carbidopa-levodopa preparation, which cannot be attributed to carbidopa-levodopa.

As levodopa competes with certain amino acids, a protein-rich diet may reduce its absorption.

**4.6 Fertility, pregnancy and lactation**

Pregnancy
The effects of carbidopa/levodopa on human pregnancy are unknown, but both levodopa and carbidopa as well as levodopa combinations have caused visceral and skeletal malformations in rabbits (see section 5.3). Administering carbidopa/levodopa to women who can become pregnant therefore requires weighing the possible benefits of the medicine and risks during pregnancy.

Breast-feeding
It is unknown whether carbidopa is excreted in human milk. Levodopa was reported to be excreted in human milk in a study in which a breastfeeding mother with Parkinson's disease received levodopa therapy. As many medicines are excreted in human milk and serious adverse effects to the child are possible, a decision must be made whether to discontinue breast-feeding or to discontinue carbidopa/levodopa therapy, taking into account the benefit of therapy for the woman.

Fertility
In preclinical studies no adverse effects on fertility were detected when administering carbidopa alone or concomitantly with levodopa. See also section 5.3.

**4.7 Effects on ability to drive and use machines**

Carbidopa/levodopa may cause adverse effects, such as dizziness and somnolence, which may affect the patient's ability to drive and operate machinery (see also section 4.8).

Patients receiving levodopa who experience somnolence and/or sudden sleep episodes must be advised to avoid driving a motor vehicle and performing other tasks (e.g. operating machinery) where impaired reaction ability might cause a risk of

serious injury or death to themselves or to others, until repeated sleep episodes and somnolence have resolved (see also section 4.4).

**4.8 Undesirable effects**

Adverse effects occurring commonly in patients receiving carbidopa/levodopa therapy are due to the neuropharmacological CNS effects of dopamine. They can usually be alleviated by reducing the dosage. The most common adverse effects are movement disorders, such as muscle tone disorders resembling chorea and other involuntary movements, and nausea. Muscle twitching and blepharospasm may be taken as early signs to consider dosage reduction.

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).

Other adverse effects reported in clinical studies or in clinical use include:

| **Organ system** | **Frequency** | **Adverse effect** |
|---|---|---|
| Infections and infestations | Very common | Urinary tract infections |
| Blood and lymphatic system disorders | Rare | Leukopaenia, haemolytic and non-haemolytic anaemia, thrombocytopaenia, agranulocytosis |
| Metabolism and nutrition disorders | Common | Loss of appetite |
| Psychiatric disorders | Common | Hallucinations, depression that may involve suicidal tendencies, confusion, abnormal dreams |
| | Uncommon | Agitation |
| | Rare | Psychotic episodes such as delusions and paranoia |
| | Not known | Dopamine dysregulation syndrome |
| Nervous system disorders | Very common | Movement disorders (such as those resembling chorea), muscle tone disorders and other compulsive movements |
| | Common | Episodes of slow movement (the "on-off" phenomenon), dizziness, sensory disturbances, somnolence including very rare cases of excessive day-time somnolence and sudden sleep episodes |
| | Uncommon | Fainting |
| | Rare | Neurolepticsyndrome (see section 4.4), dementia. Convulsions have occurredrarely, but a causal relationship with carbidopa/levodopa therapy has not been established. |
| Cardiac disorders | Common | Palpitations |
| | Rare | Irregular cardiac function |
| Vascular disorders | Common | Orthostatic effects, such as hypotensive episodes |
| | Rare | Hypertension, vein inflammation |
| Respiratory, thoracic and mediastinal disorders | Common | Shortness of breath |
| Gastrointestinal disorders | Common | Nausea, vomiting, diarrhoea |
| | Rare | Gastrointestinal bleeding, duodenal ulcer, dark saliva |
| Skin and subcutaneous tissue disorders | Uncommon | Hives |
| | Rare | Itching, Henoch Schönlein purpura, alopecia, rash, dark sweat, angioedema |
| Musculoskeletal and connective tissue disorders | Uncommon | Muscle twitching |
| Renal and urinary disorders | Rare | Dark urine |
| General disorders and administration site conditions | Common | Chest pain |

