Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 20 mg levodopa and 5 mg carbidopa monohydrate.
100 ml contain 2000 mg levodopa and 500 mg carbidopa monohydrate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Intestinal gel.

Off white to slightly yellow gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Duodopa is a gel for continuous intestinal administration. 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. Establishment of the transabdominal port and dose adjustments should be carried out in association with a neurological clinic.

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. The dose should be adjusted to an optimal clinical response for the individual patient, which means maximizing the functional ON-time during the day by minimizing the number and duration of OFF episodes (bradykinesia) and minimizing ON-time with disabling dyskinesia. See recommendations under *Dosage*.

Duodopa should be given initially as monotherapy. If required other medicinal products for Parkinson's disease can be taken concurrently. For administration of Duodopa only the CADD-legacy 1400 pump (CE Marked) should be used. *A manual with instructions for using the portable pump is delivered together with the pump*.

Treatment with Duodopa using a permanent tube can be discontinued at any time by withdrawing the tube and letting the wound heal. Treatment should then continue with oral medicinal products including levodopa/carbidopa.

Dosage:
The total dose/day of Duodopa is composed of three individually adjusted doses: the morning bolus dose, the continuous maintenance dose and extra bolus doses administered over approximately 16 hours. Treatment is usually administered during the patient's awake period. If medically justified, Duodopa may be administered for up to 24 hours.

The medicine cassettes are for single use only and should not be used for longer than 24 hours, even if some medicinal product remains. Do not reuse an opened cassette.

By the end of the storage time the gel might become slightly yellow. This does not influence the concentration of the medicine or the treatment.

Morning dose: The morning bolus dose is administered by the pump to rapidly achieve the therapeutic dose level (within 10-30 minutes). The dose should be based on the patient's previous morning intake of levodopa + the volume to fill the tubing. 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 maintenance dose is adjustable in steps of 2 mg/hour (0.1 ml/hour). The dose should be calculated according to the patient's previous daily intake of levodopa. When supplementary medicines are discontinued the Duodopa dose should be adjusted. The continuous maintenance dose is adjusted individually. It should be kept within a range of 1-10 ml/hour (20-200 mg levodopa/hour) and is usually 2-6 ml/hour (40-120 mg levodopa/hour). The maximum recommended daily dose is 200 ml (see section 4.4). In exceptional cases a higher dose may be needed.

Example:
Daily intake of levodopa as Duodopa: 1640 mg/day
Morning bolus dose: 140 mg = 7 ml (excluding the volume to fill the intestinal tube)
Continuous maintenance dose: 1500 mg/day
1500 mg/day: 20 mg/ml = 75 ml Duodopa per day
The intake is calculated over 16 hours: 75 ml/16 hours = 4.7 ml/hour.

Extra bolus doses: To be given as required if the patient becomes hypokinetic during the day. The extra dose should be adjusted individually, normally 0.5-2.0 ml. In rare cases a higher dose may be needed. If the need for extra bolus doses exceeds 5 per day the maintenance dose should be increased.

After the initial dose setting, fine adjustments of the morning bolus dose, the maintenance dose and extra bolus doses should be carried out over a few weeks.

Monitoring of treatment: A sudden deterioration in treatment response with recurring motor fluctuations should lead to the suspicion that the distal part of the tube has become displaced from the duodenum/jejunum into the stomach. The location of the tube should be determined by X-ray and the end of the tube repositioned to the duodenum/jejunum.

Special Populations
Paediatric population
There is no relevant use of Duodopa in the paediatric population in the indication of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia.

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

Renal/hepatic impairment
There are no studies on the pharmacokinetics of carbidopa and levodopa in patients with hepatic or renal impairment. Dosing with Duodopa is individualized by titration to optimal effect (which corresponds to individually optimized levodopa and carbidopa plasma exposures); therefore, potential effects of hepatic or renal impairment on levodopa and carbidopa exposure are indirectly accounted for in dose titration. Dose titration should be conducted with caution in patients with severe renal and hepatic impairment (see section 4.4).

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

In the case of *suspected or diagnosed* dementia with a decreased confusion threshold, the pump of the patient should be handled only by the nursing staff or a caregiver.

When a cassette is about to be used, it should be attached to the portable pump and the system connected to the nasoduodenal tube or duodenal/jejunal tube for administration, according to the instructions given.

