SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lecigon 20 mg/ml + 5 mg/ml + 20 mg/ml intestinal gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 20 mg levodopa, 5 mg carbidopa monohydrate (equivalent to 4.6 mg of anhydrous carbidopa) and 20 mg entacapone.

47 ml (1 cartridge) contains 940 mg levodopa, 235 mg carbidopa monohydrate and 940 mg entacapone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Intestinal gel. pH: 4.5-5.5

Yellow or yellowish-red opaque viscous gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of advanced Parkinson's disease with severe motor fluctuations and hyperkinesia or dyskinesia when available oral combinations of Parkinson medicinal products have not given satisfactory results.

4.2 Posology and method of administration

Posology

For intestinal use (see section 6.6). The dose should be titrated to achieve the optimal clinical response in the individual patient, which involves maximising the functional

ON-time during the day by minimising the number and duration of OFF episodes (bradykinesia) and minimising ON-time with disabling dyskinesia.

The total dose/day of Lecigon is composed of three individually adjusted doses: the morning bolus dose, the continuous maintenance dose, and extra bolus doses. Treatment is usually limited to the patient's awake period. If medically justified, Lecigon can be administered up to 24 hours/day. The maximum recommended daily dose is 100 ml (which corresponds to 2000 mg levodopa, 500 mg carbidopa monohydrate and 2000 mg entacapone – see also section 4.4).

During the maintenance dose, the plasma concentration/time profile of levodopa has a somewhat different appearance, with a gradually increasing levodopa concentration in plasma over the course of the day, than previously observed from intestinal gel with levodopa/carbidopa alone. An example of a plasma concentration/time profile when using Lecigon can be found in section 5.2. If individual needs exist, the pump can be preprogrammed to provide up to three maintenance doses over the course of the day/24-hour period. In case of dyskinesias in the latter part of the day, reductions of 10–20% during the middle of the day may be relevant. All maintenance doses should be titrated until the desired clinical effect is reached.

The multiple maintenance dose function may also be useful, for example, in patients with persistent dyskinesias or stiffness with recurring need of extra doses in the latter part of the day, or for patients with 24-hour treatment who need a reduction of the maintenance dose during the night.

Morning dose

The morning dose is administered by the pump to rapidly achieve the therapeutic dose level (within 30 minutes). The dose is adjusted in increments of 0.1 ml (2 mg). The total morning dose is usually 5–10 ml, corresponding to 100–200 mg levodopa. The total morning dose should not exceed 15 ml (300 mg levodopa).

Continuous maintenance dose

The continuous maintenance dose is administered by the pump to maintain the therapeutic dose level. The maintenance dose is adjusted in increments of 2 mg/hour (0.1 ml/hour). The maintenance dose is usually 0.7–5.0 ml/hour (15–100 mg levodopa/hour). The maximum recommended daily dose is 100 ml (2000 mg levodopa).

Extra bolus doses

Extra doses are given as required if the patient becomes hypokinetic. The extra dose is normally less than 3 ml but is adjusted individually. An increase in the continuous maintenance dose should be considered if the need for extra doses exceeds 5 doses per day.

Titration during transition from levodopa/carbidopa to Lecigon

Lecigon contains entacapone, which enhances the effect of levodopa. It may therefore be necessary to reduce the total daily intake of Lecigon by, on average, 20–35% compared to the patient's previous dose of levodopa and carbidopa without catechol-O-methyl transferase (COMT) inhibitors. Because the effect of entacapone on levodopa is dose dependent, a larger dose reduction is expected in high-dose patients.

The initial dose setting is based on the patient's daily levodopa intake. The size of the morning dose should be the same as the previous levodopa morning intake, to reach a therapeutic plasma concentration as quickly as possible, plus the volume required to fill the tube. The continuous maintenance dose should be based on the patient's daily levodopa intake (excluding the morning dose) and initially reduced to 65% of the previous daily levodopa intake. The doses are then titrated gradually, based on clinical symptoms, until the desired effect is achieved.

Example of initial dose setting prior to titration:

Previous total daily dose of levodopa: 1360 mg

Previous morning dose of levodopa: 100 mg

Previous daily levodopa intake (excluding the morning dose): 1260 mg/day

Morning dose: 100 mg

Corresponds to a volume of: 100 mg / 20 mg/ml = 5 ml

Total morning dose: 5 ml + 3 ml (volume to fill the tube) = 8 ml

Continuous maintenance dose: 1260 mg/day

Continuous maintenance dose reduced to 65%: 1260 mg/day x 0.65 = 819 mg/day

Intake per hour (calculated based on 16 hours of administration per day): 819 mg / 16 hours= 51 mg/hour

Corresponding to an hourly flow rate of: 51 mg/hour / 20 mg/ml = 2.5–2.6 ml/hour

Titration during transition from levodopa/benserazide to Lecigon

Entacapone increases the bioavailability of levodopa from standard preparations of levodopa/benserazide slightly more (5–10%) than from standard preparations of levodopa/carbidopa. The transition from levodopa/benserazide to Lecigon has not been studied.

