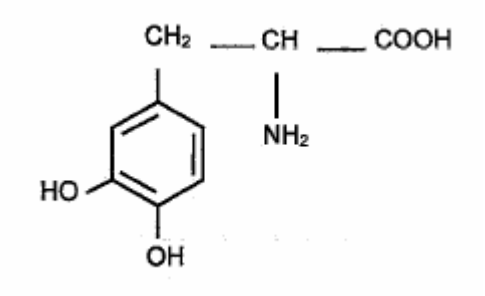
DUODOPA® Intestinal Gel

PRODUCT INFORMATION

NAME OF THE DRUG

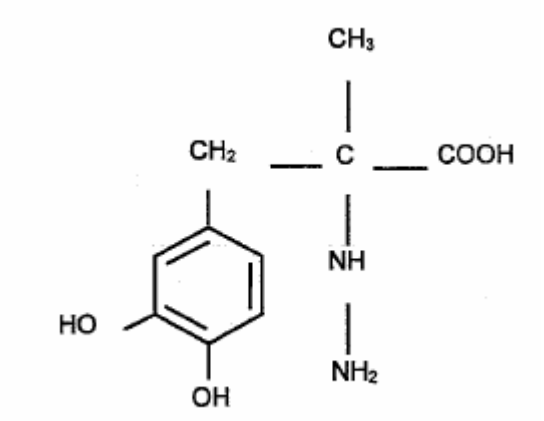
Generic Names: Levodopa
Carbidopa

Levodopa



CAS No: 59-92-7 Mol. Wt: 197.2
Molecular Formula: $C_9H_{11}NO_4$
Chemical name: (2S)-2-amino-3-(3,4-dihydroxyphenyl) propanoic acid

Carbidopa



CAS No: 38821-49-7 (monohydrate) Mol. Wt: 244.2 (hydrous)
Molecular Formula: $C_{10}H_{14}N_2O_4.H_2O$
Chemical name: (2S)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid, monohydrate

DESCRIPTION

Levodopa is an aromatic amino acid, the metabolic pre-cursor to dopamine. Levodopa is also a white or slightly cream-coloured crystalline powder, slightly soluble in water, practically insoluble in alcohol and in ether. It is freely soluble in 1 M HCl and sparingly soluble in 0.1 M HCl, and is light and oxygen sensitive.

Carbidopa is an inhibitor of aromatic amino acid decarboxylase. Carbidopa is a white or yellowish-white powder, slightly soluble in water, very slightly soluble in alcohol, practically insoluble in methylene chloride. It dissolves in dilute solutions of mineral acids, and is light and oxygen sensitive.

Duodopa Intestinal gel is a white to slightly yellow gel. 1 mL contains levodopa 20 mg and carbidopa monohydrate 5 mg.
100 ml contain levodopa 2000 mg and carbidopa monohydrate 500 mg

Duodopa Intestinal Gel also contains carmellose sodium and water purified.

PHARMACOLOGY

Pharmacodynamics

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

The intestinal gel is a combination of levodopa and carbidopa in a ratio of 4 to 1 and in a gel for continuous intestinal infusion in advanced Parkinson's disease with severe motor fluctuations and hyper-dyskinesia.

Levodopa 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 therapy with this combination gel reduces the motor fluctuations and increases the "on"-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 the fact that the plasma concentrations of levodopa are being kept at a steady level within the individual therapeutic window. Therapeutic effects on motor fluctuations and hyper-dyskinesias are often achieved during the first treatment day.

Pharmacokinetics

Absorption:

The combination intestinal gel is administered via an inserted tube directly into the duodenum. Levodopa is absorbed quickly and effectively from the intestine through a high capacity transport system for amino acids. Levodopa given in this combination gel has the same bioavailability as levodopa given as tablets (81-98%). The variation in plasma concentration within an individual is considerably smaller for the combination gel due to the fact that it is given by continuous intestinal administrationin which the gastric emptying rate has no influence on the absorption rate. With an initial high morning dose of the intestinal gel the therapeutic plasma level of levodopa is reached within 10-30 minutes.