4.3 Contraindications

Duodopa is contraindicated in patients with:

- 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
- non-selective MAO inhibitors and selective MAO type A inhibitors are contraindicated for use with Duodopa. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Duodopa. Duodopa may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g., selegiline HCl) (see section 4.5).
- conditions in which adrenergics are contraindicated, e.g. pheochromocytoma, hyperthyroidism and Cushing's syndrome.

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

4.4 Special warnings and precautions for use

Several warnings and precautions below are generic for levodopa and, therefore, also for Duodopa.

- Duodopa is not recommended for the treatment of drug-induced extrapyramidal reactions.
- Duodopa therapy should be administered with caution to patients with 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 Duodopa 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 Duodopa with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully for changes in intra-ocular pressure.
- Duodopa may induce orthostatic hypotension. Therefore, Duodopa should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension, see section 4.5.
- Levodopa has been associated with somnolence and episodes of sudden sleep onset in patients with Parkinson's disease and caution should therefore be exercised when driving and operating machines (see section 4.7).
- 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 Neuroleptic Malignant Syndrome or severe dyskinesias have been observed rarely in patients with Parkinson's disease. Therefore, patients should be carefully observed when the dose of levodopa/carbidopa combinations are abruptly reduced or discontinued, especially if the patient is receiving anti-psychotics. Neither NMS nor rhabdomyolysis has been reported in association with Duodopa.
- 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 and 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 Duodopa. 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. Therefore, patients and providers are advised to monitor for melanomas on a regular basis when using Duodopa for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g. dermatologists).
- If general anaesthesia is required, treatment with Duodopa 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, Duodopa at the same dose as before may be restarted as soon as oral intake of fluid is allowed.
- The dose of Duodopa may need to be adjusted downwards in order to avoid levodopa induced dyskinesias.
- Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy with Duodopa.

- Duodopa contains hydrazine, a degradation product of carbidopa that can be genotoxic and possibly carcinogenic. The average recommended daily dose of Duodopa is 100 ml, containing 2 g levodopa and 0.5 g carbidopa. The maximum recommended daily dose is 200 ml. This includes hydrazine at up to an average exposure of 4 mg/day, with a maximum of 8 mg/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 in the clinical studies, and seen post-marketing, include abscess, bezoar, ileus, implant site erosion/ulcer, intestinal haemorrhage, intestinal ischaemia, intestinal obstruction, intestinal perforation, intussusception, pancreatitis, peritonitis, pneumonia (including aspiration pneumonia), pneumoperitoneum, post-operative wound infection and sepsis. Bezoars are retained concretions of indigestible material (such as vegetable or fruit non-digestible fibers) in the intestinal tract. Most bezoars reside in the stomach but bezoars may be encountered elsewhere in the intestinal tract. A bezoar around the tip of the jejunal tube may function as a lead point for intestinal obstruction or the formation of intussusception. Abdominal pain may be a symptom of the above listed complications. Some events may result in serious outcomes, such as surgery and/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, tube connections) can lead to complications. In such patients 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 device for whatever reason and needs to be explored.
- Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with levodopa/carbidopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS (see also section 4.8).
- Polyneuropathy has been reported in patients treated with levodopa/carbidopa intestinal gel. Before starting therapy evaluate patients for history or signs of polyneuropathy and known risk factors, and periodically thereafter.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Duodopa. The following interactions are known from the generic combination of levodopa/carbidopa.

Caution is needed in concomitant administration of Duodopa 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 anti-hypertensives. Dosage adjustment of the antihypertensive agent may be required.

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

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 Duodopa may be needed.

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

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 Duodopa should be observed carefully for loss of therapeutic response.

Duodopa can be taken concomitantly with the recommended dose of an MAO inhibitor, which is selective for MAO type B (for instance selegiline-HCl). The dose of levodopa may need to be reduced when an MAO inhibitor selective for type B is added.

Concomitant use of selegiline and levodopa-carbidopa has been associated with serious orthostatic hypotension.

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

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.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of levodopa/carbidopa in pregnant women. Studies in animals have shown reproduction toxicity (see section 5.3). Duodopa is not recommended during pregnancy and in women of childbearing potential not using contraception unless the benefits for the mother outweigh the possible risks to the foetus.