Titration during transition from levodopa/carbidopa/entacapone to Lecigon

The initial dose setting is based on the patient's daily levodopa intake. The initial size of the morning dose should be the same as the previous levodopa morning intake plus the volume required to fill the tube. The continuous maintenance dose is converted 1:1 and is based on the patient's daily levodopa intake (excluding the morning dose). The doses are then titrated gradually, based on clinical symptoms, until the desired effect is achieved.

Transition from combination therapy with levodopa/DDC inhibitor/tolcapone to Lecigon has not been studied.

Transition from dopamine agonist therapy to Lecigon

When transitioning from dopamine agonist therapy to Lecigon monotherapy, the risk of dopamine agonist withdrawal symptoms should be taken into consideration and abrupt dopamine agonist discontinuation should be avoided.

Monitoring of treatment

After initial titration, the morning dose and maintenance dose are fine-tuned over the course of a few weeks.

Lecigon is initially given as monotherapy. If needed, other anti-Parkinsonian medicinal products can be taken concurrently (for concomitant treatment of Parkinson's disease, see also sections 4.3 and 4.5). If treatment with other anti-Parkinsonian medicinal products is discontinued or changed, it may be necessary to adjust the doses of Lecigon.

A sudden deterioration in treatment response with recurring motor fluctuations should lead to the suspicion that the duodenal/jejunal tube has been dislocated to the stomach. The location of the tube should be determined by X-ray. If the position is incorrect, the end of the tube is to be repositioned to the duodenum/upper jejunum.

Treatment in connection with dementia

In case of suspected or diagnosed dementia with a decreased confusion threshold, the pump should only be handled by a healthcare professional or caregiver.

Abuse of the medicinal product

If abuse of the medicinal product is suspected, there is a lock function in the pump used with Lecigon (Crono LECIG). This function prevents the patient from being able to change the pump settings.

<u>Special populations</u>

Paediatric population

There is no relevant use of Lecigon in the paediatric population in the indication of advanced Parkinson's disease with severe motor fluctuations and hyperkinesia/dyskinesia.

Elderly population

There is considerable experience in the use of levodopa/carbidopa/entacapone in elderly patients. Doses for all patients, including the elderly population are individually adjusted by titration.

Hepatic impairment
The dosage of Lecigon is individually adjusted by titration to the dose that provides optimal effect (which corresponds to individually optimised plasma exposure to levodopa, carbidopa and entacapone). Thus, any effects of hepatic impairment on levodopa, carbidopa and entacapone exposure are taken into account in the dose titration. There are no pharmacokinetic studies of carbidopa and levodopa in patients with hepatic impairment. The elimination of entacapone is reduced in patients with mild to moderate hepatic impairment. It is therefore recommended that dose titration be conducted with caution in patients with mild to moderate hepatic impairment. It may be necessary to reduce the dose (see section 5.2). Lecigon should not be used in patients with severe hepatic impairment; see section 4.3.

Renal impairment

The dosage of Lecigon is individually adjusted by titration to the dose that provides optimal effect (which corresponds to individually optimised plasma exposure to levodopa, carbidopa and entacapone). Thus, any effects of renal impairment on levodopa, carbidopa and entacapone exposure are taken into account in the dose titration. Renal impairment does not affect the pharmacokinetics of entacapone. There are no specific pharmacokinetic studies of levodopa and carbidopa in patients with renal impairment. It is therefore recommended that dose titration be conducted with caution in patients with severe renal impairment, including those receiving dialysis treatment (see section 5.2).

Interruption of therapy

Treatment with Lecigon can be interrupted at any time by removing the tube and allowing the wound to heal.

Patients should be carefully observed in case a sudden reduction of the dose is required or if it becomes necessary to discontinue treatment with Lecigon, particularly if the patient is receiving antipsychotics; see section 4.4.

If treatment is discontinued, the patient should receive an alternative treatment.

Method of administration

Lecigon is a gel for continuous intestinal delivery (delivery to the duodenum or upper jejunum). Only pump Crono LECIG (CE 0476) may be used for the administration of Lecigon. **A manual with instructions for using the portable pump is supplied with the pump.**

A temporary nasoduodenal/nasojejunal tube should be considered to determine if the patient responds favourably to this method of treatment before a permanent percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) is placed. In cases where the physician considers this assessment is not necessary, the nasojejunal test phase may be waived and treatment initiated directly with placement of the PEG-J.

For long-term administration, the gel should be administered with a portable pump directly into the duodenum or upper jejunum by a permanent tube via percutaneous

endoscopic gastrostomy with an outer transabdominal tube and an inner intestinal tube. Alternatively, a radiological gastrojejunostomy may be considered if percutaneous endoscopic gastrostomy is not suitable for any reason. The surgery and dose adjustment should be carried out in association with a neurological clinic.

Cartridge replacement

In order to use a new cartridge, it should be attached to the portable pump and the system connected to the tube for administration, according to the instructions given.

The cartridge is for single use only and should not be used for more than 24 hours.

The dosing pump with installed cartridge can be worn close to the body for up to 16 hours. During overnight treatment, the pump should not be worn next to the body but can, for example, be kept on the bedside table.

Once opened, a cartridge may be used into the next day, i.e. up to 24 hours after it was first opened. The cartridge is removed from the pump after 24 hours of use or when used up, whichever occurs first.