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 protein binding of levodopa in plasma is negligible.

Metabolism and Elimination:

The elimination half-life for levodopa is approximately 1-2 hours. Levodopa is eliminated completely through metabolism and the metabolites formed are excreted mainly in the urine. Four metabolic pathways are known, decarboxylation being predominant for levodopa administered without any enzyme inhibitor. 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.

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 advance 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 this combination intestinal gel.

CLINICAL TRIALS

Most patients in the Duodopa® clinical studies were over 50 years of age (39-79). Each had illnesses for 4 to 31 years, levodopa treatment for 4 to 21 years or more, and had suffered motor fluctuations for 3 to 17 years in spite of many treatment variations with levodopa/carbidopa in combination with other antiparkinsonian drugs (COMT inhibitors, dopamine agonists, anticholinergics). Hoehn and Yahr disease stage "at worst" was 2-5 on a 5-point scale and the majority had a score of 3-5. In Study NPP-001-02 three patients had a Hoehn & Yahr score "at worst" of 2 and another 3 patients 2.5. So the patients matched the indication for treatment with Duodopa®.

All studies were open label except NPP-003-00 which was discontinued due to design limitations. Blinded assessments of motor fluctuations and dyskinesias from video recordings were done in NPP-001-02.

Study NPP-001-02: Designed as an open-label, 3 + 3 week, crossover study using video-scoring with blinded, third-party assessment of motor fluctuations and dyskinesia to compare Duodopa monotherapy with any conventional anti-Parkinsonian drug combination in patients with PD and severe levodopa-related motor complications.

Twenty-four patients were randomised into two treatment groups. In one patient group, conventional PD medication was administered for three weeks followed by three weeks with Duodopa as monotherapy by upper intestinal infusion via a nasoduodenal catheter while the other patient group received Duodopa monotherapy via nasoduodenal catheter for three weeks followed by three weeks of conventional PD medication.

Duodopa doses were individualized to each patient's need and dose adjustments were allowed throughout the study except on test days. Comparators: any anti-Parkinsonian medication available in Sweden. All patients were treated with levodopa, two-thirds received dopamine agonists, and approximately half received COMT inhibitors. For patients receiving Duodopa treatment, extra doses of 2–40 mg (0.1–2 mL) could be delivered via the CADD-Legacy® Duodopa® pump. Oral levodopa/carbidopa was allowed as needed at night for both treatment groups.

The study was open-label for patients and investigators. Two independent neurologists, unaware of each patient's therapy, evaluated the video recordings. Each recording was assessed for symptoms of PD, dyskinesias, and treatment response.

Table 1. Pivotal Study NPP-001-02: Percentage of video recordings showing an acceptable response (TRS score in the range -1 to +1)				
	Conventional treatment (N=20)	Duodopa (N=21)	Between-treatment difference (Duodopa – Conventional)	
			Intention-to-treat*	Per-protocol**
Mean ± SD	75.4±24.6	90.7±19.2	13.7±20.6	18.4±22.1
Median	81.3	100.0	4.5	14.0
Range	18 to 100	37 to 100	-14.7 to 63.2	-14.7 to 63.2
P-Value***	-	-	<0.01	<0.01

* All randomised patients. Patients with less than 14 recordings for either treatment phase were assigned a between-treatment difference of 0.

** Patients who satisfied all major entry criteria, received both study treatments as planned and had at least 82% of the planned video recordings.