Breast-feeding
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 or its metabolites are excreted in human milk. Animal studies have shown excretion of carbidopa in breast milk.

There is insufficient information on the effects of levodopa/carbidopa or their metabolites in newborns/infants. Breast-feeding should be discontinued during treatment with Duodopa.

Fertility
No adverse reactions on fertility have been observed in preclinical studies with carbidopa or levodopa alone. Fertility studies in animals have not been conducted with the combination of levodopa and carbidopa.

4.7 Effects on ability to drive and use machines

Duodopa can have a major influence on the ability to drive and use machines. Levodopa and carbidopa may cause dizziness and orthostatic hypotension. Therefore, caution should be exercised when driving or using machines. Patients being treated with Duodopa 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 section 4.4.

4.8 Undesirable effects

Drug-related undesirable effects that occur frequently with the Duodopa system include nausea and dyskinesia.

Device- and procedure related undesirable effects that occur frequently with the Duodopa system include abdominal pain, complications of device insertion, excessive granulation tissue, incision site erythema, postoperative wound infection, post procedural discharge, procedural pain, and procedural 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.

Undesirable effects reported with Duodopa
The safety of Duodopa was compared to the standard oral formulation of levodopa/carbidopa (100 mg/25 mg) in a total of 71 advanced Parkinson's disease patients who participated in a randomized, double-blind, double-dummy, active controlled study

of 12 weeks duration. Additional safety information was collected in an open-label, 12-month study in 354 patients with advanced Parkinson's disease and open-label extension studies.

An analysis was performed for patients who received Duodopa in all studies, regardless of the study design (double-blind or open-label) to allow for a summary of drug-related adverse reactions. Another analysis was performed for patients who received Duodopa or placebo gel through a PEG-J to allow for a summary of procedure-related and device-related adverse reactions in all studies, regardless of the study design (double-blind or open-label).

Drug-, Procedure- and device-related adverse reactions based on treatment emergent frequencies, regardless of causality assigned, in addition to adverse reactions identified during post-approval use of Duodopa are presented in Table 1.

Table 1. Adverse Reaction Data Derived From Clinical Trials and Post-marketing Experience

Table 1. Adverse Reaction Data Derived From Clinical Trials and Post-marketing Experience

MedDRA System Organ Class	Very Common[a] (≥ 1/10)	Common[a] (≥ 1/100 to < 1/10)	Uncommon[b] (≥1/1,000 to <1/100)	Rare[b] (≥1/10,000 to <1/1,000)	Frequency Unknown Post-marketing
Drug-Related Adverse Reactions					
Infections and infestations	Urinary tract infections				
Blood and lymphatic system disorders		Anaemia	Leukopenia, Thrombo-cytopenia		
Immune System Disorders					Anaphylactic reaction
Metabolism and nutrition disorders	Weight decreased	Increased weight, Amino acid level increased (Metylmalonic acid increased), Blood homocysteine increased, Decreased appetite, Vitamin B6 deficiency, Vitamin B12 deficiency			
Psychiatric disorders	Anxiety, Depression, Insomnia	Abnormal dreams, Agitation, Confusional state, Hallucination, Impulsive behavior[c], Psychotic disorder, Sleep attacks, Sleep disorder	Completed suicide, Dementia, Disorientation, Euphoric mood, Fear, Libido increased (See Section 4.4), Nightmare, Suicide Attempt	Abnormal thinking	Dopamine dysregulation syndrome[d]
Nervous system disorders	Dyskinesia, Parkinson's disease	Dizziness, Dystonia, Headache, Hypoaesthesia, On and off phenomenon, Paraesthesia, Polyneuropathy, Somnolence, Syncope, Tremor	Ataxia, Convulsion, Gait disturbance		
Eye disorders			Angle closure glaucoma,		