The gel may become slightly yellow/reddish by the end of the shelf life. This does not influence the concentration of the medicine or the effect of treatment.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Narrow-angle glaucoma.
- Severe heart failure.
- Severe cardiac arrhythmia.
- Acute stroke.
- Severe hepatic impairment.
- Administration of non-selective MAO inhibitors and selective MAO type A inhibitors are contraindicated for use with Lecigon. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Lecigon. Lecigon 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).
- Conditions in which adrenergics are contraindicated, e.g. pheochromocytoma, hyperthyroidism and Cushing's syndrome.
- Previous neuroleptic malignant syndrome (NMS) and/or non-traumatic rhabdomyolysis.

- Suspected undiagnosed skin lesions or a history of melanoma (levodopa could activate malignant melanoma).

4.4 Special warnings and precautions for use

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

Lecigon should be administered with caution to patients with ischaemic heart disease, severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions.

In patients with a history of myocardial infarction who have residual atrial nodal or ventricular arrhythmias, cardiac function should be monitored with particular care during the period of initial dosage adjustments.

All patients treated with Lecigon should be monitored carefully for the development of mental changes, depression with suicidal tendencies, and other serious mental changes. Patients with past or current psychosis should be treated with caution.

Concomitant administration of antipsychotics with dopamine receptor blocking properties, particularly D_2 receptor antagonists, should be carried out with caution, and the patient carefully observed for loss of antiparkinsonian effect or worsening of parkinsonian symptoms; see section 4.5.

Patients with chronic wide-angle glaucoma may be treated with Lecigon with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully for changes in intra-ocular pressure.

Lecigon may induce orthostatic hypotension. Lecigon should therefore be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension; see section 4.5.

The active substances in Lecigon have been associated with somnolence and episodes of sudden sleep onset in patients with Parkinson's disease. Caution should therefore be exercised when driving and using machines (see sections 4.7 and 4.8).

A symptom complex resembling Neuroleptic Malignant Syndrome (NMS), including muscular rigidity, increased body temperature, mental changes (e.g. agitation, confusion, coma) and increased serum creatine phosphokinase, has been reported when anti-Parkinsonian medicinal products were withdrawn abruptly. Rhabdomyolysis secondary to NMS or severe dyskinesias has been observed rarely in patients with Parkinson's disease. Since entacapone was introduced on the market,

isolated cases of NMS have been reported, particularly after abrupt dose reduction or discontinuation of entacapone and other concomitant dopaminergic medicinal products. Patients should be carefully observed when the dose of Lecigon is reduced or treatment is discontinued abruptly, especially if the patient is also receiving anti-psychotics/neuroleptics.

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 pathologic 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 therapies containing levodopa, including Lecigon. Review of treatment is recommended if such symptoms develop.

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population. It is unclear whether the increased risk observed was due to Parkinson's disease or other factors, such as medicines used to treat Parkinson's disease. Patients and caregivers are therefore advised to monitor for melanomas on a regular basis when using Lecigon. Ideally, periodic skin examinations should be performed by an appropriately qualified individual (e.g. dermatologist).

If general anaesthesia is required, treatment with Lecigon may be continued for as long as the patient is permitted to take fluids and medicinal products by mouth. If therapy has to be stopped temporarily, Lecigon at the same dose as before may be restarted as soon as oral intake of fluid is allowed.

It may be necessary to adjust the dose of Lecigon downwards to avoid levodopa-induced dyskinesias.

Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy with Lecigon.

Lecigon contains hydrazine, a degradation product of carbidopa that can be genotoxic and possibly carcinogenic. The average recommended daily dose of Lecigon is 46 ml (corresponding to 1.6 mg hydrazine/day) and the maximum recommended daily dose of Lecigon is 100 ml (corresponding to maximum 3.5 mg hydrazine/day). The clinical significance of this hydrazine exposure is not known.

Previous surgery in the upper part of the abdomen may lead to difficulty in performing gastrostomy or jejunostomy.

Reported complications for levodopa/carbidopa in clinical studies and seen post-marketing include bezoar, ileus, implant site erosion/ulcer, intestinal haemorrhage, intestinal ischaemia, intestinal obstruction, intestinal perforation, intussusception, pancreatitis, peritonitis, pneumoperitoneum and post-operative wound infection. Bezoars are retained concretions of indigestible material (such as non-digestible

vegetable or fruit fibres) in the intestinal tract. A bezoar around the tip of the jejunal tube may serve as the starting point of intestinal obstruction or intussusception. Most bezoars are found in the stomach, but bezoars may be encountered elsewhere in the intestinal tract. Abdominal pain may be a symptom of the above-listed complications. Some of these events may result in serious outcomes, such as surgery or death. Patients should be advised to notify their physician if they experience any of the symptoms associated with the above events.

Reduced ability to handle the system (pump, tubes) can lead to complications. In such cases, a caregiver (e.g. nurse, assistant nurse or close relative) should assist the patient.

A sudden or gradual worsening of bradykinesia may indicate an obstruction in the tubing system for whatever reason and must be investigated.