*MedDRA Other adverse effects that have been observed in connection with levodopa therapy or carbidopa/levodopa combination therapy and that may be associated with carbidopa/levodopa therapy include:*

| **Organ system** | **Adverse effect** |
|---|---|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Malign melanoma (see section 4.3) |
| Psychiatric disorders | Insomnia, anxiety, euphoria, disorientation, bruxism |

| | |
|---|---|
| | Dopamine dysregulation syndrome (DDS) is an addictive disorder diagnosed in some patients treated with the combination of carbidopa and levodopa. It involves compulsive abuse of a dopaminergic medicine and using higher than necessary medicine doses to alleviate motor symptoms. This may sometimes result in severe dyskinesias (see also section 4.4).<br><br>Impulse control disorders:Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating have been reported in patients who have used a dopamine agonist and/or another dopaminergic medicineand in rare cases in patients who have used levodopa, including carbidopa/levodopa (see section 4.4). |
| Nervous system disorders | Impaired alertness, agitation, bitter taste in the mouth, weakness, headache, activation of latent Horner's syndrome, ataxia, increased hand tremor, numbness |
| Eye disorders | Diplopia, blurred vision, dilated pupils, eye cramp, blepharospasm |
| Vascular disorders | Hot flushes, flushing |
| Respiratory, thoracic and mediastinal disorders | Hoarseness, changes in breathing rhythm, hiccups |
| Gastrointestinal disorders | Dry mouth, increased salivation, trouble swallowing, abdominal pain and other abdominal symptoms, constipation, flatulence, upper abdominal complaints, tongue stinging |
| Skin and subcutaneous tissue disorders | Increased sweating |
| Musculoskeletal and connective tissue disorders | Muscle cramps, trismus |
| Renal and urinary disorders | Urinary retention, urinary incontinence |
| Reproductive system and breast disorders | Priapism |
| General disorders and administration site conditions | Asthenia, malaise, swelling, weakness, fatigue, walking difficulties |
| Investigations | Weight gain or loss<br>Changes in laboratory values have been detected in patients receiving combination therapy with carbidopa and levodopa and may therefore also occur with carbidopa/levodopa.<br>These include elevated liver function test results, such as alkaline phosphatase, AST, ALT and lactate dehydrogenase, bilirubin and blood urea, creatinine, urate, and positive Coombs' test.<br>Decreased haemoglobin and haematocrit values, elevated serum glucose, as well as white blood cells, bacteria and blood in the urine have occurred.<br>Carbidopa-levodopa preparations may cause false positive reactions for urinary ketone bodies when a test strip is used in the determination of ketonuria. This reaction will not be altered by boiling the urine sample.<br>False negative results may occur when glucose oxidase methods are used to test for glucosuria. |
| Injury, poisoning and procedural complications | Falling tendency |

**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 HPRA Pharmacovigilance website: www.hpra.ie.

**4.9 Overdose**

Toxicity: 100 mg administered to 2-year-old did not cause any symptoms after administration of charcoal. 5 g administered to adult gave moderate intoxication.

Symptoms:
Nausea, vomiting, restlessness, motor restlessness, agitation, dyskinesias, chorea-like movements, hallucinations, seizures, sinus tachycardia, hypertension (may be followed by postural hypotension) and electrolyte disturbances.
In some cases rhabdomyolysis and renal failure.

Treatment:
Treatment of acute overdose with carbidopa/levodopa is broadly the same as treatment of acute overdose with levodopa, however, pyridoxine does not effectively counteract the effects of carbidopa/levodopa.