			Blepharospasm, Diplopia, Optic ischaemic neuropathy, Vision blurred		
Cardiac disorders		Heart rate irregular	Palpitations		
Vascular disorders	Orthostatic hypotension	Hypertension, Hypotension	Phlebitis		
Respiratory, thoracic and mediastinal disorders		Dyspnoea, Oropharyngeal pain	Chest pain, Dysphonia	Respiration abnormal	
Gastro-intestinal disorders	Nausea, Constipation	Abdominal distension, Diarrhoea, Dry mouth, Dysgeusia, Dyspepsia, Dysphagia, Flatulence, Vomiting	Salivary hypersecretion	Bruxism, Saliva discolouration, Glossodynia, Hiccups	
Skin and subcutaneous tissue disorders		Dermatitis contact, Hyperhidrosis, Oedema peripheral, Pruritus, Rash	Alopecia, Erythema, Urticaria	Sweat discolouration, Malignant melanoma (See Section 4.4)	
Musculo-skeletal and connective tissue disorders		Muscle spasms, Neck pain			
Renal and urinary disorders		Urinary incontinence, Urinary retention	Chromaturia	Priapism	
General disorders and administration site conditions		Fatigue, Pain, Asthenia	Malaise		
Injury, poisoning and procedural complications	Fall				

Device- and Procedure-Related Adverse Reactions					
MedDRA System Organ Class	**Very Common[a] (≥ 1/10)**	**Common[a] (≥ 1/100 to < 1/10)**	**Uncommon[b] (≥1/1,000 to <1/100)**	**Rare[b] (≥1/10,000 to <1/1,000)**	**Frequency Unknown Post-marketing**
Infections and infestations	Postoperative wound infection	Incision site cellulitis, Post procedural infection	Postoperative abscess		Sepsis
Gastro-intestinal disorders	Abdominal pain	Abdominal discomfort, Abdominal pain upper,	Bezoar (see section 4.4), Colitis ischaemic,		Gastric perforation, Gastro-intestinal

		Peritonitis, Pneumo-peritoneum	Gastrointestinal ischaemia, Gastrointestinal obstruction, Intussusception, Pancreatitis, Small intestinal haemorrhage, Small intestinal ulcer, Large intestine perforation		perforation, Small intestinal ischaemia, Small intestinal perforation
Respiratory, thoracic and mediastinal disorders		Pneumonia / Aspiration pneumonia			
Skin and subcutaneous tissue disorders	Excessive granulation tissue				
General disorders and administration site conditions	Complications of device insertion[e]	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] ADRs observed in clinical trials. Frequencies assigned reflect adverse event frequencies and are regardless of causality assigned by the investigator

[b] ADRs observed with Duodopa for which estimations of frequencies were not available. Frequencies assigned are based on historical data for oral levodopa/carbidopa.

[c] Impulse control disorders: Pathological gambling, increased libido and 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 Duodopa (see section 4.4. 'Special warnings and precautions for use').

[d] Dopamine Dysregulation Syndrome (DDS) is an addictive disorder seen in some patients treated with levodopa/ carbidopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias (see also section 4.4).

[e] 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 1 or more of the following adverse reactions for the nasojejunal tube: oropharyngeal pain, abdominal distention, abdominal pain, abdominal discomfort, pain, throat irritation, gastrointestinal injury, esophageal haemorrhage, anxiety, dysphagia, and vomiting. For the PEG-J, this adverse reaction was co-reported with 1 or more of the following adverse reactions: abdominal pain, abdominal discomfort, abdominal distension, flatulence, or pneumoperitoneum. Other non-serious adverse reactions that were co-reported with complication of device insertion included abdominal discomfort, abdominal pain upper, duodenal ulcer, duodenal ulcer haemorrhage, erosive duodenitis, gastritis erosive, gastrointestinal haemorrhage, peritonitis, pneumoperitoneum, small intestine ulcer.

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

The following additional adverse reactions (listed in MedDRA preferred terms) have been observed with oral levodopa/carbidopa and could occur with Duodopa:

Table 2. Adverse Reaction Observed with Oral Levodopa/Carbidopa

MedDRA system organ class	**Rare (≥1/10,000 to <1/1,000)**	**Very Rare (<1/10,000)**
Blood and lymphatic system disorders	Haemolytic anaemia	Agranulocytosis
Nervous system disorders	Trismus, Neuroleptic malignant syndrome (see Section 4.4)	
Eye disorders	Horner's syndrome, Mydriasis, Oculogyric crises	
Skin and subcutaneous tissue disorders	Angiooedema, Henoch-Schönlein purpura	

Laboratory values: The following laboratory abnormalities have been reported with levodopa/carbidopa treatment and should, therefore, be acknowledged when treating patients with Duodopa: elevated urea nitrogen, alkaline phosphatases, S-AST, S-ALT, LDH, bilirubin, blood sugar, creatinine, uric acid and positive Coomb's test, and lowered values of haemoglobin and haematocrit. Leucocytes, bacteria and blood in the urine have been reported. Levodopa/carbidopa, and thus Duodopa, may cause a false positive result when a dipstick is used to test for urinary ketone; this reaction is not altered by boiling the urine sample. The use of glucose oxidase methods may give false negative results for glucosuria.