Weight loss has been associated with the active substances contained in Lecigon, and caregivers should therefore be aware of weight loss. Monitoring of weight is recommended to avoid severe weight loss. This applies in particular to patients with diarrhoea. Prolonged or persistent diarrhoea that appears during use of entacapone could be a sign of colitis. In case of prolonged or persistent diarrhoea, treatment with the medicinal product should be discontinued and other appropriate medical treatment and investigation considered.

Where deemed necessary, replacement of Lecigon with either levodopa and a DDC inhibitor without entacapone or other dopaminergic therapy should be done slowly. An increase in levodopa dose may be necessary.

For patients who experience progressive anorexia, asthenia and weight loss within a relatively short period of time, a general medical evaluation including liver function assessment should be considered.

Levodopa/carbidopa may cause false positive results when a dipstick is used to test for urinary ketones, and this reaction is not altered by boiling the urine sample. 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 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).

If abuse of the medicinal product is suspected, there is a lock function in the pump used with Lecigon (Crono LECIG).

This medicinal product contains 166 mg sodium per cartridge, equivalent to 8,3% of the WHO recommended maximum daily intake of 2 g sodium.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Lecigon. The following interactions are known from combinations of levodopa/carbidopa and entacapone/levodopa/carbidopa.

Caution is needed in concomitant administration of Lecigon with the following medicinal products:

Antihypertensives

Symptomatic postural hypotension has occurred when combinations of levodopa and a decarboxylase inhibitor are added to the treatment of patients already receiving antihypertensives. Dose adjustment of the antihypertensive agent may be required.

Antidepressants

Administration of non-selective MAO inhibitors and selective MAO type A inhibitors are contraindicated for use with Lecigon. Treatment with these inhibitors must be discontinued at least two weeks prior to initiating therapy with Lecigon (see section 4.3).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant administration of tricyclic antidepressants and carbidopa/levodopa preparations.

A significant number of patients with Parkinson's disease have been treated with the combination of levodopa, carbidopa, entacapone and tricyclic antidepressants and no pharmacodynamic interactions have been observed. However, caution should be exercised when using antidepressants at the same time as Lecigon.

Anticholinergics

Anticholinergics may act synergistically with levodopa to reduce tremors. 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 Lecigon may be required.

Other anti-Parkinsonian medicinal products

Lecigon can be taken concomitantly with the recommended dose of an MAO inhibitor with selectivity for MAO type B, e.g. selegiline hydrochloride. Concomitant use of selegiline and levodopa/carbidopa has been associated with serious orthostatic hypotension. A reduction of the dose of Lecigon may therefore be required when adding selective MAO-B inhibitor.

Amantadine and dopamine agonists like piribedil have a synergistic effect with levodopa and may increase levodopa-related adverse events. An adjustment of the dose of Lecigon may be required.

Other medicinal products

Dopamine receptor antagonists (some antipsychotics, e.g. phenothiazines, butyrophenons and risperidone, and antiemetics, e.g. metoclopramide), benzodiazepines, isoniazide, phenytoin and papaverine can reduce the therapeutic effect of levodopa. Patients taking these medicinal products together with Lecigon should be observed carefully for loss of therapeutic response.

Sympathicomimetics may increase cardiovascular adverse events related to levodopa.

Levodopa forms a chelate with iron in the gastrointestinal tract, leading to reduced absorption of levodopa. Lecigon and oral iron preparations should therefore be taken at least 2–3 hours apart. For example, the iron preparation can be taken before bedtime if the patient does not use the pump during the night.

Due to entacapone's affinity for P450 2C9 in vitro (see section 5.2), Lecigon may affect medicinal products whose metabolism is dependent on this isoenzyme, such as S-warfarin. However, in an interaction study with healthy volunteers, entacapone did not change plasma levels of S-warfarin, while the area under the curve (AUC) for R-warfarin increased on average by 18% (90% confidence interval: 11–26%). The INR values increased on average by 13% (90% confidence interval: 6–19 %). A control of INR is therefore recommended when treatment with Lecigon is initiated for patients receiving warfarin.

The effect of administration of antacids and Lecigon on the bioavailability of levodopa has not been studied.

Food interactions

As levodopa is competitive with certain amino acids, the absorption of levodopa may be disturbed in patients who are on a protein-rich diet.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of levodopa/carbidopa/entacapone in pregnant women. Studies in animals have shown reproductive toxicological effects from the individual substances (see section 5.3). The potential risk to humans is unknown. Lecigon is not recommended during pregnancy or in women of childbearing potential not using contraception unless the benefits for the mother outweigh the possible risks to the foetus.

Breastfeeding

Levodopa and possibly levodopa metabolites are excreted in human milk. There is evidence that lactation is suppressed during treatment with levodopa.

It is unknown whether carbidopa and entacapone or their metabolites are excreted in human milk. Animal studies have shown excretion of carbidopa and entacapone in milk.

There is insufficient information on the effects of levodopa/carbidopa/entacapone or their metabolites in newborns/infants. Breastfeeding should therefore be avoided during treatment with Lecigon.

Fertility

No negative effects on fertility have been observed in preclinical studies with carbidopa, levodopa or entacapone as individual substances. No fertility studies in animals have been conducted with the combination of levodopa, carbidopa and entacapone.