ECG monitoring should be initiated and the patient monitored carefully for any arrhythmias. Appropriate antiarrhythmic therapy should be given as necessary. It should also be noted that in addition to carbidopa/levodopa tablets, the patient may also have taken other medicines. To date, there is no experience of the use of dialysis, and therefore its significance in the management of an overdose is unknown.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-parkinson drugs, Dopa and dopa derivatives, ATC code: N04BA02

Mechanism of action
Carbidopa/levodopa is a combination of carbidopa, an aromatic amino acid decarboxylase inhibitor, and levodopa, the metabolic precursor of dopamine, for the treatment of Parkinson's disease. Carbidopa/levodopa is effective in alleviating many symptoms of Parkinson's disease, particularly muscle stiffness and bradykinesia. Carbidopa/levodopa reduces tremor, swallowing difficulties, sialorrhoea and postural instability often associated with Parkinson's disease.
The symptoms of Parkinson's disease have been associated with the emptying of dopamine stores in the *corpus striatum* of the brain. Levodopa alleviates symptoms of Parkinson's disease by decarboxylating into dopamine in the brain.
Following oral administration, levodopa is rapidly decarboxylated into dopamine in extracerebral tissues, and only a small amount of levodopa enters the central nervous system unchanged. Therefore, administration of high levodopa doses at short intervals is necessary to achieve a sufficient therapeutic response. This often causes various adverse effects, some of which are due to dopamine formed in extracerebral tissues.

Carbidopa, which does not cross the blood-brain barrier, inhibits decarboxylation of levodopa in extracerebral tissues, leaving more levodopa available for transport to the brain and subsequent conversion to dopamine. As carbidopa/levodopa reduces some of the adverse effects that occur with levodopa monotherapy, achieving alleviation of symptoms of Parkinson's disease with carbidopa/levodopa is possible in a greater number of patients.

Pharmacodynamic effects
The decarboxylase-inhibiting effect of carbidopa is limited to extracerebral tissues, so the combination use of carbidopa and levodopa permits a higher amount of levodopa to enter the brain. When carbidopa and levodopa were administered concomitantly, the levodopa concentration in plasma was considerably higher than with the same dose of levodopa alone, while the plasma concentrations of the two main metabolites of levodopa, dopamine and homovanillic acid, were considerably reduced.

The carbidopa component of carbidopa/levodopa does not reduce adverse effects caused by the CNS effects of levodopa. As carbidopa/levodopa permits higher amounts of levodopa to enter the brain, particularly when nausea and vomiting are not dose-limiting factors, certain adverse effects of CNS origin, e.g. dyskinesias, may occur at lower dose levels and sooner during carbidopa/levodopa therapy than with levodopa therapy.

At oral doses of 10–25 mg, pyridoxine hydrochloride (vitamin B6) has been found to reverse the antiparkinsonian effects of levodopa rapidly.
Pyridoxine hydrochloride (vitamin $B_6$) is known to accelerate the metabolism of levodopa into dopamine in peripheral tissues, but carbidopa prevents this effect. No cancellation of therapeutic effect was seen in a study where patients receiving a combination of carbidopa and levodopa were given 100–500 mg of pyridoxine daily.

Paediatric population

Instructions on the treatment of paediatric patients, see section 4.2.

**5.2 Pharmacokinetic properties**

Absorption

*Half-life.* The half-life of levodopa in plasma is approximately 50 minutes. When carbidopa and levodopa are administered concurrently, the half-life of levodopa is prolonged to about 1.5 hours.

*Onset of action when using standard doses.* Response has been observed within one day, occasionally already after one dose. Full therapeutic effect is usually achieved within seven days.

Biotransformation

*Metabolism of carbidopa.* When radiolabelled carbidopa was administered orally to healthy subjects and to patients with Parkinson's disease, the peak plasma levels of radioactivity were achieved within 2–4 hours in healthy subjects and within 1.5–5 hours in patients. Approximately equal quantities were excreted in the urine and in the faeces in both groups.

Comparison of urinary metabolites in healthy subjects and patients indicated that the medicinal agent was metabolised to the same extent in both groups. In practical terms, unchanged medicinal agent was excreted in the urine for 7 hours and accounted for 35% of the total radioactivity excreted in the urine. After this, only metabolites were excreted. No hydrazines were observed.

Metabolites observed in the human body include α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid. In studies, these accounted for 14% and 10%, respectively, of the total amount of radioactive metabolites excreted. In addition, two minor metabolites were detected; one was identified as 3,4-dihydroxyphenylacetone and the other was tentatively identified as N-methylcarbidopa. Both accounted for less than 5% of the total amount of metabolites excreted in the urine. Unchanged carbidopa was also excreted in the urine. No conjugates were observed.