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 HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

Most prominent clinical symptoms of an overdose with levodopa/carbidopa are dystonia and dyskinesia. Blepharospasms can be an early sign of overdose.
The treatment of an acute overdose of Duodopa is in general the same as that of an acute overdose of levodopa: However, pyridoxine has no effect on the reversal of the action of Duodopa. 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 Duodopa should be taken into consideration. To date experiences with dialysis have not been reported, therefore its value in the treatment of overdose is unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parkinson drugs, levodopa and decarboxylase inhibitor
ATC code: N04BA02.

Mechanism of action
Duodopa is a combination of levodopa and carbidopa (ratio 4:1) in a gel for continuous intestinal infusion in advanced Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia. Levodopa is a metabolic precursor of dopamine that relieves symptoms of Parkinson's disease following decarboxylation to dopamine in the brain. Carbidopa, which does not cross the blood-brain barrier, inhibits the extracerebral decarboxylation of levodopa, which means that a larger amount of levodopa becomes available for transportation to the brain and transformation into dopamine. Without the simultaneous administration of carbidopa much larger amounts of levodopa would be required to achieve the desired effect. Intestinal infusion of individualized doses of Duodopa maintains plasma concentrations of levodopa at steady levels within the individual therapeutic windows.

Pharmacodynamic effects
Intestinal therapy with Duodopa reduces the motor fluctuations and decreases the "Off" time for patients with advanced Parkinson's disease who have received tablet treatment with levodopa/decarboxylase inhibitor for many years. The motor fluctuations and hyper-/dyskinesias are reduced due to less variable plasma concentrations than oral carbidopa/levodopa

which allows treatment in a narrow therapeutic window. Therapeutic effects on motor fluctuations and hyper-/dyskinesias are often achieved during the first treatment day.

Clinical efficacy and safety

The efficacy of Duodopa was confirmed in two identically-designed Phase 3, 12-week, randomized, double-blind, double-dummy, active-controlled, parallel group, multicenter studies to evaluate the efficacy, safety, and tolerability of Duodopa against levodopa/carbidopa 100/25 mg tablets. The studies were conducted with patients with advanced Parkinson's disease who were levodopa-responsive and had persistent motor fluctuations despite optimized treatment with oral levodopa carbidopa and other available anti-Parkinson's disease medications and enrolled a total of 71 patients. The results of the two studies were combined and a single analysis was conducted.

The primary efficacy endpoint, change in normalized "Off" time (baseline to endpoint) based on Parkinson's Disease Diary© data using last observation carried forward demonstrated a statistically significant least square (LS) mean difference in favor of the Duodopa treatment group (Table 3).

The primary end point results were supported by a Mixed Model Repeated Measures (MMRM) analysis which examined the change from baseline to each post-baseline study visit. This analysis of "Off" time demonstrated a statistically significant greater improvement of the Duodopa group over the LC-oral group at Week 4, and that improvement was shown to be statistically significant at Weeks 8, 10, and 12.

This change in "Off" time was associated with a statistically significant LS mean difference from baseline in the average daily normalized "On" time without troublesome dyskinesia between the Duodopa treatment group and the active control group based on Parkinson's Disease Diary© data. The baseline values were collected three days prior to randomization and after 28 days of oral therapy standardization.