4.7 Effects on ability to drive and use machines

Lecigon can have a major influence on the ability to drive and use machines. Levodopa, carbidopa and entacapone may cause orthostatic hypotension and dizziness. Therefore, caution should be exercised when driving and using machines.

Patients being treated with Lecigon and presenting with somnolence and/or sudden sleep episodes must be advised to refrain from driving or engaging in activities where impaired alertness may put them, or others, at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved; see also sections 4.4 and 4.8.

4.8 Undesirable effects

Summary of the safety profile

The expected safety profile for Lecigon is based on available data from clinical trials and post-marketing experience of levodopa/carbidopa intestinal gel and oral levodopa/carbidopa/entacapone.

Drug-related undesirable effects that occur frequently with levodopa/carbidopa intestinal gel and could therefore occur with Lecigon include nausea and dyskinesia. Device and procedure-related undesirable effects that occur frequently with levodopa/carbidopa intestinal gel and could therefore occur with Lecigon include abdominal pain, complications of tube insertion, excessive granulation tissue, incision

site erythema, postoperative wound infection, post-procedural discharge, procedure-related pain, and incision site reaction. Most of these adverse reactions were reported early in the studies, subsequent to the percutaneous endoscopic gastrostomy procedure, and occurred during the first 28 days.

The most commonly reported adverse reactions with oral levodopa/carbidopa/entacapone are dyskinesias (affecting approximately 19% of patients); gastrointestinal symptoms including nausea and diarrhoea (affecting approximately 15% and 12% of patients respectively); muscle and connective tissue disorders (affecting approximately 12% of patients); and harmless maroon discolouration of urine (chromaturia) (affecting approximately 10% of patients).
Serious adverse reactions for gastrointestinal haemorrhage (uncommon) and angioedema (rare) have been identified from clinical trials with oral levodopa/carbidopa/entacapone or entacapone in combination with levodopa/DDC inhibitor.
Serious hepatitis with mainly cholestatic elements, rhabdomyolysis and neuroleptic malignant syndrome may occur with oral levodopa/carbidopa/entacapone, although no case has been identified from clinical trials.

A pharmacokinetic study with Lecigon that included 11 patients with advanced Parkinson's disease was performed. Adverse reactions considered to be associated with Lecigon were headache, nausea and dizziness. No serious adverse reactions were reported in this 2-day study. No adverse reactions were considered to be associated with the pump during administration of Lecigon.

Table of adverse reactions
Adverse reactions related to the medicinal product, device and procedure-related adverse reactions observed in clinical trials and during post-marketing use of levodopa/carbidopa intestinal gel and oral levodopa/carbidopa/entacapone are summarised in Table 1 below by system organ class and frequency.

For oral levodopa/carbidopa/entacapone, the adverse reactions listed in Table 1 have been compiled from double-blind clinical trials and data collected during post-marketing use of entacapone for combination therapy with levodopa/DDC inhibitor.

Table 1. Adverse reactions from clinical trials and post-marketing experience of levodopa/carbidopa intestinal gel and/or oral levodopa/carbidopa/entacapone.

MedDRA system organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Frequency unknown (cannot be estimated from available data)
Drug-related adverse reactions					
Infections and infestations	Urinary tract infection				
Blood and lymphatic system disorders		Anaemia	Leukopenia, Thrombocytopenia		Agranulocytosis
Immune system disorders					Anaphylactic reaction

MedDRA system organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Frequency unknown (cannot be estimated from available data)
Metabolism and nutrition disorders	Weight loss	Elevated amino acid level (elevated methylmalonic acid), Elevated homocysteine in the blood, Decreased appetite, Weight gain, Vitamin B6 deficiency, Vitamin B12 deficiency			
Psychiatric disorders	Anxiety, Depression, Insomnia	Nightmares, Agitation, Confused state, Hallucination, Impulse control disorder, Psychotic disorders, Sleep attacks, Sleep disorder	Completed suicide, Disorientation, Euphoria, Fear, Increased libido (see section 4.4) Suicide attempt/ suicidal behaviour	Abnormal thoughts	Dopamine dysregulation syndrome[a]
Nervous system disorders	Dyskinesia, Parkinson's disease/ Exacerbation of parkinsonism (e.g. bradykinesia)	Dizziness, Dystonia, Headache, Hypoaesthesia, On-off phenomenon, Paraesthesia, Polyneuropathy, Somnolence, Syncope, Tremor Hyperkinesia	Ataxia, Convulsions		Neuroleptic malignant syndrome, Memory impairment, Dementia
Eye disorders		Blurred vision	Angle closure glaucoma, Blepharospasm, Diplopia, Optic ischaemic neuropathy		
Cardiac disorders		Irregular heart rate, Ischaemic heart disease other than myocardial infarction (e.g. angina pectoris)	Palpitations, Myocardial infarction		
Vascular disorders	Orthostatic hypotension	Hypertension, Hypotension	Phlebitis		