*Metabolism of levodopa.* Levodopa is rapidly absorbed from the gastrointestinal tract and extensively metabolised. More than 30 metabolites may be formed, but it is mainly metabolised to dopamine, epinephrine and norepinephrine, and further to dihydroxyphenylacetic acid, homovanillic acid and vanillylmandelic acid. 3-O-methyldopa appears in plasma and cerebrospinal fluid. Its significance is unknown.

When single doses of radioactive levodopa are given to fasting patients with Parkinson's disease, the peak plasma level of radioactivity is achieved within 0.5–2 hours, and the radioactivity remains measurable for 4–6 hours.
About 30% of the radioactivity in connection with peak concentrations appears as catecholamines, 15% as dopamine, and 10% as dopa. The radioactive compounds are rapidly excreted in the urine, and one-third of the dose can be detected in the urine within 2 hours. In the urine, 80–90 % of the metabolites are phenylcarboxylic acids, mainly homovanillic acid. Over 24 hours, 1–2 % of recovered radioactivity is dopamine, and less than 1% is epinephrine, norepinephrine and unchanged levodopa.

*The effect of carbidopa on the metabolism of levodopa*. In studies on healthy subjects, carbidopa increased the plasma levodopa concentration statistically significantly compared to placebo. The effect was observed both when carbidopa was given before levodopa and when both medicinal agents were administered simultaneously. In one study, prior carbidopa administration increased the plasma levodopa concentration achieved with a single dose about 5-fold and extended the duration of measurable plasma levodopa concentrations from 4 hours to 8 hours. Similar results have been achieved in studies where the medicinal agents were administered simultaneously.

In a study where patients with Parkinson's disease were given carbidopa and subsequently a single dose of stem-labelled levodopa, the half-life of total plasma radioactivity derived from levodopa was prolonged from 3 hours to 15 hours. Carbidopa increased the proportion of radioactivity derived from unchanged levodopa at least 3-fold. Prior carbidopa administration reduced the amount of dopamine and homovanillic acid in both plasma and urine.

**5.3 Preclinical safety data**

*Toxicology examinations*. The $LD_{50}$ value of orally administered carbidopa is 1 750 mg/kg in adult female mice, 4 810 mg/kg in young adult female rats, and 5 610 mg/kg in young adult male rats. The acute toxicity of orally administered carbidopa is similar in recently weaned and adult rats, but it is more toxic for newborn rats. In studies, the effects of the medicinal agent

were similar in mice and rats, causing ptosis of the eyelids, ataxia, and reduced activity. Decrease in breathing rhythm was observed in mice. The animals usually died within 12 hours, but some deaths were observed up to 12 days later.

The $LD_{50}$ value of orally administered levodopa varies from 800 mg/kg observed in newborn male and female rats to 2 260 mg/kg observed in young adult female rats. In animal studies, levodopa caused vocalisation, irritability, excitation, ataxia and increased activity that were followed by reduced activity within 1–2 hours. The animals usually died within 30 minutes to 12 hours, but some deaths were observed up to 5 days later.

The $LD_{50}$ values of various oral combinations of carbidopa and levodopa in mice vary from 1 930 mg/kg (carbidopa/levodopa ratio 1:1) to 3 270 mg/kg (carbidopa/levodopa ratio 1:3). The figures indicate the total carbidopa/levodopa dose. In studies, $LD_{50}$ values observed with the ratio of 1:3 were not essentially changed at ratios of 1:4, 1:5 and 1:10. Ratios of 1:3, 1:4, 1:5 and 1:10 were less toxic than ratios of 1:1 and 1:2. Symptoms of toxicity included vertical position of the tail, piloerection, ataxia, lacrimation and increased activity. At 1 500 mg/kg and higher doses, clonic convulsions and increased irritability were observed. At 4 120 mg/kg and higher doses, coarse tremor of the head and the body was observed. At doses of 4 120–5 780 mg/kg, the animals usually died within 30 minutes to 12 hours, and at the dose level of 2 940 mg/kg deaths were observed up to 12 days later.