Table 3 Change from Baseline to Endpoint in "Off" Time and in "On" Time Without Troublesome Dyskinesia

Treatment Group	**N**	**Baseline Mean (SD) (hours)**	**Endpoint (SD) (hours)**	**LS Mean (SE) of Change (hours)**	**LS Mean (SE) of Difference (hours)**	***P value***
Primary Measure						
"Off" time Active Control[a]	31	6.90 (2.06)	4.95 (2.04)	–2.14 (0.66)		
Duodopa	35	6.32 (1.72)	3.05 (2.52)	–4.04 (0.65)	–1.91 (0.57)	0.0015
Secondary Measure						
"On" time without troublesome dyskinesia Active Control	31	8.04 (2.09)	9.92 (2.62)	2.24 (0.76)		
Duodopa	35	8.70 (2.01)	11.95 (2.67)	4.11 (0.75)	1.86 (0.65)	0.0059

SD = standard deviation; SE = standard error

[a] Active control, oral levodopa/carbidopa 100/25 mg tablets

Analyses of other secondary efficacy endpoints, in order of the hierarchical testing procedure, demonstrated statistically significant results for Duodopa compared to oral levodopa/-carbidopa for the Parkinson's Disease Questionnaire (PDQ-39) Summary Index (*an index Parkinson's disease-related quality of life*), Clinical Global Impression (CGI-I) score, and Unified Parkinson's Disease Rating Scale (UPDRS) Part II score (*Activities of Daily Living (ADL)*). The PDQ-39 Summary Index showed a decrease from baseline of 10.9 points at week 12. Other secondary endpoints, UPDRS Part III score, EQ-5D Summary Index, and ZBI total score, did not meet statistical significance based on the hierarchical testing procedure.

A Phase 3, open-label, single-arm, multicenter study was conducted to assess the long-term safety and tolerability of Duodopa over 12 months in 354 patients. The target population was levodopa-responsive patients with advanced Parkinson's disease and motor fluctuations despite optimized treatment with available Parkinson's disease medications. The average daily normalized "Off" time changed by – 4.44 hours from Baseline to Endpoint (6.77 hours at Baseline and 2.32 hours at Endpoint) with a corresponding 4.8 hour increase in "On" time without dyskinesia.

A Phase 3, open-label, randomized, multicenter study was conducted to assess the effect of Duodopa on dyskinesia compared with optimized medical treatment (OMT) over 12 weeks in 61 patients. The target population was levodopa-responsive patients with advanced PD and motor fluctuations inadequately controlled with OMT and with a baseline Unified Dyskinesia Rating Scale (UDysRS) Total Score ≥30. The change from baseline to Week 12 in UDysRS total score (primary efficacy endpoint) demonstrated a statistically significant LS Mean difference (-15.05; $P < 0.0001$) in favour of the Duodopa treatment group compared with OMT group. Analysis of secondary efficacy endpoints using a fixed sequence testing procedure, demonstrated statistically significant results in favour of Duodopa compared with OMT for "On" time without troublesome dyskinesia as measured by PD diary, for Parkinson's Disease Questionnaire-8 (PDQ-8) summary index, Clinical Global Impression Change (CGI-C) score, UPDRS Part II score, and for "Off" time as measured by PD diary. The UPDRS Part III score did not meet statistical significance.

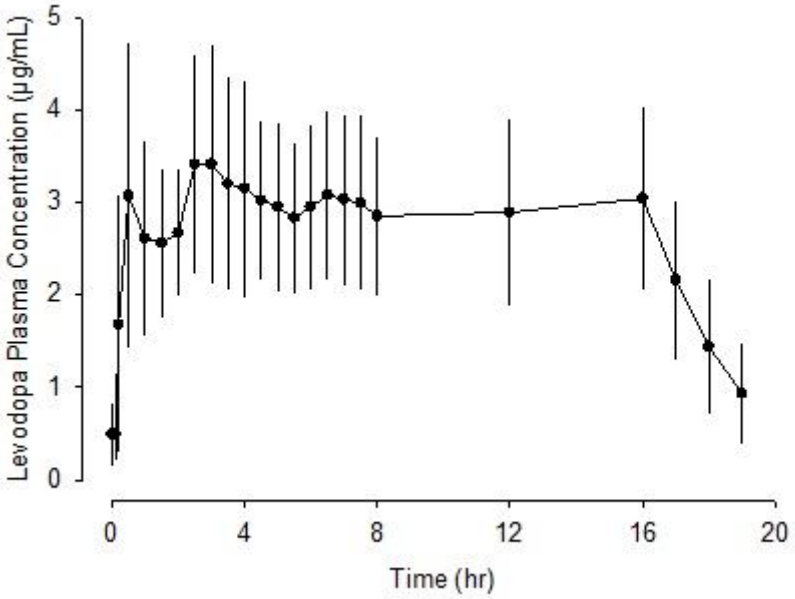
Pediatric population
The safety of Duodopa in patients under 18 years of age has not been established and its use in patients below the age of 18 is not recommended.