MedDRA system organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Frequency unknown (cannot be estimated from available data)
Respiratory, thoracic and mediastinal disorders		Dyspnoea, Oropharyngeal pain, Aspiration pneumonia	Dysphonia	Abnormal breathing pattern	
Gastrointestinal disorders	Nausea, Constipation, Diarrhoea	Abdominal distension, Abdominal pain, Abdominal discomfort, Dry mouth, Dysgeusia, Dyspepsia, Dysphagia, Flatulence, Vomiting	Colitis, Gastrointestinal haemorrhage, Hypersalivation	Bruxism, Glossodynia, Hiccups, Saliva discolouration	
Hepatobiliary disorders			Abnormal liver function test		Hepatitis with mainly cholestatic elements
Skin and subcutaneous tissue disorders		Contact dermatitis, Hyperhidrosis, Pruritus, Skin rash	Alopecia, Erythema, Urticaria, Discolouration of the skin, hair, nails and sweat	Malignant melanoma (see section 4.3) Angioedema	
Musculoskeletal and connective tissue disorders	Pain in muscles and tissues, and musculoskeletal pain	Arthralgia, Muscle spasms, Neck pain			Rhabdomyolysis
Renal and urinary disorders	Chromaturia	Urinary incontinence, Urinary retention-			
Reproductive system and breast disorders				Priapism	
General disorders and administration site conditions		Asthenia, Chest pain, Fatigue, Gait disturbance, Pain, Peripheral oedema	Malaise		
Injury, poisoning and procedural complications	Fall				
Device and procedure-related adverse reactions					

MedDRA system organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Frequency unknown (cannot be estimated from available data)
Infections and infestations	Postoperative wound infection	Incision site cellulitis, Post-procedural infection	Postoperative abscess		
Gastrointestinal disorders	Abdominal pain	Abdominal discomfort, Upper abdominal pain, Peritonitis, Pneumoperitoneum	Bezoar, Ischaemic colitis, Gastrointestinal ischaemia, Gastrointestinal obstruction, Pancreatitis, Small intestinal haemorrhage, Small intestinal ulcer, Large intestine perforation, Intussusception		Gastric perforation, Gastrointestinal perforation, Small intestinal ischaemia, Small intestinal perforation
Skin and subcutaneous tissue disorders	Excessive granulation tissue				
General disorders and administration site conditions	Complications of device insertion[b]	Device dislocation, Device occlusion			
Injury, poisoning and procedural complications	Incision site erythema, Post-procedural discharge, Procedural pain, Procedural site reaction	Gastrointestinal stoma complication, Incision site pain, Postoperative ileus, Post-procedural complication, Post-procedural discomfort, Post-procedural haemorrhage			

[a] 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 section 4.4).

[b] Complication of device insertion was a commonly reported adverse reaction for both the nasojejunal tube and the PEG-J. This adverse reaction was co-reported with one or more of the following adverse reactions for the nasojejunal tube: oropharyngeal pain, abdominal distension, abdominal pain, abdominal discomfort, pain, throat irritation, gastrointestinal injury, oesophageal haemorrhage, anxiety, dysphagia, and vomiting. For the PEG-J, this adverse reaction was co-reported with one or more of the following adverse reactions: abdominal pain, abdominal discomfort, abdominal distension, flatulence, or pneumoperitoneum. Other adverse reactions that were co-reported with complication of device insertion included abdominal discomfort,

duodenal ulcer, haemorrhage, erosive duodenitis, erosive gastritis, gastrointestinal haemorrhage, peritonitis, pneumoperitoneum, and small intestine ulcer.

Dislocation of the intestinal tube backwards into the stomach or an obstruction of the device leads to reappearance of the motor fluctuations.

The following additional adverse reactions have been observed with oral levodopa/carbidopa and have been classified as rare (≥1/10,000 to <1/1000): haemolytic anaemia, trismus, Horner's syndrome, mydriasis, oculogyric crises, and Henoch-Schönlein purpura. The following additional adverse reaction has been reported as very rare (<1/10,000): agranulocytosis

Laboratory values:
The following laboratory abnormalities have been reported with levodopa/carbidopa treatment: elevated urea nitrogen, alkaline phosphatases, S-AST, S-ALT, LDH, bilirubin, blood sugar, creatinine, uric acid, positive Coomb's test, and lowered haemoglobin and haematocrit levels. Leucocytes, bacteria and blood in the urine have been reported.

Description of selected adverse reactions
The introduction of entacapone to an existing treatment with levodopa/DDC inhibitor may cause an initial increase in dopaminergic activity (e.g. dyskinesia, nausea and vomiting). Reducing the levodopa dose reduces the severity and frequency of these dopaminergic reactions.

Impulse control disorders
Compulsive 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 therapies containing levodopa, including Lecigon (see section 4.4).

Somnolence and sudden sleep attacks
Entacapone in combination with levodopa has been associated with somnolence and sudden sleep attacks in patients with Parkinson's disease. Caution should therefore be exercised when driving and using machines (see sections 4.4 and 4.7).

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

The most prominent clinical symptoms of overdose with levodopa/carbidopa are dystonia and dyskinesia. Blepharospasms can be an early sign of overdose. Pyridoxine does not counteract the effects of Lecigon. Electrocardiographic monitoring should be used and the patient observed carefully for the development of

cardiac arrhythmias. If necessary, an appropriate antiarrhythmic therapy should be given. The possibility that the patient took other medicinal products together with Lecigon should be taken into consideration. The value of dialysis in the treatment of overdose is not known.