*** Wilcoxon. A non-parametric test was used because the data were skewed.

The following secondary efficacy end-points were assessed in the intention-to-treat (ITT) and/or per-protocol (PP) populations in the pivotal trial:

- **Wider TRS interval (ITT and PP):** The percentage of video recordings in the wider TRS interval of -1 to +2 was significantly greater with Duodopa than conventional treatment.
- **Percentage of time with dyskinesia (ITT and PP):** The percentage of time with moderate to severe dyskinesia (TRS+2 to +3) was low (6-8%) and did not differ significantly between treatments.
- **UPDRS (PP):** There was a significant between-treatment difference in favour of Duodopa for the UPDRS total score and for Parts I, II and IV subscores. The UPDRS part III subscore showed a non-significant trend in favour of Duodopa.
- **PDQ-39 and PDQ-8 (PP):** Duodopa was significantly better than conventional therapy in regard to the PDQ-39 summary index, the PD-8 summary index, and 7 of the 8 dimensions of the PDQ-39 (excluding 'Social Support').
- **15D (PP):** Quality of life, as measured by the 15D, was significantly better with Duodopa than conventional therapy.
- **Electronic Diary (PP):** Duodopa was significantly better than conventional therapy in relation to responses to the morning question regarding ability to turn in bed, and the morning and daytime questions regarding difficulty walking, having been "off", difficulty with chores and satisfaction with functioning. Duodopa was not significantly different to conventional therapy in regard to the responses to the morning question regarding overnightsleep, nor the morning and daytime questions regarding hyperkinesia, muscular cramps/spasms, and depression.

The efficacy of Duodopa was also assessed in the following non-pivotal studies:

- **NPP-001-99: A**n open-label, randomized, 3+3 week crossover study in which 12 patients received Duodopa and controlled-release levodopa/carbidopa.
- **NPP-001-92: A**n open-label study in which 7 patients who had been taking optimized oral levodopa/carbidopa were switched to a developmental Duodopa formulation for 6 months.

The efficacy findings in these studies were generally consistent with those of the pivotal trial, although confounded by various factors. For example, the assessments were not blinded and were not optimally timed to assess mobility fluctuations.

Adverse events related to Duodopa were consistent with those known to occur during oral levodopa/carbidopa treatment (see **ADVERSE EFFECTS**). Adverse events related to the delivery system and stoma were generally minor (see **ADVERSE EFFECTS**). There was no consistent pattern of laboratory, ECG, or vital sign abnormalities during Duodopa therapy.

INDICATIONS

For the treatment of advanced idiopathic Parkinson's disease with severe motor fluctuations despite optimized oral treatment. A positive clinical response to Duodopa administered via a temporary nasoduodenal tube should be confirmed before a permanent percutaneous endoscopic gastrostomy (PEG) tube is inserted.

CONTRAINDICATIONS

Duodopa is contraindicated in patients with:

- Hypersensitivity to levodopa, carbidopa, or any of the excipients
- Narrow-angle glaucoma
- Severe liver or renal insufficiency
- Severe heart failure
- Severe cardiac arrhythmia
- Acute stroke
- Conditions in which adrenergics are contraindicated, e.g. phaeochromocytoma, hyperthyroidism and Cushing's syndrome

Duodopa is also contraindicated in:

- Pregnancy (See PRECAUTIONS – Use in Pregnancy)
- Lactation (See PRECAUTIONS – use in Lactation)
- Women of child-bearing potential unless effective contraception is used.

Non-selective MAO-inhibitors and selective MAO type A inhibitors must not be given concomitantly with Duodopa and should be withdrawn at least two weeks before initiation of Duodopa (See PRECAUTIONS – Interactions).

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

PRECAUTIONS

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

- Duodopa is not recommended for the treatment of drug-induced extrapyramidal reactions.
- Duodopa therapy should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or a history of peptic ulcer disease or convulsions.
- As with levodopa, there is a possibility of upper gastrointestinal haemorrhage in patients with a history of peptic ulcer.
- 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 D2 receptor antagonists should be carried out with caution, and the patient carefully observed for loss of antiparkinsonian effect or worsening of parkinsonian symptoms (See PRECAUTIONS – Interactions).
- 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 PRECAUTIONS – Interactions).
- 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 also effects on ability to drive and use machines).
- 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 antipsychotics. Neither NMS nor rhabdomyolysis has been reported in association with Duodopa.
- Pathologic gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including levodopa/carbidopa.
- 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.
- Previous surgery in the upper part of the abdomen may lead to difficulty in performing gastrostomy or jejunostomy.
- 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 (see Dosage and Administration section).
- A sudden or gradual worsening of bradykinesia may indicate an obstruction in the device or tube and needs to be explored. The onset of fluctuations in the therapeutic effect of Duodopa may indicate that the tip of the tube has migrated into the stomach and needs to be repositioned.
- Patients using Duodopa should be advised not to swim or bathe. The pump cannot be taken into the water. If the pump is disconnected to go swimming, bradykinesia may develop without warning and the patient could drown.