Long-term toxicity of orally administered carbidopa has been investigated at daily doses of 25–135 mg/kg in one-year studies in monkeys and in 96-week studies in rats. No effects attributable to the medicinal agent were observed in monkeys. Atony occurred in some rats in all dosage groups. In the group of rats receiving the highest dosage, the average weight of kidneys was significantly greater than in comparable controls, although no macroscopical or microscopical changes explaining this finding were found. There were no histological changes attributable to the exposure. Carbidopa had no effect on tumour types or the incidence of tumours in a 96-week study in rats.

In dogs, carbidopa caused pyridoxine deficiency, which could be prevented by concurrent administration of pyridoxine.

With the exception of pyridoxine deficiency observed in dogs, no hydrazine-associated toxicity has been observed with carbidopa.

When carbidopa and levodopa were administered orally at three different dose ratios to monkeys for 54 weeks and to rats for 106 weeks, the primary physical effects were due to the pharmacological effects of the medicinal agents. The dosages used in the study were (carbidopa/levodopa) 10/20, 10/50 and 10/100 mg/kg/day. No clear physical effects were observed at the dose level of 10/20 mg/kg/day.

Hyperactivity was observed in monkeys at the dose levels of 10/50 and 10/100 mg/kg/day. Hyperactivity persisted for 32 weeks at the dosage of 10/100 mg/kg/day, but at the dosage of 10/50 mg/kg/day it was reduced as the study continued and was no longer observed after 14 weeks. At the dose level of 10/100 mg/kg/day, reduced muscular coordination and muscle weakness were observed up until study week 22. No morphological changes were observed in pathological examinations.

Reduced activity and abnormalities in body posture were observed in rats receiving a combination of carbidopa and levodopa at 10/50 or 10/100 mg/kg/day. The latter dose caused excessive salivation. Weight gain slowed down. In pathological examinations, minor hypertrophy of submaxillary adenocytes was observed in two rats with the dosage of 10/100 mg/kg/day for 26 weeks. No histomorphological changes were observed at any dose level after 54 weeks and 106 weeks. Hypertrophy of salivary gland adenocytes has been observed in rats receiving either the combination product for shorter periods at higher doses or levodopa alone.

*Teratological studies and reproduction studies*. Carbidopa did not show to cause malformations in mice or rats at doses of 120 mg/kg/day.

Levodopa caused visceral and skeletal malformations in rabbits at the dosages of 125 and 250 mg/kg/day.

The combination of carbidopa and levodopa at the dosages of 25/250–100/500 mg/kg/day did not cause malformations in mice, but rabbits developed visceral and skeletal malformations that were quantitatively and qualitatively similar to those caused by levodopa alone.

Oral carbidopa at doses of 30, 60 or 120 mg/kg/day did not influence reproduction behaviour, fertility, or the viability of offspring in rats. The highest dose resulted in moderate delay in weight gain in males.

The combination of carbidopa and levodopa at doses of 10/20, 10/50 or 10/100 mg/kg/day did not impair fertility or reproduction ability in female or male rats or the growth and viability of offspring.

*Carcinogenicity studies*. In a study where carbidopa was administered orally to rats at doses of 25, 45 or 135 mg/kg/day for 96 weeks, there were no significant differences in mortality or frequency of tumours between the exposed rats and the control rats.

In the studies, rats were given the combination of carbidopa and levodopa (10/20, 10/50 or 10/100 mg/kg/day) orally for 106 weeks. No effects on mortality, incidence of tumours or tumour types were observed when the exposed rats were compared with concurrent controls.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Croscarmellose sodium
Magnesium stearate
Maize starch
Mannitol (E421)
Povidone

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

### 6.5 Nature and contents of container

HDPE bottle with a child resistant tamper-evident PP-closure
Pack size: 100 tablets

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

## 8 MARKETING AUTHORISATION NUMBER

PA1327/021/002

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

Date of first authorisation: 16th December 2022

**10 DATE OF REVISION OF THE TEXT**

February 2025