Data includes isolated cases of overdose, where the highest reported daily dose of oral levodopa and entacapone has been at least 10,000 mg and 40,000 mg, respectively. Acute symptoms and signs in these cases included agitation, confusion, coma, bradycardia, ventricular tachycardia, Cheyne-Stokes respiration, discolouration of skin, tongue and conjunctiva, and discoloured urine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parkinson drugs, dopa and dopa derivatives, ATC code: N04BA03

Mechanism of action

Lecigon is a combination of levodopa, carbidopa monohydrate and entacapone (ratio 4:1:4) in a gel for continuous intestinal infusion in advanced Parkinson's disease with severe motor fluctuations and hyperkinesia/dyskinesia.

According to current knowledge, the symptoms of Parkinson's disease are related to the lack of dopamine in the corpus striatum. Dopamine does not cross the blood-brain barrier.

Levodopa, a metabolic precursor of dopamine, crosses the blood-brain barrier and relieves the symptoms of the disease. Since levodopa is extensively metabolised peripherally in tissues, only a small proportion of the given dose reaches the central nervous system when levodopa is administered without metabolic enzyme inhibitors.

Carbidopa is a peripheral DDC inhibitor which reduces the peripheral metabolism of levodopa to dopamine, thereby making more levodopa available to the brain. When decarboxylation of levodopa is reduced through co-administration of a DDC inhibitor, a lower dose of levodopa can be used and the incidence of adverse events such as nausea may be reduced.

When decarboxylase is inhibited with a DDC inhibitor, COMT becomes the dominant peripheral metabolic pathway. Entacapone is a reversible, specific and mainly peripherally-acting COMT inhibitor designed for co-administration with levodopa. Entacapone reduces clearance of levodopa from the blood, resulting in an increased AUC in the pharmacokinetic profile of levodopa. Consequently, the clinical response of levodopa is prolonged.

Intestinal infusion of individually tested doses of Lecigon maintains the plasma concentration of levodopa at an even level within an individual therapeutic window.

5.2 Pharmacokinetic properties

Absorption

Lecigon is administered via an inserted tube directly into the duodenum or upper jejunum. There are major inter- and intraindividual variations in the absorption of levodopa, carbidopa and entacapone. Both levodopa and entacapone are absorbed and eliminated quickly. Carbidopa is absorbed and eliminated slightly slower that levodopa. When administered separately without the two other active substances, the oral bioavailability is 15–33% for levodopa, 40–70% for carbidopa, and 29–46% for entacapone. Meals rich in large neutral amino acids can delay and reduce the absorption of levodopa. Food does not significantly affect the absorption of entacapone.

In an open-label, randomised clinical trial with cross-over design, including Duodopa as a comparator, intestinal administration of Lecigon rapidly led to therapeutic plasma levels of levodopa. Comparable levodopa levels were maintained during the infusion for both Lecigon and Duodopa, but a gradually increasing plasma levodopa concentration was observed during the day for Lecigon relative to Duodopa. Lecigon had a statistically significant higher bioavailability of levodopa compared to Duodopa calculated during the infusion, AUC_{014h} /dose (ratio: 1.38; 95% confidence interval [CI]: 1.26–1.51). After completion of infusion, the levels of levodopa decreased rapidly. The variability of levodopa plasma concentrations in the individual was small (13.8%) within the 3 to 14 hour interval after the start of Lecigon infusion.

An example of the expected plasma concentration/time profile with a constant maintenance dose is shown in Figure 1. If necessary, it is possible to use multiple maintenance doses per day/24-hour period (described in section 4.2 Posology).

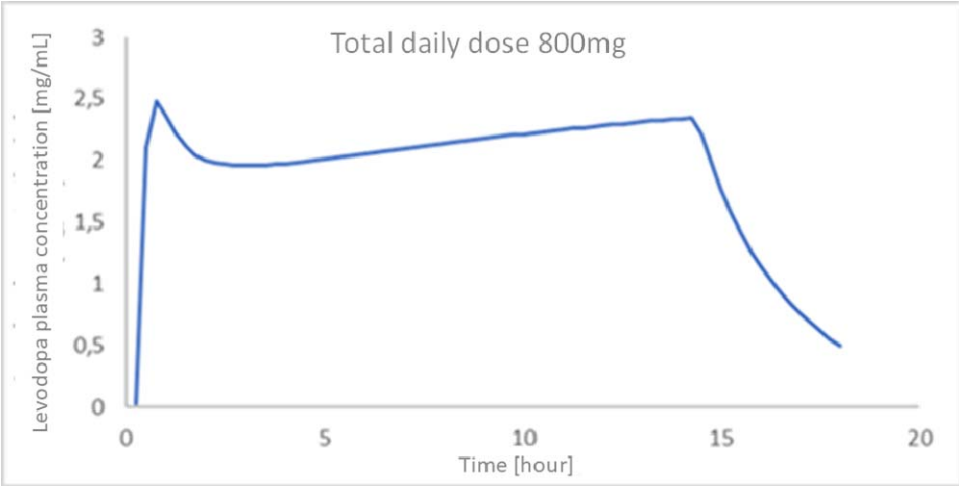

Figure 1: Example of levodopa plasma concentration/time profile for a total daily dose of 800 mg levodopa with morning dose (176 mg) and continuous maintenance dose (45 mg/h) over the day.