Carcinogenicity

There was no evidence of carcinogenicity following daily oral administration of a combination of levodopa and carbidopa to rats for 106 weeks or following daily oral administration of carbidopa alone to rats for 96 weeks.

Genotoxicity

Carbidopa was positive in bacterial and mammalian gene mutation assays, but negative in an *in vivo* assay for clastogenicity. A combination of levodopa, carbidopa and entacapone was negative in a bacterial gene mutation assay and two in vivo assays for clastogenicity.

Effects on fertility

Oral administration of combinations of levodopa and carbidopa to male and female rats prior to mating and during gestation had no adverse effects on fertility, reproductive performance, or pup survival.

The immediate container for Duodopa® is transparent PVC with di(2-ethylhexyl)phthalate (DEHP) as a plasticizer. Leaching of DEHP into the drug suspension is possible. DEHP has been shown to cause adverse effects on male reproductive organs in studies in laboratory animals. The effects on human fertility are unknown.

Use in Pregnancy: (**Category B3)**

Levodopa and combinations of carbidopa and levodopa, but not carbidopa alone, have caused visceral and skeletal malformations in rabbits. Carbidopa and combinations of levodopa and carbidopa were not teratogenic in mice. An oral combination of levodopa, carbidopa and entacapone was not teratogenic in rats and rabbits.

The effects of Duodopa® on human pregnancy are unknown. Therefore, use of Duodopa® in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards, should pregnancy occur.

Use in Lactation

Oral administration of combinations of levodopa + carbidopa to rats from late gestation to weaning had no adverse effects on reproductive performance or on pup growth and survival. It is not known whether levodopa and carbidopa are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in infants, Duodopa® should not be used by breast-feeding mothers.

Use in Elderly

There is wide experience in the use of levodopa/carbidopa in elderly patients (see Dosage and Administration).

Use in Children and Adolescents (<18 years of age)

Since there is no clinical experience in patients under the age of 18 years use in children is not recommended.

Interactions

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

Caution is needed in the 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. (See contraindications for patients receiving MAOIs).

Anticholinergics – These 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, butyrophenones 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 selective for MAO type B (e.g. seligiline-HCl).
Concomitant use of selegiline and levodopa-carbidopa has been associated with serious orthostatic hypotension.

Amantadine has a synergistic 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 antacids on the bioavailability of Duodopa has not been studied.

Effects 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 PRECAUTIONS).

ADVERSE EFFECTS

Adverse reactions frequently observed with levodopa/carbidopa are those due to the central neuropharmacological activity of dopamine. These reactions can usually be diminished by levodopa dosage reduction.

ADVERSE REACTIONS EXPERIENCED BY PATIENTS TAKING LEVODOPA/CARBIDOPA

MedDRA System organ class	Common (1.0 – 10%)	Uncommon (0.1 – 1.0%)	Rare (0.01% - 0.1%)	Very Rare <0.01% incl. isolated reports
Blood and lymphatic system disorders			Agranulocytosis Leucopenia Haemolytic & non-haemolytic anaemia Thrombocytopenia	
Metabolism and nutrition disorders	Anorexia	Weight loss Weight gain		
Psychiatric disorders	Hallucinations Confusion Nightmares Sleepiness Fatigue Asthenia Sleeplessness Depression with very rare suicide attempts Euphoria Dementia Psychotic episodes Feeling of stimulation		Agitation Fear Reduced thinking capacity Disorientation Increased libido Numbness anxiety	Suicide attempts
Nervous system disorders	Dyskinesias Chorea Dystonia “ON-OFF” episodes Dizziness Bradykinesia (“ON-OFF” episodes)[1] Somnolence[2]	Ataxia Increased hand tremor	Neuroleptic malignant syndrome Paraesthesias Falling Walking defects Trismus Headache Convulsions	
Eye disorders			Blurred vision Blepharospasm Activation of a latent Horner’s syndrome Double vision Dilated pupils Oculogyric crises	
Cardiac disorders	Palpitations Irregular heartbeat			