5.2 Pharmacokinetic properties

Absorption
Duodopa is administered *via* an inserted tube directly into the duodenum or jejunum. Levodopa is absorbed quickly and effectively from the intestine through a high capacity transport system for amino acids. The absolute bioavailability of levodopa from oral levodopa/carbidopa immediate release tablets is reported to be 84-99%. A cross-study population pharmacokinetic analysis suggested that Duodopa has comparable levodopa bioavailability to the oral levodopa/carbidopa (100/25 mg) tablets.

In a Phase 1 study, intrajejunal administration of Duodopa rapidly achieved therapeutic plasma levels of levodopa and maintained consistent levodopa levels over the course of infusion. Following termination of infusion, levodopa levels declined rapidly (Figure 1). The intra-subject variability in levodopa plasma concentrations starting from hour 2 to hour 16 following initiation of infusion was low (13%).

Figure 1. Plasma Concentrations (mean ± standard deviation) versus Time Profile of Levodopa with Duodopa 16-Hour Infusion



In a Duodopa double-blind, active-controlled, Phase 3 Study, the intra-subject variability in levodopa plasma concentrations was lower for patients treated with Duodopa (21%) than in patients treated with oral levodopa/carbidopa 100/25 mg over-encapsulated tablets (67%).

Distribution
Levodopa is co-administered with carbidopa, a decarboxylase inhibitor, which increases the bioavailability and decreases clearance for levodopa. Clearance and volume of distribution for levodopa is 0.3 l/hour/kg and 0.9-1.6 l/kg, respectively, when given together with a decarboxylase inhibitor. The partitioning ratio for levodopa between erythrocytes and plasma is

approximately 1. The protein binding of levodopa in plasma is negligible (about 10%-30%). Levodopa is transported into the brain by the carrier mechanism for large neutral amino acids.

Carbidopa is approximately 36% bound to plasma protein. Carbidopa does not cross the blood-brain barrier.

Biotransformation and elimination
When administered with carbidopa, the elimination half-life for levodopa is approximately 1.5 hours. Levodopa is eliminated completely through metabolism and the metabolites formed are excreted mainly in the urine. Four metabolic pathways are known, but levodopa is mainly eliminated via metabolism by the aromatic amino acid decarboxylase (AAAD) and the catechol-O-methyl-transferase (COMT) enzymes. Other routes of metabolism are transamination and oxidation. The decarboxylation of levodopa to dopamine by AAAD is the major enzymatic pathway when no enzyme inhibitor is co-administered. When levodopa is co-administered with carbidopa, the decarboxylase enzyme is inhibited, so that metabolism via catechol-O-methyl-transferase (COMT) becomes the dominant metabolic pathway. O-methylation of levodopa by COMT forms 3-O-methyldopa.

Carbidopa is metabolized to two main metabolites (α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid). These 2 metabolites are primarily eliminated in the urine unchanged or as glucuronide conjugates. Unchanged carbidopa accounts for 30% of the total urinary excretion. The elimination half-life of carbidopa is approximately 2 hours.

Pharmacokinetic-pharmacodynamic relationship
The reduced fluctuations in the plasma concentration of levodopa reduce fluctuations in the treatment response. The levodopa dose needed varies considerably in advanced Parkinson's disease and it is important that the dose is individually adjusted based on the clinical response. Development of tolerance over time has not been observed with Duodopa.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. In reproductive toxicity studies both levodopa and the combination of carbidopa/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
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 15 weeks.
Once opened: Use immediately. The product is to be used for up to 24 hours once it is out of the refrigerator. Discard any unused portion.

6.4 Special precautions for storage

Store and transport refrigerated (2°C-8°C).

Keep the cassette in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Total amount of 100 ml in PVC bag inside a hard plastic cassette for protection, carton with 7 cassettes.

6.6 Special precautions for disposal and other handling

Cassettes are for single use only.
Do not re-use an opened cassette.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Empty/used cassettes should be returned to the pharmacy for destruction.

7 MARKETING AUTHORISATION HOLDER

AbbVie Limited
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1824/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 November 2005
Date of last renewal: 21 January 2009

10 DATE OF REVISION OF THE TEXT

November 2023