Distribution

The distribution volume for both levodopa (0.36–1.6 l/kg) and entacapone (0.27 l/kg) at steady state is relatively small, while data for carbidopa is not available.

Levodopa is bound to plasma proteins to a low extent (approximately 10–30%) and carbidopa is bound to approximately 36%, while entacapone is highly bound (approximately 98%) – mainly to serum albumin. At therapeutic concentrations, entacapone does not interfere with other highly protein-bound active substances (e.g. warfarin, salicylic acid, phenylbutazone or diazepam), nor is it significantly impaired by any of these drugs at therapeutic or higher concentrations.

Biotransformation and elimination

Levodopa is largely metabolised to different metabolites: decarboxylation with dopadecarboxylase (DDC) and O-methylation with COMT are the major metabolic pathways.

Carbidopa is metabolised to two main metabolites that are primarily eliminated in the urine as glucuronides or unconjugated compounds. Unchanged carbidopa accounts for 30% of the total urinary excretion.

Entacapone is almost completely metabolised, and the metabolites are excreted via urine (10–20%) and bile/faeces (80–90%). The primary metabolic pathway is glucuronidation of entacapone and its active metabolite, cis-isomer. The cis-isomer accounts for approximately 5% of the total amount in plasma.

Total clearance is within the range 0.55–1.38 l/kg/hour for levodopa and approximately 0.70 l/kg/hour for entacapone. The half-life is 0.6–1.3 hours for levodopa, 2–3 hours for carbidopa, and 0.4–0.7 hours for entacapone when given separately. The mean estimated half-life for levodopa during treatment with Lecigon was 2.0 hours.

Data from in vitro studies with human liver microsome preparations indicates that entacapone inhibits cytochrome P450 2C9 (IC_{50} ~ 4 µM). Entacapone showed little or no inhibition of other types of P450 isoenzymes (CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A and CYP2C19).

Special populations

Elderly

When levodopa is administered without carbidopa and entacapone, the absorption of levodopa is higher and elimination slower in the elderly than in younger subjects. However, following administration of levodopa in combination with carbidopa, the absorption of levodopa is similar between elderly and younger subjects, but the AUC is still 1.5 times higher in elderly due to age-related decrease in DDC activity and clearance. There are no significant AUC differences for carbidopa or entacapone between younger (45–64 years) and elderly (65–75 years) subjects.

Gender

The bioavailability of levodopa is significantly higher in women than in men, even in the presence of entacapone. This difference is mainly due to the difference in body weight. There is no difference between gender with regard to the bioavailability of carbidopa or entacapone.

Hepatic impairment
The metabolism of entacapone is slowed in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B), leading to an increased plasma concentration of entacapone in both the absorption and elimination phases (see sections 4.2, 4.3 and 4.4). There are no specific pharmacokinetic studies of levodopa and carbidopa in patients with hepatic impairment. However, it is recommended that Lecigon is administered with caution in patients with mild to moderate hepatic impairment. Lecigon should not be used in patients with severe hepatic impairment; see section 4.3.

Renal impairment

Renal impairment does not affect the pharmacokinetics of entacapone. There are no specific pharmacokinetic studies of levodopa and carbidopa in patients with renal impairment. It is therefore recommended that dose titration is made with caution in patients with severe renal impairment, including those receiving dialysis treatment (see section 4.2).

5.3 Preclinical safety data

Preclinical data of levodopa, carbidopa and entacapone, tested alone or in combination, revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

In repeated dose toxicity studies with entacapone, anaemia most likely due to iron chelating properties of entacapone was observed. In relation to the reproductive toxicity of entacapone, decreased foetal weight and slightly delayed skeletal

development were observed in rabbits at systemic exposure levels within the therapeutic range.

Both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits.

Hydrazine is a degradation product of carbidopa. In animal studies, hydrazine showed notable systemic toxicity, particularly by inhalation exposure. These studies reported that hydrazine is hepatotoxic, has CNS toxicities (although not described after oral treatment), and is genotoxic as well as carcinogenic (see also section 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose sodium

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

26 weeks

Opened cartridge: Use immediately. The product can be used for up to 24 hours once it is out of the refrigerator. The dosing pump with installed cartridge can be worn close to the body for up to 16 hours. During overnight treatment, the pump should not be worn next to the body but can, for example, be kept on the bedside table. Discard any unused portion.

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C). Do not freeze.

Store in the original package in order to protect from light.

For storage instructions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

47 ml gel in polypropylene cartridge. The wide end is sealed with a plunger stopper made of polyisoprene rubber and the opening is sealed with a stopper made of polypropylene.

Carton of 7 cartridges.

6.6 Special precautions for disposal

The cartridges are intended for single use only. Do not reuse an opened cartridge.

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

7 MARKETING AUTHORISATION HOLDER

LobSor Pharmaceuticals AB

Kålsängsgränd 10 D

SE-753 19 Uppsala, Sweden

8 MARKETING AUTHORISATION NUMBER(S)

PL 53856/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/05/2022

10 DATE OF REVISION OF THE TEXT

18/05/2022