Vascular disorders	Orthostatic hypotension Tendency to faint Syncope	Hypertension	Phlebitis	
Respiratory, thoracic and mediastinal disorders		Hoarseness Chest pain	Dyspnoea Abnormal breathing	
Gastrointestinal disorders	Nausea Vomiting Dry mouth Bitter taste	Constipation Diarrhoea Sialorrhoea Dysphagia Flatulence	Dyspepsia Gastro-intestinal pain Dark saliva Bruxism Hiccups GI bleeding Burning sensation of tongue Duodenal ulceration	
Skin and sub-cutaneous tissue disorders		Oedema	Angioedema Urticaria Pruritus Facial redness Hair loss Exanthema Increased perspiration Dark perspiration fluid Schönlein-Henoch purpura	Bad odour Malignant melanoma
Musculoskeletal, connective tissue disorders		Muscle spasms		Muscle cramps
Renal and urinary disorders		Dark urine	Urinary retention Urinary incontinence Priapism	Haematuria
General disorders and administration site conditions		Weakness Malaise Hot flushes		
Investigations			Haemoglobin decreased	

[1] Bradykinesia ("ON-OFF" episodes) may appear some months to years after the beginning of treatment with levodopa and is probably related to the progression of the disease. The adaptation of dose schedule and dose intervals may be required.

[2] Levodopa/carbidopa is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

Blepharospasm and muscle twitching may be early signs of overdose. If these occur, dose reduction should be considered.

Laboratory values:
The following laboratory abnormalities have been reported with levodopa/carbidopa: Elevated serum urea, alkaline phosphatases, AST, ALT, LDH, bilirubin, creatinine, and uric acid; elevated blood sugar; positive Coombs test; reduced 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.

Patients treated with dopamine agonists for treatment of Parkinson's disease, including levodopa/carbidopa, especially at high doses, have been reported as showing pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

The device:
Complications with the devices are very common (>1/10), e.g. connector leakage, dislocation of the intestinal tube. Dislocation of the intestinal tube backwards into the stomach leads to reappearance of motor fluctuations (due to erratic gastric emptying of Duodopa into the small intestines). Generally relocation of the tube can be done using a guide-wire to steer the tube into the duodenum under fluoroscopy. Occlusion, kinking or knotting of the intestinal tube leads to high pressure signals from the pump. Occlusions are usually remedied by flushing the tube with tap water; kinking, knotting, or a tube displacement may need readjustment of the tubing. Should complete failure of the intestinal tube or pump occur the patient must be treated with oral levodopa/carbidopa until the problem is solved. The stoma usually heals without complications. Though abdominal pain, infection and leakage of gastric fluid may occur shortly after surgery, these are rarely long-term problems. Reported complications include perforation of adjacent anatomical structures, especially during PEG placement, and bleeding, wound infection (the most common complication) and peritonitis. Local infections around the stoma may be treated conservatively with a disinfectant as treatment with antibiotics is rarely needed.

The safety of Duodopa was assessed in the following studies:

- **NPP-003-00:** A double-blind, double-dummy, randomised trial which was terminated after the enrolment of 5 patients.
- **NPP-002-02**: A retrospective, open-label, medical records-based, safety analysis of 65 patients who had used developmental and/or final Duodopa formulations for up to 10.7 years (mean 4.1 years in the 52 patients who received Duodopa for 12 months or more). This analysis included all but one of the patients from the non-pivotal trials, plus an additional 44 patients who received Duodopa under a compassionate use program. It did not include the 24 patients from the pivotal trial, which was conducted at a later date).

There were no deaths in the pivotal trial. A total of 8 patients died while receiving Duodopa during the period covered by the retrospective safety analysis, NPP-002-02. Death was due to pneumonia (6 patients), myocardial infarction (1 patient) or stroke (1 patient). Pneumonia is a common cause of death in end-stage Parkinson's disease and none of the deaths were considered to be due to Duodopa or the delivery system.

In the pivotal trial, 3 patients had non-fatal serious adverse events: 2 during Duodopa treatment and 1 during conventional treatment. Of these, 1 serious event (insomnia and confusion during Duodopa use) was considered to be treatment-related. Non-fatal serious adverse events were reported in 2 patients during the period covered by the retrospective safety analysis, NPP-002-02: 1 patient developed a sub-diaphragmatic abscess following PEG surgery; 1 patient had episodic atrial fibrillation during levodopa/carbidopa treatment and during Duodopa therapy.

DOSAGE AND ADMINISTRATION

Duodopa is intended for continuous daytime intestinal administration. For long-term administration the gel should be administered with a portable pump directly into the duodenum by a permanent tube via percutaneous endoscopic gastrostomy (PEG) with an outer transabdominal tube and an inner intestinal tube. Alternatively a radiological gastrojejunostomy may be considered if PEG 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 tube should be used to find out if the patient responds favourably to this method of treatment and to adjust the dose before treatment with a permanent tube is started.

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 of OFF episodes and the time OFF (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 Duodopa pump (CE 0473) 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 medication including levodopa/carbidopa.

Dosage:
The total dose per day of Duodopa is composed of three individually adjusted doses: the morning bolus dose, the continuous maintenance dose and extra bolus doses.
Morning dose: the morning 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/hr (0.1 mL/hr). 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 individiually. 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). 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 (including 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 bolus 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 during a few weeks.

Overnight break
Continuous levodopa administration may lead to the development of tolerance and reduction of therapeutic effect. In addition, the Duodopa cassette must be discarded after it has been at room temperature for 16 hours. For these reasons, Duodopa infusion is normally stopped overnight. If medically justified, Duodopa may be administered continuously without an overnight break, but the cassette must be changed every 16 hours. Overnight breaks should be reinstituted if tolerance develops.

Prolonged interruption or cessation of therapy
Patients should be carefully observed in case of a sudden reduction of the dose or if it is necessary to discontinue treatment with Duodopa, particularly in the patient who is receiving antipsychotics. (See Precautions section).

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 into the stomach. The location of the tube should be determined by X-ray and the end of the tube repositioned to the duodenum under radiological control.

Replacement therapy: For convenience, patients receiving levodopa and carbidopa from tablets may instead wish to receive the combination intestinal gel.

Use in renal dysfunction

No dose adjustment necessary.

Use in hepatic dysfunction

No dose adjustment necessary.

Handling of the pump and cassette
In the case of *suspected or diagnosed* dementia and lowered confusion threshold, the pump should be handled only by the nursing staff or a close relative who is experienced to do so.

When the cassette is to be used it should be attachd to the portable pump and the system connected to the nasoduodenal tube or the transabdominal port/duodenal tube for administration, according to the instructions given. The drug cassettes are for single use only and should not be used for longer than one day (16 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 drug or the treatment.

OVERDOSAGE

Most prominent clinical symptoms of an overdose with levodopa/carbidopa are dystonia and dyskinesia. Blepharospasm 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 Duodopa overdose is unknown.

STORAGE

DUODOPA Intestinal Gel should be stored between 2 and 8°C. Shelf life 15 weeks.

Chemical and physical in-use stability has been demonstrated for 16 hours at 40°C.

The cassettes should be stored before use in the outer carton to protect from light.

PRESENTATION

DUODOPA Intestinal Gel is provided in 100 ml PVC bags each inside a hard plastic cassette for protection. Carton with seven cassettes.

SCHEDULE

Schedule 4 – Prescription only medicine.

SPONSOR

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